

# Real-World Users of Triple Therapy for Asthma in the US

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**A**sthma affects more than 25 million individuals in the US and is a major clinical and economic burden.<sup>1,2</sup> In 2018-2019, asthma accounted for 1.6 million emergency department (ED) visits and nearly 180,000 hospitalizations per year in the US,<sup>2</sup> with total asthma costs of \$82 billion in 2008-2013.<sup>3</sup>

The Global Initiative for Asthma report recommends a stepwise approach to asthma treatment.<sup>1</sup> Addition of a long-acting muscarinic antagonist (LAMA) is recommended for patients who remain symptomatic on at least a medium-dose inhaled corticosteroid/long-acting  $\beta_2$  agonist (ICS/LABA), administered as either single- or multiple-inhaler triple therapy (SITT or MITT).<sup>1</sup> A study of triple-therapy use for asthma in 2014-2017 found that 90% of patients initiated on MITT had used at least 1 prior asthma controller therapy.<sup>4</sup> Addition of a LAMA to ICS/LABA improves lung function and symptoms and reduces exacerbation rates in patients with uncontrolled asthma.<sup>5-8</sup> Until recently, triple therapy for asthma was only available as MITT, often with different dosing regimens or devices.<sup>1</sup> Real-world studies in the US, Japan, and Spain have shown low adherence and persistence with MITT among patients with asthma.<sup>4,9-11</sup> A real-world study in Spain found that many patients receiving MITT stepped down 12 months after initiating therapy (30.0%), usually to ICS/LABA (84.5%).<sup>11</sup> Some patients in this study discontinued MITT, leaving many untreated (68.5%).<sup>11</sup> This is concerning given the association between poor adherence and uncontrolled asthma.<sup>12</sup>

SITT is a good treatment option in patients with asthma uncontrolled by ICS/LABA, especially in those with key “treatable traits” (airflow limitation and small airway dysfunction).<sup>13</sup> In Europe, approved SITTs include beclometasone dipropionate/formoterol fumarate dihydrate/glycopyrronium bromide (Trimbow)<sup>14</sup> and indacaterol/glycopyrronium bromide/mometasone furoate (Enerzair Breezhaler).<sup>15</sup> In addition, the fixed-dose ICS/LAMA/LABA combination of fluticasone furoate, umeclidinium, and vilanterol (FF/UMEC/VI; 100/62.5/25  $\mu$ g; Trelegy) administered via the Ellipta dry powder inhaler was approved by the FDA for the treatment of chronic obstructive pulmonary disease (COPD) in 2017<sup>16</sup> and for maintenance treatment of asthma in adults at 2 doses (100/62.5/25  $\mu$ g and

## ABSTRACT

**OBJECTIVES:** For patients with asthma who remain symptomatic on a medium-dose inhaled corticosteroid/long-acting  $\beta_2$  agonist, addition of a long-acting muscarinic antagonist as a supplementary controller is a recommended option. However, real-world data on the characteristics and treatment patterns of these patients are limited. This study described the demographics and clinical characteristics of new users of single- or multiple-inhaler triple therapy and treatment patterns preceding triple-therapy initiation.

**STUDY DESIGN:** This retrospective cohort study used medical and pharmacy claims data from the IQVIA PharMetrics Plus database.

**METHODS:** The study population comprised adults with asthma with or without chronic obstructive pulmonary disease (COPD) initiating triple therapy with single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI; 100/62.5/25  $\mu$ g) or multiple-inhaler triple therapy (MITT) between September 18, 2017, and September 30, 2019. Demographics, clinical characteristics, and treatment patterns in the 12 months preceding triple-therapy initiation were described (baseline period).

**RESULTS:** A total of 12,395 patients were included. Among FF/UMEC/VI initiators with asthma ( $n = 1301$ ), the mean age was 49.0 years and 59.3% were women. During the baseline period, 81.5% of patients used controller therapy, 94.7% used rescue medications, and 42.0% reported at least 1 asthma-related exacerbation; the annual mean exacerbation rate was 0.96. Similar trends were observed among patients with asthma initiating MITT and patients with comorbid asthma-COPD initiating FF/UMEC/VI or MITT.

**CONCLUSION:** In real-world practice, triple therapy is often utilized following other asthma controller medication use. High disease burden, as evidenced by substantial use of rescue medications and continued asthma-related exacerbations, suggests that patients may not have achieved adequate asthma control prior to triple-therapy initiation.

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200/62.5/25 µg) in 2020<sup>17</sup>; however, its off-label use in asthma was previously reported in a US claims database.<sup>18</sup> Although both MITT and SITT are suitable treatment options for patients with asthma uncontrolled by ICS/LABA,<sup>19</sup> a real-world study has demonstrated that adherence and persistence with single-inhaler FF/UMEC/VI are significantly improved vs MITT in US patients with asthma.<sup>18</sup> FF/UMEC/VI also appears to be cost-effective vs dual therapy with FF/VI or UMEC/VI<sup>20</sup> or budesonide/formoterol (Symbicort)<sup>21</sup> based on analysis of 2 UK trials in COPD<sup>20,21</sup>; similar cost-effectiveness may occur in asthma.<sup>19</sup>

Real-world data provide valuable insights into the use of asthma therapies beyond the tightly defined patient populations used in clinical studies. However, real-world data on the demographics, clinical characteristics, and prior medication use of patients with asthma treated with SITT or MITT are scarce. This retrospective cohort study aimed to address this data gap using insurance claims data from adults with asthma, with or without comorbid COPD, who were newly treated with FF/UMEC/VI (ie, SITT) or MITT. Patients with asthma and comorbid COPD were included because they often have poorer outcomes than those with asthma alone.<sup>22,23</sup>

## METHODS

### Study Design

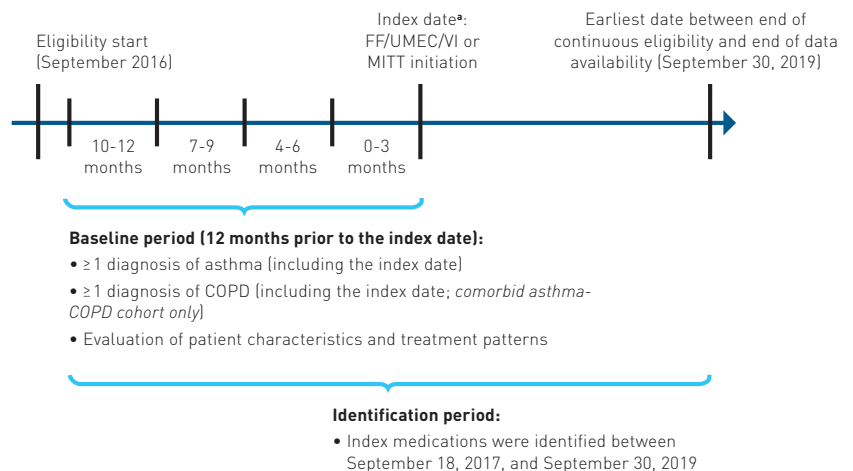
This retrospective cohort study used deidentified medical and pharmacy claims data, including enrollment information, from the IQVIA PharMetrics Plus database from September 18, 2016, to September 30, 2019. Further details are included in the **eAppendix** (available at [ajmc.com](http://ajmc.com)). The index date was the date of the first FF/UMEC/VI (100/62.5/25 µg) dispensing or the date of the first overlapping days of supply with all triple-therapy components for new MITT users during the identification period (September 18, 2017, to September 30, 2019) (**Figure 1**). Patients initiating treatment with both FF/UMEC/VI and MITT during the identification period were included in the FF/UMEC/VI cohort. The baseline period included 12 months preindex, during which demographics, clinical characteristics, and treatment patterns (controller and rescue medications) were assessed. The baseline period was stratified into 3-month intervals from the index date to assess treatment patterns over time (Figure 1). No end points were evaluated during the postindex period. The study was conducted in compliance with all applicable laws regarding participant privacy (see eAppendix).

## TAKEAWAY POINTS

High levels of disease burden and unmet need exist among commercially insured US patients with asthma who are newly initiating triple therapy.

- ▶ This real-world study provides a comprehensive evaluation of characteristics and treatment patterns among a geographically diverse sample of US patients in the 12 months prior to triple-therapy initiation.
- ▶ Triple therapy is often utilized following asthma maintenance medications that likely left symptoms uncontrolled; more than 81.5% of patients used controller medication, and more than 94.7% used rescue medication.
- ▶ Furthermore, patients had high exacerbation burden: 32.6% to 53.4% reported at least 1 asthma-related exacerbation, and the annual mean exacerbation rate was 0.53 to 0.96 across patient cohorts.

**FIGURE 1.** Study Design



COPD, chronic obstructive pulmonary disease; FF/UMEC/VI, fluticasone furoate, umeclidinium, and vilanterol; MITT, multiple-inhaler triple therapy.

\*Index date was defined as the date of initiation of FF/UMEC/VI or the date of the first overlapping days of supply with all 3 components of triple therapy for new MITT users.

### Study Population

Patients were classified into 4 mutually exclusive cohorts based on their index medication (FF/UMEC/VI or MITT) and diagnosis during the baseline period (asthma: ≥ 1 medical claim with a primary or secondary diagnosis of asthma during the baseline period or on the index date; comorbid asthma and COPD [comorbid asthma-COPD]: ≥ 1 medical claim with a primary or secondary diagnosis of asthma and COPD during the baseline period or on the index date). Full inclusion/exclusion criteria are described in the eAppendix.

### Study End Points

Primary end points included baseline demographics and clinical characteristics of new FF/UMEC/VI users and treatment patterns preceding FF/UMEC/VI initiation among adult patients with asthma. Secondary end points included baseline demographics, clinical characteristics, and treatment patterns among patients with asthma

who newly initiated MITT and patients with comorbid asthma-COPD who newly initiated FF/UMEC/VI or MITT. The combinations of medications comprising patients' triple-therapy regimen on the index date were reported among MITT users.

## Data Analyses

Data analyses are described in the eAppendix.

# RESULTS

## Study Population

Of 58,219 patients identified as initiating treatment with FF/UMEC/VI or MITT between September 18, 2017, and September 30, 2019, 12,395 patients were included in the study (eAppendix Figure 1). Overall, 3983 patients initiating FF/UMEC/VI (asthma: n = 1301; comorbid asthma-COPD: n = 2682) and 8412 patients initiating MITT (asthma: n = 4643; comorbid asthma-COPD: n = 3769) were included (eAppendix Figure 1).

## New Users of FF/UMEC/VI With Asthma

**Baseline demographics and clinical characteristics.** Baseline demographics, clinical characteristics, and asthma-related health care resource utilization and costs are presented in Table 1. New FF/UMEC/VI users with asthma had a mean (SD) age of 49.0 (13.2) years and 59.3% (n = 771) were women; most patients were from the South (55.5%) or Midwest (21.5%) regions of the US. The most common prescribing physician specialties on the index date were respiratory specialists (41.5% [n = 540]) and primary care (40.3% [n = 524]). Overall, 42.0% (n = 547) of patients reported at least 1 asthma-related exacerbation during baseline, with an annual mean (SD) exacerbation rate of 0.96 (1.27). Among patients in this cohort, 2.8% (n = 37) had at least 1 asthma-related inpatient (IP) stay during baseline and 75.1% (n = 977) had at least 1 outpatient visit. Mean (SD) total asthma-related baseline health care costs were \$5508 (\$11,478), including \$3080 (\$10,521) in medical and \$2428 (\$3936) in pharmacy costs. Mean (SD) total all-cause baseline health care costs were \$20,551 (\$55,255) (eAppendix Table 1).

Patients had a mean (SD) Quan-Charlson Comorbidity Index (Quan-CCI) score of 1.40 (1.05) (Table 1). The most common asthma-related comorbidities were allergic rhinitis (50.0% [n = 650]), sinusitis (39.7% [n = 516]), upper respiratory tract infection (38.7% [n = 504]), and gastroesophageal reflux disease (34.4% [n = 447]) (eAppendix Table 1). The most common baseline Elixhauser comorbidities were hypertension (46.2% [n = 601]), obesity (23.2% [n = 302]), and diabetes (17.5% [n = 228]) (eAppendix Table 1).

**Treatment patterns.** In new users of FF/UMEC/VI, 81.5% (n = 1060) had previous controller medication use during the baseline period (Table 2). Considering all controller medication use during the baseline period, the most used medication classes were ICS/LABA (63.3% [n = 823]), followed by leukotriene receptor antagonists (LTRA), ICS, LAMA, and MITT. The mean (SD) asthma medication ratio was 0.70 (0.24). Most patients (94.7% [n = 1232]) used at least 1 rescue

medication during baseline, of which systemic corticosteroids, antibiotics (used frequently for treatment of acute exacerbations despite lack of supporting evidence),<sup>24</sup> and short-acting  $\beta_2$  agonists were the most common (Table 2).

When considering mutually exclusive controller medication use closest to the index date, most patients stepped up from either ICS/LABA (35.3% [n = 459]) or LTRA (30.5% [n = 397]), followed by ICS (4.5% [n = 59]) and MITT (4.4% [n = 57]) (Figure 2 [A]).

The proportion of patients using any ICS/LABA increased to 42.6% in the 0 to 3 months prior to the index date from 37.7% in the 10 to 12 months prior (Figure 3). Similarly, the proportions of patients using LTRA or ICS as controller medication or short-acting  $\beta_2$  agonists or systemic corticosteroids as rescue medication increased in the 0 to 3 months prior to the index date vs the 10 to 12 months prior.

## New Users of FF/UMEC/VI With Comorbid Asthma-COPD and New Users of MITT With Asthma or Comorbid Asthma-COPD

**Baseline demographics and clinical characteristics.** Baseline demographics and clinical characteristics were generally similar across the remaining 3 cohorts (Table 1). The mean age ranged from 51.7 to 58.6 years, and 58.5% to 66.9% of patients were women; the MITT asthma cohort included the highest proportion of women. Most new users of FF/UMEC/VI with comorbid asthma-COPD were from the South (58.8%), with 19.2% and 15.9% from the Midwest and Northeast regions of the US, respectively. In the MITT cohorts, 43.0% were from the South, and 22.0% to 25.2% and 21.6% to 25.5% were from the Midwest and Northeast, respectively.

Fewer (32.6%) new users of FF/UMEC/VI with comorbid asthma-COPD reported at least 1 asthma-related exacerbation during baseline vs 42.1% of new users of MITT with comorbid asthma-COPD and 53.4% of new users of MITT with asthma. The prescribing physician specialty at index was generally equally divided between respiratory specialists and primary care, except for the MITT asthma cohort, in which the prescribing physician was predominantly a respiratory specialist (52.2%) vs a primary care physician (30.7%).

Among those initiating MITT, 10.1% (n = 380) of patients with comorbid asthma-COPD had at least 1 asthma-related IP stay during baseline vs 4.6% (n = 214) and 5.0% (n = 134) in the MITT asthma and FF/UMEC/VI comorbid asthma-COPD cohorts, respectively. At least 1 asthma-related outpatient visit during baseline was recorded for 54.4% (n = 1460) of those with comorbid asthma-COPD initiating FF/UMEC/VI, 61.3% (n = 2309) of those with comorbid asthma-COPD initiating MITT, and 85.2% (n = 3958) of those with asthma initiating MITT. The mean (SD) all-cause total baseline health care costs for patients with comorbid asthma-COPD initiating FF/UMEC/VI were \$36,529 (\$62,327). Among patients initiating MITT, the costs were \$16,988 (\$27,347) and \$30,706 (\$48,616) in the asthma and comorbid asthma-COPD cohorts, respectively (eAppendix Table 1).

Mean (SD) asthma-related health care cost for FF/UMEC/VI initiators with comorbid asthma-COPD was \$6352 (\$15,722), including \$3847 (\$15,324) in medical and \$2505 (\$2882) in pharmacy costs.

**TABLE 1.** Baseline Demographics and Clinical Characteristics of New Users of FF/UMEC/VI and MITT With Asthma or Comorbid Asthma-COPD

	FF/UMEC/VI with asthma n = 1301	FF/UMEC/VI with comorbid asthma-COPD n = 2682	MITT with asthma n = 4643	MITT with comorbid asthma-COPD n = 3769
Age in years, <sup>a</sup> mean (SD)	49.0 (13.2)	57.5 (9.6)	51.7 (11.6)	58.6 (8.6)
Age in years, <sup>a</sup> n (%)				
18-64	1179 (90.6)	2218 (82.7)	4278 (92.1)	3121 (82.8)
≥ 65	122 (9.4)	464 (17.3)	365 (7.9)	648 (17.2)
Female, <sup>a</sup> n (%)	771 (59.3)	1569 (58.5)	3107 (66.9)	2322 (61.6)
Region, <sup>a</sup> n (%)				
South	722 (55.5)	1577 (58.8)	1995 (43.0)	1619 (43.0)
Midwest	280 (21.5)	515 (19.2)	1168 (25.2)	831 (22.0)
West	139 (10.7)	164 (6.1)	475 (10.2)	358 (9.5)
Northeast	160 (12.3)	426 (15.9)	1005 (21.6)	961 (25.5)
Physician specialty, <sup>a,b</sup> n (%)				
Primary care	524 (40.3)	1104 (41.2)	1427 (30.7)	1594 (42.3)
Respiratory specialist	540 (41.5)	1147 (42.8)	2425 (52.2)	1543 (40.9)
Allergist	276 (21.2)	173 (6.5)	1294 (27.9)	262 (7.0)
Pulmonologist	266 (20.4)	981 (36.6)	1150 (24.8)	1290 (34.2)
Other specialty	237 (18.2)	431 (16.1)	791 (17.0)	632 (16.8)
Patients with ≥ 1 asthma-related exacerbation during baseline, <sup>c</sup> n (%)				
Overall	547 (42.0)	873 (32.6)	2481 (53.4)	1587 (42.1)
SCS defined	487 (37.4)	700 (26.1)	2133 (45.9)	1176 (31.2)
IP/ED defined	132 (10.1)	272 (10.1)	645 (13.9)	653 (17.3)
Annual exacerbation rate, <sup>c</sup> PPPY, mean (SD)				
Overall	0.96 (1.27)	0.75 (1.25)	0.78 (1.27)	0.53 (1.00)
SCS defined	0.77 (1.10)	0.50 (0.96)	0.64 (1.09)	0.39 (0.83)
IP/ED defined	0.19 (0.59)	0.25 (0.71)	0.14 (0.49)	0.13 (0.47)
≥ 1 asthma-related HCRU, <sup>c</sup> n (%)				
IP stay	37 (2.8)	134 (5.0)	214 (4.6)	380 (10.1)
ED visit	104 (8.0)	162 (6.0)	509 (11.0)	385 (10.2)
OP visit	977 (75.1)	1460 (54.4)	3958 (85.2)	2309 (61.3)
Asthma-related health care costs, <sup>c</sup> US\$ 2019, mean (SD)				
Total costs (medical <sup>d</sup> + pharmacy)	5508 (11,478)	6352 (15,722)	4473 (11,336)	4821 (11,416)
Total medical costs <sup>d</sup>	3080 (10,521)	3847 (15,324)	2344 (9737)	2073 (10,519)
Total pharmacy costs	2428 (3936)	2505 (2882)	2129 (4757)	2749 (3350)
Quan-CCI score, <sup>c</sup> mean (SD)	1.40 (1.05)	2.05 (1.70)	1.41 (1.12)	2.03 (1.69)

COPD, chronic obstructive pulmonary disease; ED, emergency department; FF/UMEC/VI, fluticasone furoate, umeclidinium, and vilanterol; HCRU, health care resource utilization; IP, inpatient; MITT, multiple-inhaler triple therapy; OP, outpatient; PPPY, per patient per year; Quan-CCI, Quan-Charlson Comorbidity Index; SCS, systemic corticosteroid.

<sup>a</sup>Evaluated on the index date.

<sup>b</sup>Based on medical claims within 30 days prior to the index date, including the index date.

<sup>c</sup>Evaluated during the 12-month baseline period, excluding the index date.

<sup>d</sup>Medical costs included hospitalization, ED visit, and OP visit costs.

Among patients initiating MITT, asthma-related health care costs were \$4821 (\$11,416) for patients with comorbid asthma-COPD and \$4473 (\$11,336) for those with asthma. Overall, FF/UMEC/VI initiators with comorbid asthma-COPD had a mean (SD) Quan-CCI score of 2.05 (1.70). Among MITT initiators, mean (SD) Quan-CCI scores were 1.41 (1.12) and 2.03 (1.69) for patients with asthma and comorbid

asthma-COPD, respectively. The most common asthma-related comorbidities during baseline were allergic rhinitis, sinusitis, upper respiratory tract infection, and gastroesophageal reflux disease (eAppendix Table 1), similar to the FF/UMEC/VI asthma cohort. The most common baseline Elixhauser comorbidities were hypertension, obesity, and diabetes (eAppendix Table 1).

**TABLE 2.** Baseline Respiratory Medication Use of New Users of FF/UMEC/VI and MITT With Asthma or Comorbid Asthma-COPD

	FF/UMEC/VI with asthma n = 1301	FF/UMEC/VI with comorbid asthma-COPD n = 2682	MITT with asthma n = 4643	MITT with comorbid asthma-COPD n = 3769
Controller medications, <sup>a</sup> n [%]				
Any use of controller medication	1060 (81.5)	2341 (87.3)	4495 (96.8)	3548 (94.1)
ICS/LABA	823 (63.3)	1732 (64.6)	3815 (82.2)	2617 (69.4)
LTRA	682 (52.4)	1098 (40.9)	2979 (64.2)	1677 (44.5)
ICS	208 (16.0)	388 (14.5)	1001 (21.6)	712 (18.9)
LAMA	155 (11.9)	609 (22.7)	1119 (24.1)	1206 (32.0)
MITT	150 (11.5)	592 (22.1)	—	—
Biologics	70 (5.4)	70 (2.6)	286 (6.2)	135 (3.6)
LAMA/LABA	54 (4.2)	415 (15.5)	87 (1.9)	288 (7.6)
Methylxanthines	15 (1.2)	70 (2.6)	43 (0.9)	79 (2.1)
LABA	11 (0.8)	34 (1.3)	39 (0.8)	76 (2.0)
PDE4 inhibitors	1 (0.1)	90 (3.4)	3 (0.1)	54 (1.4)
Mast cell stabilizers	1 (0.1)	1 (0.0)	9 (0.2)	3 (0.1)
Rescue medications, <sup>a</sup> n [%]				
Any use of rescue medications	1232 (94.7)	2619 (97.7)	4520 (97.4)	3688 (97.9)
SCS <sup>b</sup>	1015 (78.0)	2229 (83.1)	3816 (82.2)	3198 (84.9)
Antibiotics	1011 (77.7)	2298 (85.7)	3680 (79.3)	3215 (85.3)
SABA	984 (75.6)	2279 (85.0)	3931 (84.7)	3304 (87.7)
SABA/SAMA	152 (11.7)	653 (24.3)	625 (13.5)	901 (23.9)
SAMA	34 (2.6)	110 (4.1)	171 (3.7)	194 (5.1)
AMR, <sup>c</sup> mean [SD]	0.70 (0.24)	0.60 (0.27)	0.71 (0.26)	0.61 (0.28)

AMR, asthma medication ratio; COPD, chronic obstructive pulmonary disease; FF/UMEC/VI, fluticasone furoate, umeclidinium, and vilanterol; ICS, inhaled corticosteroid; LABA, long-acting β<sub>2</sub> agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; MITT, multiple-inhaler triple therapy; OCS, oral corticosteroid; PDE4, phosphodiesterase 4; SABA, short-acting β<sub>2</sub> agonist; SAMA, short-acting muscarinic antagonist; SCS, systemic corticosteroid.

<sup>a</sup>Evaluated during the 12-month baseline period, excluding the index date.

<sup>b</sup>SCS category of rescue medications included OCS.

<sup>c</sup>AMR measures the units of controller medications dispensed divided by the sum of the units of controller and rescue medications dispensed.

**Treatment patterns.** Most patients had previous controller medication use in the 12 months prior to initiation of therapy (87.3%-96.8% across cohorts) (Table 2). The most common medication classes used during the baseline period were ICS/LABA, LTRA, LAMA, and ICS. MITT was used during the baseline period by 22.1% (n = 592) of FF/UMEC/VI initiators with comorbid asthma-COPD. The mean (SD) baseline asthma medication ratio was 0.60 (0.27) among new users of FF/UMEC/VI with comorbid asthma-COPD and 0.71 (0.26) and 0.61 (0.28) among those initiating MITT with asthma and comorbid asthma-COPD, respectively. Across all 3 cohorts, more than 97% of patients used at least 1 rescue medication at baseline (Table 2). When considering mutually exclusive controller medication use closest to the index date, most patients stepped up from ICS/LABA across all 3 cohorts (Figure 2 [B-D]).

Similar treatment patterns were observed during the baseline period stratified by 3-month intervals across all 3 cohorts. In general, the proportion of patients using asthma controller or rescue medications increased in the 0 to 3 months prior to the index date vs the 10 to 12 months prior (eAppendix Figures 2-4).

### Triple-Therapy Treatment Patterns at Index Among MITT Initiators

Among new users of MITT with comorbid asthma-COPD or asthma, the most common combination of triple therapy on the index date was ICS/LABA plus LAMA (89.0% [n = 3356] and 96.2% [n = 4468], respectively) (eAppendix Table 2). Medium-dose ICS/LABA was the most frequently used, followed by high-dose ICS/LABA. Other MITT combinations included ICS plus LAMA/LABA (comorbid asthma-COPD: 9.6% [n = 361]; asthma: 3.1% [n = 145]) and ICS plus LAMA plus LABA (comorbid asthma-COPD: 1.4% [n = 52]; asthma: 0.6% [n = 30]). Among the ICS plus LAMA/LABA and ICS plus LAMA plus LABA combinations, low-dose ICS was the most used form.

## DISCUSSION

This retrospective cohort study provides real-world data on the characteristics and treatment patterns of adult patients with asthma in the US, with or without comorbid COPD, who were early adopters of SITT with FF/UMEC/VI or who newly initiated MITT.

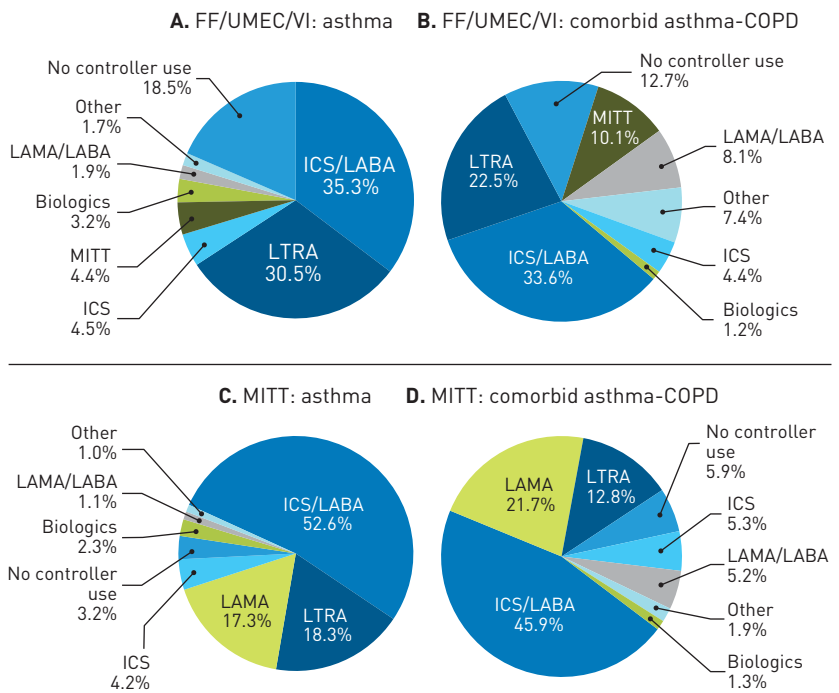
Although patients initiating FF/UMEC/VI or MITT had broadly similar characteristics during the baseline period, fewer patients in the FF/UMEC/VI cohort were women, and they experienced fewer asthma-related exacerbations. Interestingly, the asthma MITT cohort was less frequently prescribed treatment by a primary care physician vs other cohorts. The mean age in the FF/UMEC/VI asthma cohort was 49.0 years, consistent with the mean age of patients reported in the phase 3 CAPTAIN study (NCT02924688), which investigated FF/UMEC/VI in uncontrolled moderate to severe asthma,<sup>8</sup> and other SITT studies in asthma.<sup>25</sup> However, the proportion of patients experiencing at least 1 exacerbation in the year prior to treatment (42%) was lower than in the CAPTAIN study (61%).<sup>8</sup> Patients with comorbid asthma-COPD were, on average, older than those with asthma and had slightly higher prevalence of other chronic diseases, higher comorbidity burden, slightly lower prevalence of asthma-related exacerbations (except for IP-/ED-defined exacerbations), higher all-cause health care costs, and more frequent asthma-related health care resource utilization and IP stays.

More than 80% of patients initiating single-inhaler FF/UMEC/VI or MITT used controller therapy in the 12 months preceding triple-therapy initiation, of whom a large proportion were using controller medication in the 0 to 3 months prior to triple-therapy initiation. This suggests that triple therapy may have been initiated as a step up from previous controller medications, as recommended by the Global Initiative for Asthma, instead of as an initial therapy option.<sup>1</sup>

Among patients with asthma, those initiating FF/UMEC/VI mostly stepped up from ICS/LABA, LTRA, or ICS, whereas those initiating MITT mostly stepped up from ICS/LABA, LTRA, or LAMA. Among patients with comorbid asthma-COPD, those stepping up to FF/UMEC/VI did so mostly from ICS/LABA, LTRA, or MITT, whereas those stepping up to MITT mostly did so from ICS/LABA, LAMA, or LTRA.

Consistent with this study, a retrospective cohort study of US patients with asthma initiating MITT using the Optum Research Database found that 90.4% of MITT initiators had baseline asthma controller medication use in the 12 months prior to triple-therapy initiation.<sup>4</sup> Additionally, the most common MITT regimen initiated was ICS/LABA plus LAMA (85.3%),<sup>4</sup> as was observed in MITT users with asthma or comorbid asthma-COPD in the present study (89.0% and 96.2%, respectively). Another retrospective cohort study, which included patients (aged 15-75 years) from the Japan Medical Data Center claims database, similarly demonstrated that patients with asthma or asthma-COPD

**FIGURE 2.** Mutually Exclusive Controller Medication Use Closest to Index Date of New Users of FF/UMEC/VI and MITT With Asthma or Comorbid Asthma-COPD\*



COPD, chronic obstructive pulmonary disease; FF/UMEC/VI, fluticasone furoate, umeclidinium, and vilanterol; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$  agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; MITT, multiple-inhaler triple therapy; PDE4, phosphodiesterase 4.

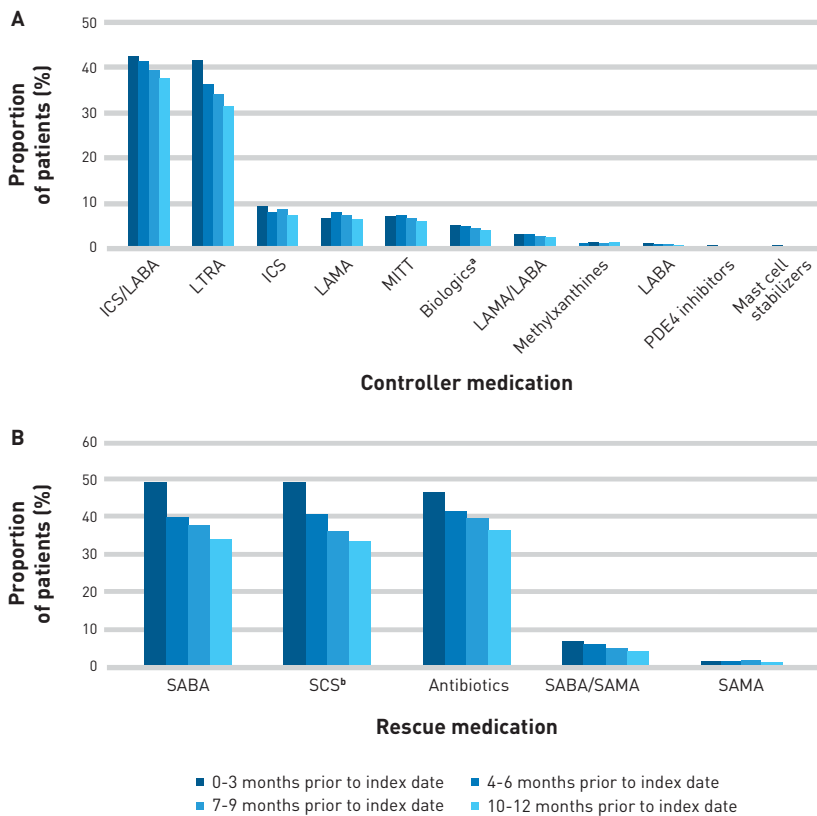
\*Evaluated on the date closest to the index date, not including the index date. Among patients with multiple controller medications on the same date, a hierarchy was imposed such that use of ICS, LABA, LAMA, ICS/LABA, LAMA/LABA, or MITT was prioritized over the use of an add-on therapy (LTRA, biologics, methylxanthines, mast cell stabilizers, and PDE4 inhibitors). Use of LTRA was prioritized over all other add-on therapies.

overlap who initiated MITT with ICS/LABA plus LAMA (tiotropium) were mostly prescribed dual therapy as controller medication in the year prior to MITT initiation, at 99.6% and 94.9%, respectively.<sup>9</sup> The most common form of controller medication was ICS/LABA in both groups (asthma: 99.6%, asthma-COPD overlap: 80.8%).<sup>9</sup>

Although asthma control was not directly assessed in this study, these findings suggest that patients' asthma was inadequately controlled by their previous controller medication. Use of rescue medications was high; a large proportion of patients had asthma-related exacerbations and substantial comorbidities, and many patients were under respiratory specialist care. Furthermore, there was a relatively high frequency of asthma-related outpatient visits across all patient groups. Taken together, this suggests a high level of disease burden and unmet need in this population.

The annual asthma-related total health care costs were \$4821 and \$4473 among those initiating MITT with asthma and comorbid asthma-COPD, respectively, which align closely with \$4558 reported in the previous US study.<sup>4</sup> As expected, these costs are relatively higher than those reported for well-controlled asthma in other countries.<sup>26</sup>

**FIGURE 3.** Baseline Treatment Patterns of New Users of FF/UMEC/VI With Asthma for (A) Any Controller Medications and (B) Any Rescue Medications



FF/UMEC/VI, fluticasone furoate, umeclidinium, and vilanterol; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$  agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; MITT, multiple-inhaler triple therapy; OCS, oral corticosteroid; PDE4, phosphodiesterase 4; SABA, short-acting  $\beta_2$  agonist; SAMA, short-acting muscarinic antagonist; SCS, systemic corticosteroid.

\*Biologics included omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab.

\*SCS category of rescue medications included OCS.

A strength of our study was the use of a geographically diverse sample of the commercially insured US population with asthma, thereby facilitating a comprehensive evaluation of demographics, clinical characteristics, and treatment patterns. Additionally, this study used real-world data to evaluate FF/UMEC/VI use in patients with asthma, which is currently scarce in the literature due to its recent approval in asthma. Finally, the relatively short lag time between patient health care encounters and data availability provided more current and relevant results.

**Limitations**

Medications not recorded in claims data (eg, drug samples, OTC medications, medications received during an IP stay) were unavailable in the database and were not included in this analysis. Administrative claims data may be vulnerable to coding inaccuracies and may include “rule-out” diagnoses such that the presence of a diagnosis code may not indicate presence of disease. Such data also lack information

on specific clinical measures (eg, asthma control scores, pulmonary function tests). Although the study included a geographically diverse sample of the commercially insured US population, the generalizability of the results to the broader US population is limited. The reasons for patients stepping up to triple therapy were not captured in the database. It cannot be confirmed that patients’ asthma symptoms were uncontrolled on their baseline controller medication; treatment may have been stepped up for other reasons. Despite the lack of confirmatory reasons for prescribing triple therapy, the patterns of baseline characteristics and medication use observed in this study highlight a population of patients with high symptomatic burden. Further limitations of the study include the lack of data on lung function, disease severity, medication adherence, and patients’ inhaler technique—all of which are important considerations in asthma management.<sup>18,19</sup> In addition, absenteeism and other indirect costs were not assessed in this study, despite being reported by patients with asthma<sup>27</sup> and a contributing factor to economic costs. There also was limited evaluation of patients older than 65 years, a group that is often excluded from clinical trials but is associated with high numbers of hospital admissions, economic costs, and mortality.<sup>28</sup> Finally, the trends observed in this study represent the experiences of early adopters of FF/UMEC/VI for asthma, and treatment patterns and patient characteristics may change over time.

**CONCLUSIONS**

This study found that triple therapy is often initiated following the use of other asthma controller medications. The high levels of rescue medication use, disease burden, and asthma-related exacerbations in this patient population suggest that patients may have had uncontrolled asthma prior to triple-therapy initiation. Further research is needed into the clinical features that may influence triple-therapy initiation and into the long-term clinical and economic impact of treatment with FF/UMEC/VI administered as a single inhaler. ■

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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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**Authorship Information:** Concept and design (CMA, GG, FL, MM, MSD); acquisition of data (GG, FL, MM); analysis and interpretation of data (NNH, CBA, CMA, GG, FL, MM, MSD, RAS); drafting of the manuscript (NNH, CBA, CMA, GG, FL, MM, MSD, RAS); critical revision of the manuscript for important intellectual content (NNH, CBA, CMA, GG, FL, MM, MSD, RAS); statistical analysis (FL); obtaining funding (MSD); and supervision (MSD).

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## REFERENCES

1. *Global Strategy for Asthma Management and Prevention*. Global Initiative for Asthma; 2022. Accessed May 17, 2022. <https://ginasthma.org/wp-content/uploads/2022/05/GINA-Main-Report-2022-FINAL-22-05-03-WMS.pdf>
2. Learn how to control asthma: what is asthma? CDC. Updated June 1, 2023. Accessed July 8, 2021. <https://www.cdc.gov/asthma/faqs.htm>
3. Nurmagambetov T, Kuwahara R, Garbe P. The economic burden of asthma in the United States, 2008-2013. *Ann Am Thorac Soc*. 2018;15(3):348-356. doi:10.1513/AnnalsATS.201703-259OC
4. Oppenheimer J, Bogart M, Bengtson LGS, et al. Treatment patterns and disease burden associated with multiple-inhaler triple-therapy use in asthma. *J Allergy Clin Immunol Pract*. 2022;10(2):485-494.e5. doi:10.1016/j.jaip.2021.09.033
5. Virchow JC, Kuna P, Paggiaro P, et al. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. *Lancet*. 2019;394(10210):1737-1749. doi:10.1016/s0140-6736(19)32215-9
6. Kerstjens HA, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med*. 2012;367(13):1198-1207. doi:10.1056/NEJMoa1208606
7. Kerstjens HAM, Maspero J, Chapman KR, et al; IRIDIUM Trial Investigators. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. *Lancet Respir Med*. 2020;8(10):1000-1012. doi:10.1016/S2213-2600(20)30190-9
8. Lee LA, Bailes Z, Barnes N, et al. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial. *Lancet Respir Med*. 2021;9(1):69-84. doi:10.1016/s2213-2600(20)30389-1
9. Suzuki T, Fairburn-Beech J, Sato K, Kaise T. Clinical characteristics, treatment patterns, disease burden, and persistence/adherence in patients with asthma initiating inhaled triple therapy: real-world evidence from Japan. *Curr Med Res Opin*. 2020;36(6):1049-1057. doi:10.1080/03007995.2020.1763937
10. Averell CM, Laliberté F, Duh MS, Wu JW, Germain G, Faison S. Characterizing real-world use of tiotropium in asthma in the USA. *J Asthma Allergy*. 2019;12:309-321. doi:10.2147/jaa.s216932
11. Barrecheguren M, Monteagudo M, Miravittles M, et al. Characteristics and treatment patterns of patients with asthma on multiple-inhaler triple therapy in Spain. *NPJ Prim Care Respir Med*. 2022;32(1):11. doi:10.1038/s41533-022-00270-2
12. Braido F, Brusselle G, Guastalla D, et al; LIAISON Study Group. Determinants and impact of suboptimal asthma control in Europe: The International Cross-Sectional and Longitudinal Assessment on Asthma Control (LIAISON) study. *Respir Res*. 2016;17(1):51. doi:10.1186/s12931-016-0374-z
13. Cazzola M, Braido F, Calzetta L, et al. The 5T approach in asthma: triple therapy targeting treatable traits. *Respir Med*. 2022;200:106915. doi:10.1016/j.rmed.2022.106915
14. Trimbrow. Prescribing information. Chiesi Farmaceutici S.p.A.; 2017. Accessed November 13, 2022. [https://www.ema.europa.eu/en/documents/product-information/trimbow-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/trimbow-epar-product-information_en.pdf)
15. Enerzair Breezhaler. Prescribing information. Novartis Farmaceutica, S.A. and Novartis Pharma GmbH; 2020. Accessed November 11, 2022. [https://www.ema.europa.eu/en/documents/product-information/enerzair-breezhaler-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/enerzair-breezhaler-epar-product-information_en.pdf)
16. Trelegy Eliipta. Prescribing information. GlaxoSmithKline; 2017. Accessed July 8, 2021. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/209482s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209482s0001bl.pdf)
17. Trelegy Eliipta. Prescribing information. GlaxoSmithKline; 2020. Accessed November 26, 2022. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/209482s010s011bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209482s010s011bl.pdf)
18. Busse WW, Abbott CB, Germain G, et al. Adherence and persistence to single-inhaler versus multiple-inhaler triple therapy for asthma management. *J Allergy Clin Immunol Pract*. 2022;10(11):2904-2913.e6. doi:10.1016/j.jaip.2022.06.010
19. Braido F, Tiotiu A, Guidos-Fogelbach G, et al. Manifesto on inhaled triple therapy in asthma: an Interasma (Global Asthma Association - GAA) document. *J Asthma*. 2022;59(12):2402-2412. doi:10.1080/02770903.2021.2022160
20. Martin A, Shah D, Ndirangu K, et al. Is single-inhaler triple therapy for COPD cost-effective in the UK? the IMPACT trial. *ERJ Open Res*. 2022;8(1):00333-2021. doi:10.1183/23120541.00333-2021
21. Fenwick E, Martin A, Schroeder M, et al. Cost-effectiveness analysis of a single-inhaler triple therapy for COPD in the UK. *ERJ Open Res*. 2021;7(1):00480-2020. doi:10.1183/23120541.00480-2020
22. *Diagnosis and Initial Treatment Of Asthma, COPD, and Asthma-COPD Overlap*. Global Initiative for Asthma; April 2017. Accessed December 12, 2022. <https://ginasthma.org/wp-content/uploads/2022/05/GINA-GOLD-ACOS-2017-WMS.pdf>
23. Maselli DJ, Hanania NA. Asthma COPD overlap: impact of associated comorbidities. *Pulm Pharmacol Ther*. 2018;52:27-31. doi:10.1016/j.pupt.2018.08.006
24. Shrikant Kulkarni N. More evidence against antibiotics for acute asthma exacerbations. *Am Fam Physician*. 2019;100(3):185.
25. Agustí A, Fabbri L, Lahousse L, Singh D, Papi A. Single inhaler triple therapy (SITT) in asthma: systematic review and practice implications. *Allergy*. 2022;77(4):1105-1113. doi:10.1111/all.15076
26. Vervloet D, Williams AE, Lloyd A, Clark TJH. Costs of managing asthma as defined by a derived Asthma Control Test score in seven European countries. *Eur Respir Rev*. 2006;15(98):17-23. doi:10.1183/09059180.06.00009803
27. Gonzalez Barcala EJ, La Fuente-Cid RD, Alvarez-Gil R, Tafalla M, Nuevo J, Caamaño-Isona F. Factors associated with a higher prevalence of work disability among asthmatic patients. *J Asthma*. 2011;48(2):194-199. doi:10.3109/02770903.2010.539294
28. Perpiñá Tordera M, Álvarez Gutiérrez EJ, Blanco Aparicio M. Asthma exists in older people too. Article in English, Spanish. *Arch Bronconeumol*. 2022;58(5):390-391. doi:10.1016/j.arbres.2022.02.010

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## **Supplemental eAppendix**

### **eMethods**

#### ***Database- and study design***

The IQVIA PharMetrics Plus database contains fully adjudicated claims data from approximately 40 million enrollees with an average enrollment length of 39 months, covering all 50 US states, and is generally representative of the commercially insured population <65 years of age with respect to age and gender. It contains historical information on demographics, plan enrollment, and IP, OP, and pharmacy claims.

#### ***Inclusion and exclusion criteria***

Patients included in this study had  $\geq 1$  pharmacy claim for single-inhaler fixed-dose FF/UMEC/VI 100/62.5/25 mcg (FF/UMEC/VI 200/62.5/25 mcg was excluded as it was not FDA-approved pre-2020) or  $\geq 1$  overlapping days of supply with all three MITT controller medications from 09/18/2017 to 09/30/2019 (date of first therapy defined the index date),  $\geq 12$  months of continuous health insurance coverage preceding the index date (baseline period),  $\geq 1$  medical claim with a primary or secondary diagnosis of asthma (as defined by the International Classification of Diseases [ICD], Tenth Revision, codes J45.3x–J45.5x and J45.9xx) during the baseline period or on the index date, and  $\geq 18$  years of age at the index date.<sup>1</sup> As the IQVIA PharMetrics Plus database generally represents the commercially insured population <65 years of age, most patients in this study were 18–64 years of age at the index date.

MITT refers to the concomitant use of two different inhalers in the form of ICS/LABA +LAMA or LABA/LAMA +ICS, or three different inhalers in the form of ICS +LAMA +LABA. MITT users were identified based on an overlap of  $\geq 1$  day of supply of all three triple therapy components; this algorithm was based on previous studies.<sup>2-4</sup>

Patients were excluded from this study if they had  $\geq 1$  pharmacy claim for a dispensing of FF/UMEC/VI and  $\geq 1$  overlapping day of supply with all three MITT components on the index date. Patients were excluded from the FF/UMEC/VI cohort if they had  $\geq 1$  pharmacy claim for a dispensing of FF/UMEC/VI during the baseline period, or from the MITT cohort if they had  $\geq 1$  overlapping days of supply with all three MITT components during the baseline period, and from

the asthma cohort if they had  $\geq 1$  medical claim with a primary or secondary diagnosis of COPD (as defined by the ICD Tenth Revision codes J41–J44) during the eligibility period.

### *Data analyses*

All results were summarized by treatment regimen (FF/UMEC/VI or MITT) and disease condition (patients with asthma or patients with comorbid asthma-COPD). Baseline characteristics were reported using descriptive statistics, including mean and standard deviation (SD) for continuous variables, and frequencies and proportions for categorical variables.

Overall asthma-related exacerbations were defined as an asthma-related IP or ED visit (IP-/ED-defined exacerbation), or an asthma-related ED or OP visit with an SCS (including OCS category) dispensing within  $\pm 5$  days (SCS-defined exacerbation). If  $\geq 2$  exacerbations occurred within 14 days of each other they were considered as a single event and classified according to the highest severity. Asthma-related IP, ED, or OP visits were identified as visits including a claim with a primary diagnosis of asthma.

Asthma-related and all-cause HCRU were reported as the mean number of events and percent of patients with at least one HCRU event. Healthcare costs were reported as costs incurred and were inflation-adjusted to USD 2019 using the US Medical Care consumer price index from the Bureau of Labor Statistics, US Department of Labor.

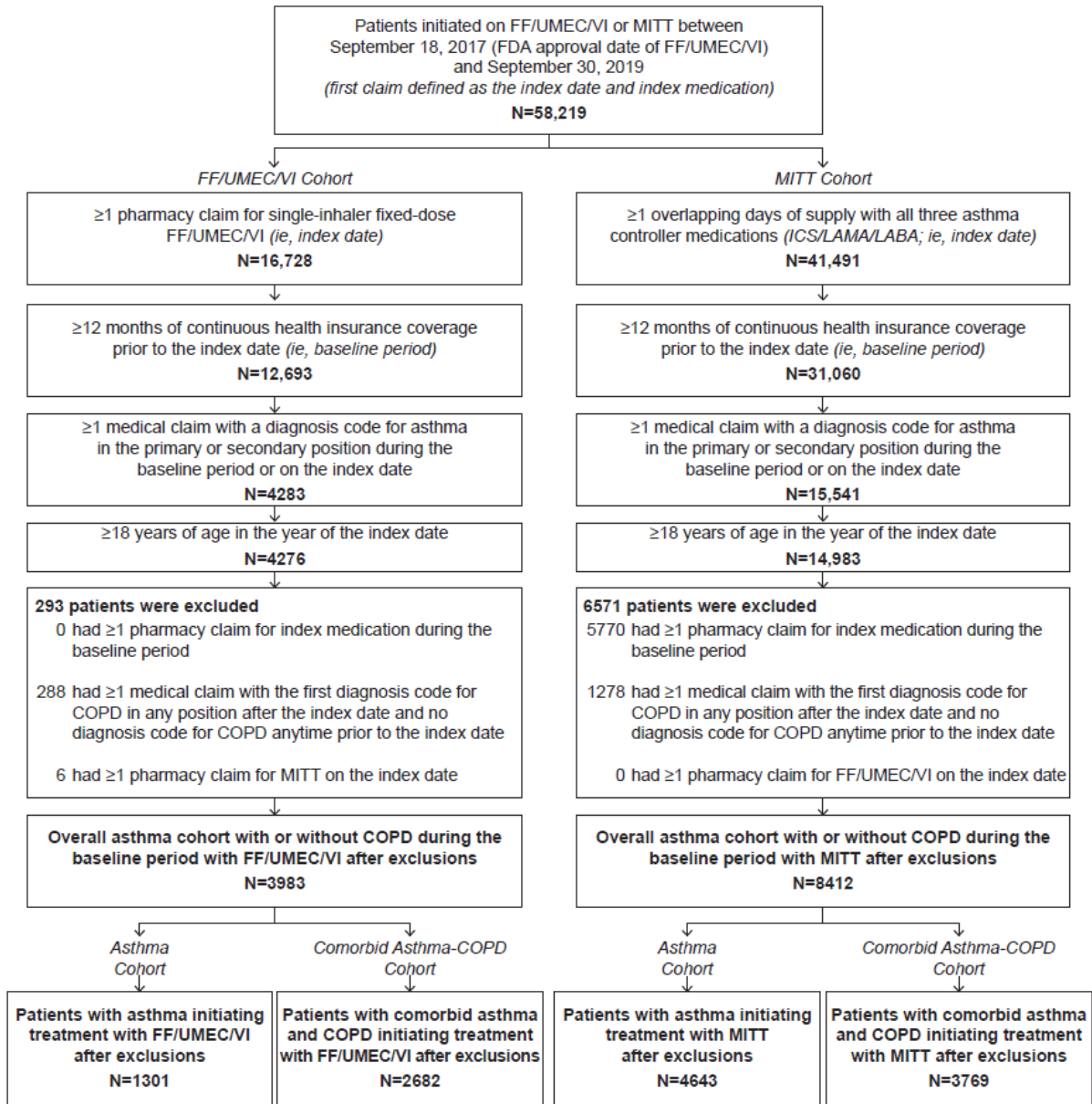
Asthma medication use was described as the proportion of patients taking each class of medication during the entire baseline period and over 3-month intervals starting from the index date to 12 months pre-index. To establish mutually exclusive groups of controller medication use closest to the index date, a hierarchy was imposed for patients who may have been using multiple medications at the same time. As such, use of ICS, LABA, LAMA, ICS/LABA, LAMA/LABA, or MITT was prioritized over the use of add-on therapy (ie, LTRA, biologics, methylxanthines, mast cell stabilizers, and PDE-4 inhibitors) with use of LTRA prioritized over all remaining add-on therapies.

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

### ***Ethics***

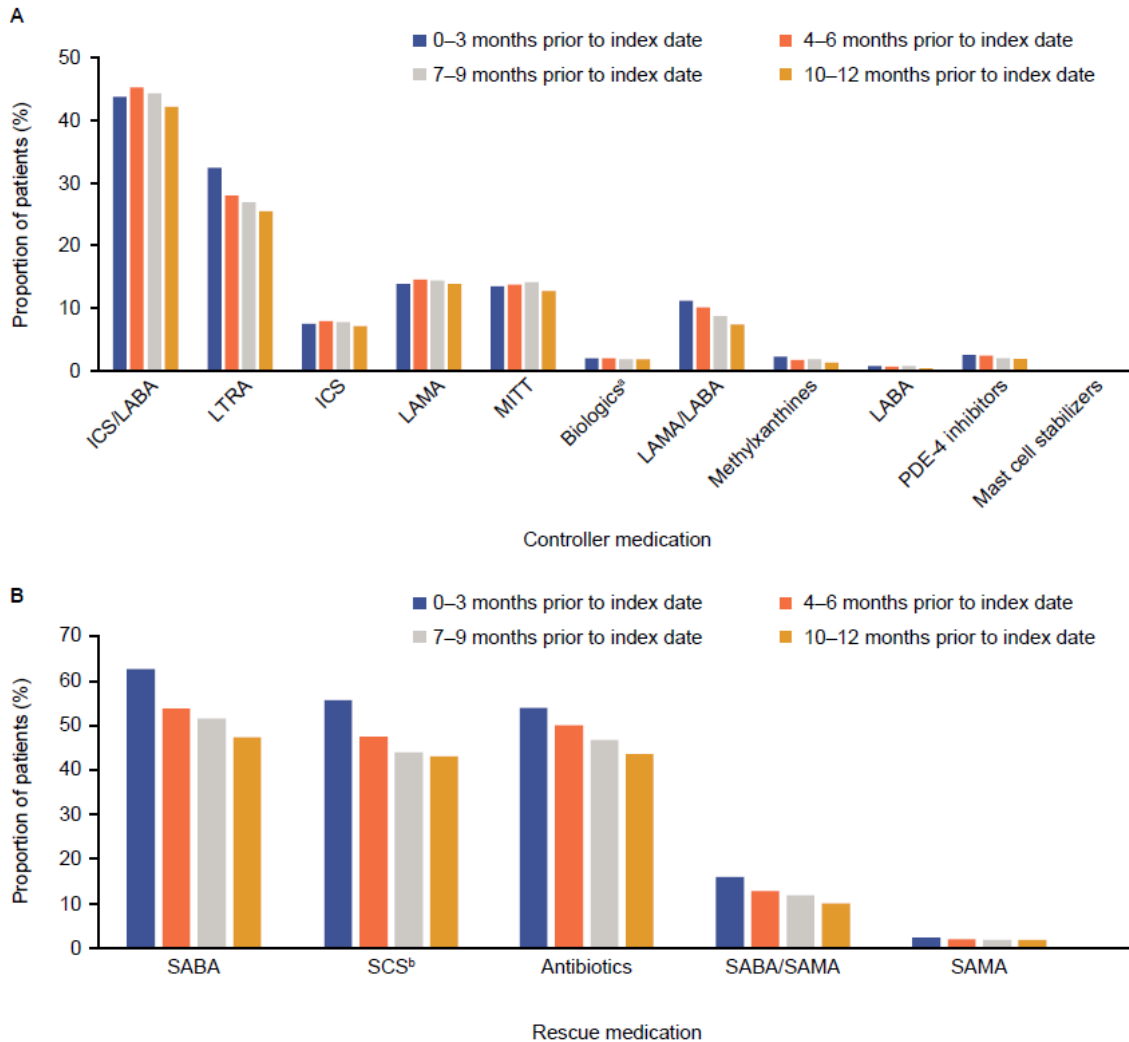
The study was conducted in compliance with all applicable laws regarding subject privacy. No direct subject contact or primary collection of individual human subject data occurred. Study results were in tabular form and aggregate analyses omitted subject identification; therefore, patient informed consent, ethics committee, or Institutional Review Board approval were not required. Moreover, this study used de-identified data that complied with the requirements of the Health Insurance Portability and Accountability Act.

## eAppendix Figure 1. Patient disposition



COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; FF, fluticasone furoate; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy; UMEC, umeclidinium; VI, vilanterol.

**eAppendix Figure 2.** Baseline treatment patterns of new users of FF/UMEC/VI with comorbid asthma-COPD for controller medications (A) and rescue medications (B)

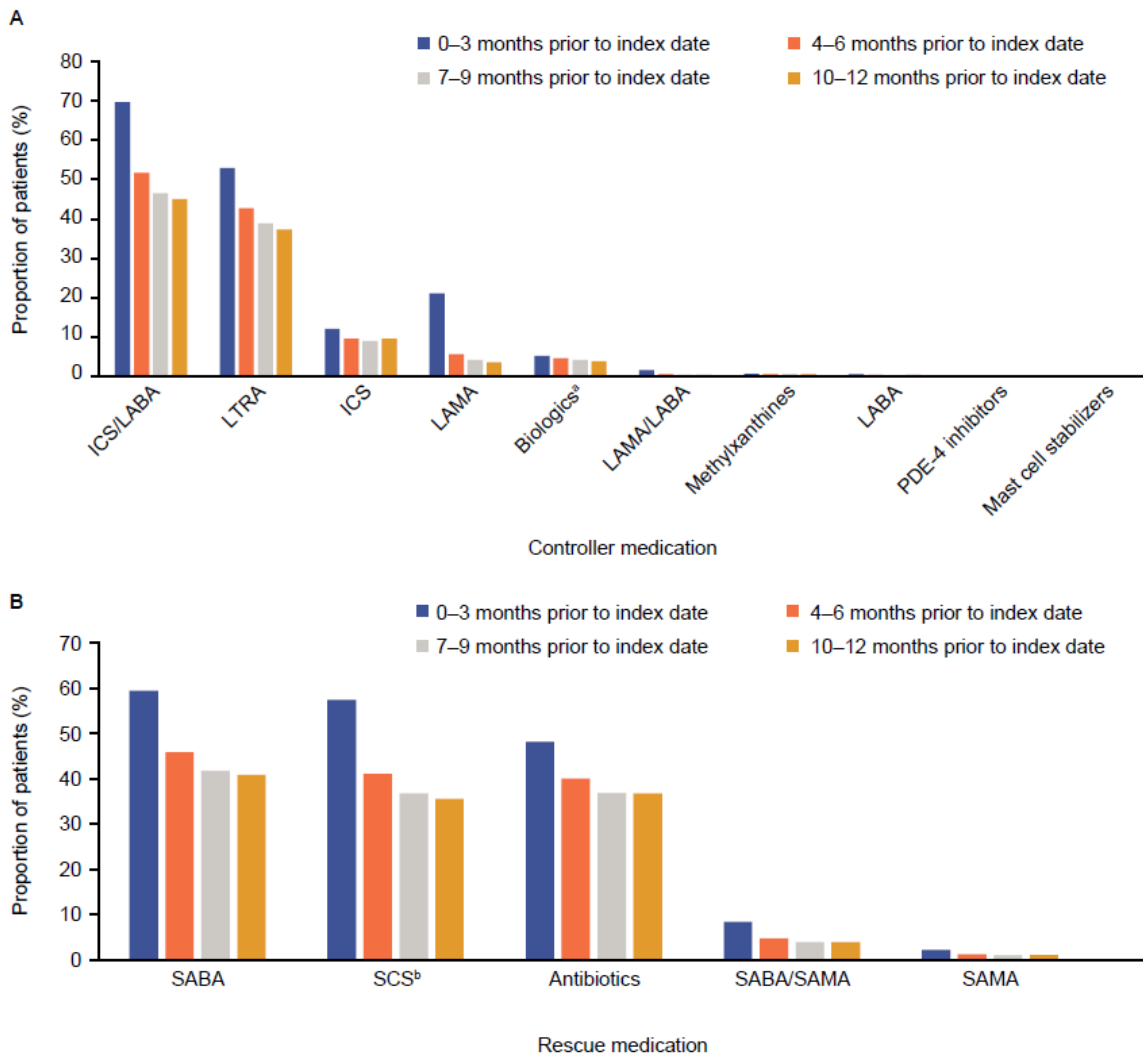


<sup>a</sup>Biologics included omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab;

<sup>b</sup>SCS category of rescue medications included OCS.

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; MITT, multiple-inhaler triple therapy; OCS, oral corticosteroid; PDE, phosphodiesterase; SABA, short-acting  $\beta_2$ -agonist; SAMA, short-acting muscarinic antagonist; SCS, systemic corticosteroid.

**eAppendix Figure 3.** Baseline treatment patterns of new users of MITT with asthma for controller medications (A) and rescue medications (B)

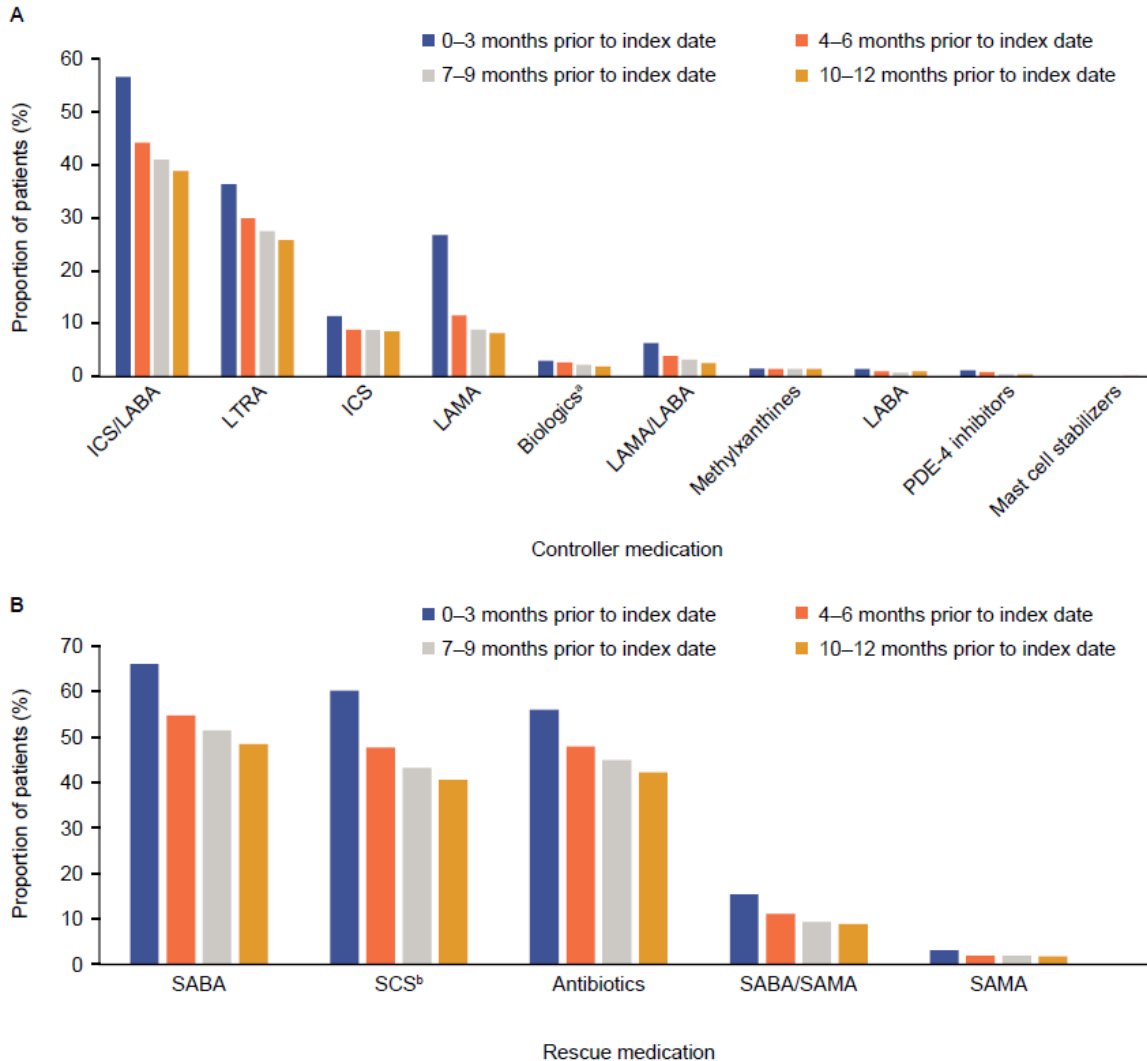


<sup>a</sup>Biologics included omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab;

<sup>b</sup>SCS category of rescue medications included OCS.

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; MITT, multiple-inhaler triple therapy; OCS, oral corticosteroid; PDE, phosphodiesterase; SABA, short-acting  $\beta_2$ -agonist; SAMA, short-acting muscarinic antagonist; SCS, systemic corticosteroid.

**eAppendix Figure 4.** Baseline treatment patterns of new users of MITT with comorbid asthma-COPD for controller medications (A) and rescue medications (B)



<sup>a</sup>Biologics included omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab;

<sup>b</sup>SCS category of rescue medications included OCS.

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; MITT, multiple-inhaler triple therapy; OCS, oral corticosteroid; PDE, phosphodiesterase; SABA, short-acting  $\beta_2$ -agonist; SAMA, short-acting muscarinic antagonist; SCS, systemic corticosteroid.

**eAppendix Table 1.** Baseline all-cause healthcare costs and comorbidities of new users of FF/UMEC/VI and MITT with asthma or comorbid asthma-COPD

	<b>FF/UMEC/VI, asthma (N=1301)</b>	<b>FF/UMEC/VI, comorbid asthma-COPD (N=2682)</b>	<b>MITT, asthma (N=4643)</b>	<b>MITT, comorbid asthma- COPD (N=3769)</b>
<b>All-cause healthcare costs,<sup>a</sup> USD 2019,<sup>b</sup> mean (SD)</b>				
Total costs <sup>c</sup> (medical+pharmacy)	20,551 (55,255)	36,529 (62,327)	16,988 (27,347)	30,706 (48,616)
<b>Asthma-related comorbidities,<sup>a</sup> n (%)</b>				
Allergic rhinitis	650 (50.0)	853 (31.8)	2634 (56.7)	1220 (32.4)
Sinusitis	516 (39.7)	751 (28.0)	1839 (39.6)	1170 (31.0)
Upper respiratory tract infection	504 (38.7)	836 (31.2)	1794 (38.6)	1286 (34.1)
Gastroesophageal reflux disease	447 (34.4)	995 (37.1)	1614 (34.8)	1473 (39.1)
Obesity	302 (23.2)	772 (28.8)	1161 (25.0)	1210 (32.1)
Anxiety disorders	272 (20.9)	776 (28.9)	1053 (22.7)	1102 (29.2)
Obstructive sleep apnea	261 (20.1)	816 (30.4)	902 (19.4)	1072 (28.4)
Depressive disorders	183 (14.1)	601 (22.4)	854 (18.4)	926 (24.6)
Pneumonia	135 (10.4)	577 (21.5)	497 (10.7)	820 (21.8)
Acute respiratory failure	22 (1.7)	350 (13.0)	158 (3.4)	575 (15.3)
Eosinophilic disorders	14 (1.1)	25 (0.9)	58 (1.2)	36 (1.0)
Cystic fibrosis	0 (0.0)	1 (0.0)	4 (0.1)	9 (0.2)
<b>Elixhauser comorbidities,<sup>a,d</sup> n (%)</b>				
Hypertension	601 (46.2)	1750 (65.2)	1888 (40.7)	2428 (64.4)
Obesity	302 (23.2)	772 (28.8)	1161 (25.0)	1210 (32.1)
Diabetes	228 (17.5)	660 (24.6)	676 (14.6)	987 (26.2)
Cardiac arrhythmias	150 (11.5)	636 (23.7)	630 (13.6)	960 (25.5)
Rheumatoid arthritis/collagen vascular disease	100 (7.7)	262 (9.8)	343 (7.4)	405 (10.7)
Valvular disease	70 (5.4)	333 (12.4)	232 (5.0)	511 (13.6)
Congestive heart failure	50 (3.8)	394 (14.7)	155 (3.3)	561 (14.9)
Peripheral vascular disorder	45 (3.5)	341 (12.7)	136 (2.9)	414 (11.0)

<sup>a</sup>Evaluated during the 12-month baseline period, excluding the index date; <sup>b</sup>Costs were inflated to USD 2019 using the US Medical Care consumer price index from the Bureau of Labor



Statistics, US Department of Labor; <sup>c</sup>Healthcare costs a payer-paid amounts; <sup>d</sup>Occurring in >10% of patients in at least one cohort.

COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; MITT, multiple-inhaler triple therapy; SD, standard deviation; UMEC, umeclidinium; USD, United States Dollar; VI, vilanterol.

**eAppendix Table 2.** Triple therapy patterns on the index date of MITT initiators

Triple therapy treatment pattern	MITT cohort	
	Asthma N=4643	Comorbid asthma-COPD N=3769
<b>ICS/LABA +LAMA, n (%)</b>	4468 (96.2)	3356 (89.0)
ICS/LABA daily dose		
Low	503 (10.8)	519 (13.8)
Medium	2102 (45.3)	1815 (48.2)
High	1863 (40.1)	1022 (27.1)
Dispensing days of supply, <sup>a</sup> mean (SD)	22.5 (15.4)	23.7 (17.0)
<b>ICS +LAMA+LABA, n (%)</b>	30 (0.6)	52 (1.4)
ICS/LABA daily dose		
Low	11 (0.2)	11 (0.3)
Medium	3 (0.1)	4 (0.1)
High	3 (0.1)	1 (0.0)
Dispensing days of supply, <sup>a</sup> mean (SD)	18.7 (9.7)	17.9 (8.9)
<b>ICS +LAMA/LABA, n (%)</b>	145 (3.1)	361 (9.6)
ICS/LABA daily dose		
Low	89 (1.9)	207 (5.5)
Medium	18 (0.4)	33 (0.9)
High	18 (0.4)	58 (1.5)
Dispensing days of supply, <sup>a</sup> mean (SD)	23.0 (16.3)	21.0 (14.3)

<sup>a</sup>Dispensing days of supply was calculated as the overlapping days of supply between each MITT component.

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$ -agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy, SD, standard deviation.

## References

1. World Health Organization. *ICD-10 International Statistical Classification of Diseases and Related Health Problems 10th Revision* 2010 Edition. Accessed August 2021.  
[https://www.who.int/classifications/icd/ICD10Volume2\\_en\\_2010.pdf](https://www.who.int/classifications/icd/ICD10Volume2_en_2010.pdf)
2. Bogart M, Stanford RH, Laliberte F, Germain G, Wu JW, Duh MS. Medication adherence and persistence in chronic obstructive pulmonary disease patients receiving triple therapy in a USA commercially insured population. *Int J Chron Obstruct Pulmon Dis*. 2019;14:343-352. doi: 10.2147/COPD.S184653
3. Xie L, Frech-Tamas F, Marrett E, Baser O. A medication adherence and persistence comparison of hypertensive patients treated with single-, double- and triple-pill combination therapy. *Curr Med Res Opin*. 2014;30(12):2415-22. doi: 10.1185/03007995.2014.964853
4. Davis JR, Wu B, Kern DM, et al. Impact of Nonadherence to Inhaled Corticosteroid/LABA Therapy on COPD Exacerbation Rates and Healthcare Costs in a Commercially Insured US Population. *Am Health Drug Benefits*. 2017;10(2):92-102.