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ORIGINAL RESEARCH

Effectiveness of Switching from Multiple-Inhaler to Once-Daily Single-Inhaler Triple Therapy in Patients with COPD in a Real-World Setting in Japan

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Purpose: Following the relatively recent introduction of single-inhaler triple therapies in Japan, this study compared the effectiveness of switching from multiple-inhaler triple therapy (MITT) to once-daily fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) by investigating COPD exacerbations and adherence among patients with chronic obstructive pulmonary disease (COPD) in Japan.

Methods: This retrospective, pre–post cohort study using the Medical Data Vision Co. Ltd database identified patients with ≥1 inpatient diagnosis and/or ≥2 outpatient diagnoses of COPD at age ≥40 years prior to the index date (first/earliest date of single-inhaler FF/UMEC/VI initiation from May 1, 2019–February 28, 2022, following a switch from MITT). The proportion of patients with ≥1 overall (moderate-to-severe), moderate, or severe COPD exacerbation and rate of exacerbations were assessed at 6 months pre- and post-index. Medication adherence (proportion of days covered [PDC]) was also assessed.

Results: In total, 2365 patients were included, with a mean (standard deviation) age of 75.3 (9.7) years, and 77.1% were male. In the 6 months post-switch from MITT to FF/UMEC/VI, there was a statistically significant decrease in the proportion of patients who experienced ≥1 overall (11.2% to 8.8%; p=0.0014) and severe exacerbation (4.6% to 3.2%; p=0.0069). There was a similar proportion of patients who experienced ≥1 moderate exacerbation pre- and post-switch (6.9% to 6.2%; p=0.2394). Rates of overall (rate ratio [RR]: 0.86, 95% confidence interval [CI]: 0.74–1.00; p=0.0528) and moderate exacerbations (RR: 0.95, 95% CI: 0.79–1.13; p=0.5796) were numerically lower post-switch. There was a significant reduction in severe exacerbations post-switch (RR: 0.68, 95% CI: 0.51–0.90; p=0.0084). Mean PDC was significantly higher in the 6 months post- versus pre-switch (0.83 versus 0.80; p<0.0001).

Conclusion: Patients who switched from MITT to FF/UMEC/VI had reduced exacerbations and improved adherence. These results may help inform healthcare providers on the optimum management strategy for patients with COPD in Japan.

Plain language summary: Current guidelines recommend that patients with chronic obstructive pulmonary disease (COPD) who experience exacerbations (flare-ups of their symptoms) should be treated with a combination of three treatments, known as triple therapy. Patients can receive multiple-inhaler triple therapy (MITT) or single-inhaler triple therapy (SITT). SITT offers an easier and more convenient treatment plan than MITT and has been shown to improve adherence (the extent to which patients use their treatments as recommended/prescribed). Two SITTs have been approved for use in Japan, including once-daily fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI). Following the relatively recent introduction of SITTs in Japan, this study compared the effectiveness of switching from MITT to FF/UMEC/VI by investigating COPD exacerbations and adherence among patients with COPD in Japan. Patients included in this study were identified from the Medical Data Vision Co. Ltd database, who had switched from using MITT to using FF/UMEC/VI. We assessed COPD exacerbations and adherence to treatment in the 6 months before

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patients switched from MITT to FF/UMEC/VI and the 6 months following the switch. We found that patients who switched from MITT to FF/UMEC/VI had lower rates of exacerbations in the 6 months after the switch compared with the 6 months before the switch. Patients also had improved treatment adherence in the 6 months post-switch compared with the 6 months pre-switch. The findings of this study may help healthcare providers to prescribe the best treatment plan for patients with COPD in Japan, to help improve their treatment outcomes.

Keywords: adherence, chronic obstructive pulmonary disease exacerbations, claims database, fluticasone furoate/umeclidinium/vilanterol, multiple-inhaler triple therapy

Introduction

Chronic obstructive pulmonary disease (COPD) presents an increasingly significant burden worldwide due to its high prevalence, morbidity, and mortality, accounting for around three million deaths annually.[1,2] In Japan, it is estimated that the prevalence of COPD in the general population of people aged ≥40 years is approximately 10%, and it may be as high as 30–40% among smokers with cardiovascular disease who live in areas of high pollution.[3]

Exacerbations are an important driver of the clinical and economic burden of COPD, with hospitalizations due to COPD exacerbations being associated with high costs and increased risk of death.[4,5] Additionally, poor adherence and persistence to medication can contribute to worse clinical outcomes and cost of care arising from increased exacerbation risk, reduced health status, and urgent care use.[6–9]

The aim of maintenance therapy for COPD is to improve lung function, relieve symptoms, and reduce the frequency of exacerbations.[2] Although maintenance therapy typically follows an escalating, stepwise approach, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2024 report suggests that inhaled triple therapy (an inhaled corticosteroid [ICS] plus a long-acting β2 agonist [LABA] and a long-acting muscarinic antagonist [LAMA]) may be considered as initial maintenance treatment for patients with COPD with ≥2 moderate exacerbations or ≥1 severe exacerbation in the past year and elevated blood eosinophil counts (≥300 cells/μL).[2] Additionally, for patients experiencing recurrent exacerbations while receiving mono or dual bronchodilator therapy, an escalation to triple therapy is recommended.[2] In Japan, the Japanese Respiratory Society (JRS) guidelines recommend the incorporation of ICS for patients with COPD and concomitant asthmatic features, frequent exacerbations, or both, as well as blood eosinophilia.[10]

Triple therapy has traditionally required the use of multiple inhalers; however, real-world adherence and persistence to multiple-inhaler triple therapy (MITT) is known to be poor.[11,12] Single-inhaler triple therapy (SITT) offers a simple and convenient dosing strategy that has been shown to increase adherence, health status, and lung function compared with MITT in real-world studies.[2,13,14]

In Japan, two SITTs are approved for the maintenance treatment of patients with COPD: fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI; approved in March 2019)[15] and budesonide/formoterol/glycopyrrolate (approved in June 2019).[16]

The efficacy of FF/UMEC/VI versus MITT has been assessed previously using data from Western Europe.[14] Patients initiating treatment with FF/UMEC/VI had improved health status and lung function compared with those initiating MITT. Improvements were also seen when the analysis was stratified by patients who entered the trial with prior MITT use, demonstrating health outcome improvements for those switching from MITT to single-inhaler FF/UMEC/VI. Studies conducted in the United States (US)[17] and the United Kingdom (UK)[18] have also demonstrated a lower rate of moderate and severe COPD exacerbations following a switch from MITT to SITT.

Notably, the patient profile for COPD is different in Japan to that of Europe or the US. Compared with those in Western countries, patients with COPD in Japan have typically been observed as being older and having a lower body mass index, which may lead to differences in comorbidity patterns.[19]

Given the relatively recent introduction of SITT in Japan, there is a need to assess the impact of switching from MITT to FF/UMEC/VI in Japanese patients with COPD in order to optimize future treatment strategies. This real-world study compared the effectiveness of switching from MITT to once-daily FF/UMEC/VI by investigating COPD exacerbations and adherence among patients with COPD in Japan.

Materials and Methods

Study Design

This was a retrospective pre–post cohort study conducted using health insurance claims data (outpatient and inpatient) provided by Medical Data Vision Co. Ltd. (MDV; Tokyo, Japan). The index date was the first or earliest date of single-inhaler FF/UMEC/VI initiation (May 1, 2019, to February 28, 2022) following a period of MITT use (≥1 day of overlap in the days of supply of all three triple-therapy components; Figure 1). Demographic and clinical characteristics were assessed during the baseline period (defined as the 12 months prior to index), in the 0–3 months prior to index exclusively, and in the 12–15 months prior to index. The minimum follow-up period required for inclusion in the study was 6 months, which spanned from index until the earliest of study end date (August 31, 2022) or end of data availability (last claim/diagnosis data record), whichever occurred first.

Outcomes were assessed in patients with sufficient observation time in the 6 months pre- and post-index, as well as in the 12 months pre- and post-index (exploratory objectives only), where data were available. COPD exacerbation rates incurred prior to (while receiving MITT) and post-initiation of single-inhaler FF/UMEC/VI were reported. In addition, medication adherence (defined as proportion of days covered [PDC]), and all-cause and COPD-related costs were evaluated at 6 and 12 months prior to and following a switch from MITT to FF/UMEC/VI.

This study complied with all applicable laws regarding subject privacy, per the Declaration of Helsinki. No direct subject contact or primary collection of individual human subject data occurred in this study. Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Data Collection

MDV is one of the largest healthcare datasets in Japan, constructed from longitudinal, representative anonymised data from predominately tertiary hospitals. The MDV database covers a broad range of health data, spanning approximately 28% of advanced public and/or private healthcare facilities nationally (approximately 460 facilities), and representing approximately 45 million patients.[20] Data are available on administrative claims, and Diagnosis Procedure Combination (DPC) information from hospitals participating in the DPC system are also available for inpatient data. DPC hospitals in Japan provide a range of medical care including acute-phase patient care. MDV data capture information on patient demographics, healthcare provider (eg hospital size), procedures undertaken, pharmacy claims for medications dispensed in inpatient and outpatient settings (including date, dosage, days of supply), reimbursement data, disease data on diagnoses (including primary diagnosis), and discharge summary information. Laboratory data are also available in the database, but these are limited. Coding systems utilised in MDV include European Pharmaceutical Market Research

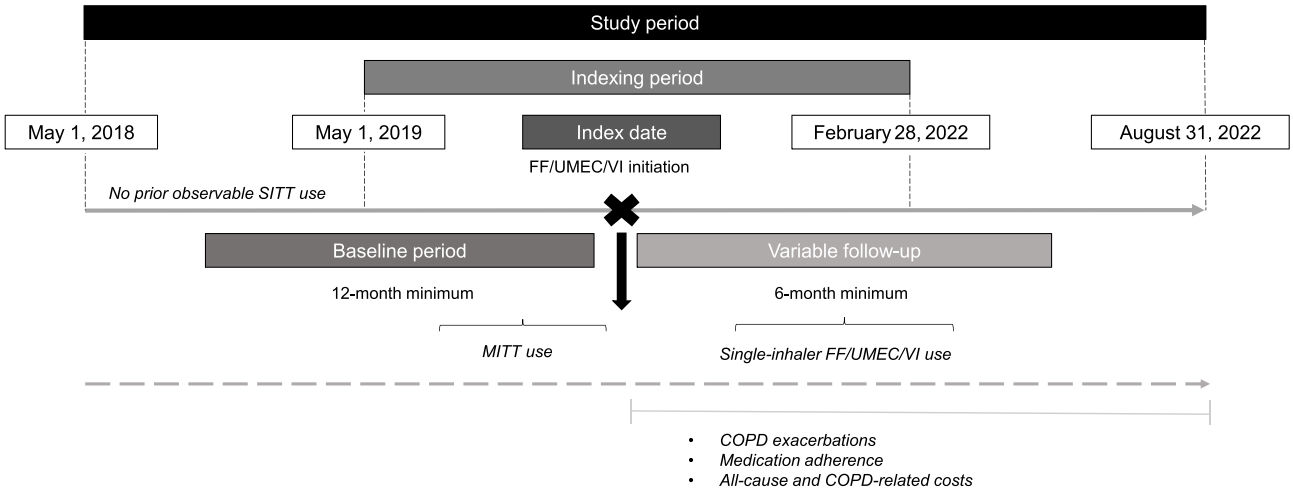

Figure 1 Study design.
Abbreviations: COPD, chronic obstructive pulmonary disease; FF/UMEC/VI, fluticasone furoate/umeclidinium bromide/vilanterol; MITT, multiple-inhaler triple therapy; SITT, single-inhaler triple therapy.

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Association Anatomical Therapeutic Chemical codes for dispensed medications and International Classification of Diseases, Tenth Revision (ICD-10) codes for diagnostic data.

Study Population

To be included in this study, patients were required to have ≥1 inpatient diagnosis and/or ≥2 outpatient diagnoses of COPD (in separate calendar months; ICD-10 codes J42–44) at ≥40 years of age at any time prior to and including the index month. Patients were also required to have ≥12 months of continuous enrollment prior to the index date, excluding the index date, and ≥6 calendar months of data availability following, but not including the index calendar month up to last/most recent diagnosis, medical claim record, or end of study period, whichever was earliest. Finally, patients were required to have ≥1 pharmacy claim for FF/UMEC/VI within the indexing period and ≥1 day of MITT use within the 6 months prior to the index date.

There were no restrictions placed on the treatments patients could or could not be prescribed between the end of MITT and the start of SITT. There was no minimum required cumulative or continual use of MITT or single-inhaler FF/UMEC/VI in the primary analysis of this study, in order to be less restrictive with regard to treatment adherence and disease severity. Therefore, patients switching from MITT to single-inhaler FF/UMEC/VI were included in the analysis even if they discontinued treatment. Patients who switched to the comparator arm were excluded from this study.

Patients were excluded if they had ≥1 ICD-10 diagnostic code of any medical conditions incompatible with a COPD diagnosis (please see Supplement) at any time in their medical history, prior to and including the month of index, and/or if they had any prior SITT use.

Study Objectives

The primary objectives of this study were to compare the proportion of patients with ≥1 overall (moderate-to-severe), moderate, or severe COPD exacerbations and the rate of overall, moderate, or severe COPD exacerbations among patients with COPD in the 6 months prior to and following a switch from MITT to treatment with FF/UMEC/VI.

The secondary objective was to compare the rate of overall, moderate, or severe COPD exacerbations among patients with COPD in the 6 months prior to and following a switch from MITT to FF/UMEC/VI in patients who experienced ≥1 overall COPD exacerbation while receiving MITT.

The first exploratory objective was to compare the proportion of patients with ≥1 overall, moderate, or severe COPD exacerbation among patients with COPD in the 12 months prior to and following a switch from MITT to FF/UMEC/VI. The second exploratory objective was to compare medication adherence, assessed by PDC as a continuous variable, among patients with COPD at 6 and 12 months prior to and following a switch from MITT to FF/UMEC/VI. The final exploratory objective was to compare direct medical costs among patients with COPD, at 6 and 12 months prior to and following a switch from MITT to FF/UMEC/VI.

Sensitivity Analyses

Due to the potential for introducing bias by prematurely removing patients with extreme non-adherence from the analysis (ie not true discontinuation of treatment), a sensitivity analysis was conducted using a 30, 60, and 90-day permissible gap between prescriptions to be considered as continuous treatment. Patients were required to have a minimum of 6 months continual MITT and FF/UMEC/VI use prior to and following the index date (treatment switch).

In another sensitivity analysis, the 28 days prior to the treatment switch were removed from the patient's observation time when assessing COPD exacerbations. This was to determine whether the benefit of switch held true when the exacerbations potentially causing the switch were removed.

Data Analysis

A sample size of 1886 patients switching from MITT to SITT was determined to be needed to detect a significant 20% reduction (rate ratio of 0.8) in overall exacerbations in the 6 months following SITT initiation compared to the 6 months prior to SITT initiation, using a Poisson regression with an over-dispersion factor of 0.2 and assuming an exacerbation

rate of 0.8 on MITT, a two-sided type I error of 5% and a power of 80%. The exacerbation rate of 0.8 was sourced from a recent MITT to SITT switch study conducted in the UK.[18]

Patient demographics and clinical characteristics were assessed at baseline and at 12–15 and 0–3 months prior to index. These different time points were used to visually see if the patients' demographics and clinical characteristics changed in the lead up to the switch to SITT (index date). Bivariate comparisons of the proportion of patients with ≥1 COPD exacerbation prior to and following a switch from MITT to FF/UMEC/VI were performed using McNemar's test for the difference between two proportions. Overall rates of COPD exacerbations were calculated as the number of events divided by person-years of observation and compared prior to and following a switch from MITT to FF/UMEC/VI using rate ratios (RRs), 95% confidence intervals (CIs), and *p*-values. Adherence to treatment at 6 and 12 months prior to and following a switch from MITT to FF/UMEC/VI was assessed using a continuous measure of the PDC (number of days covered divided by the number of days in the period; Supplementary Figure 1). Overall all-cause and COPD-related direct medical costs at 6 and 12 months prior to and following a switch from MITT to FF/UMEC/VI were calculated and reported per-patient-per-year, by dividing the costs incurred prior to and following a switch from MITT to FF/UMEC/VI by the person-years of observation. Mean costs were compared prior to and following a switch from MITT to FF/UMEC/VI using paired t-tests.

Results

Patient Attrition

A total of 2365 patients with 6 months of follow-up data were included in this study, of whom 2101 (88.8%) were exacerbation-naïve (no prior COPD exacerbations) and 264 (11.1%) had ≥1 COPD exacerbation prior to index in the baseline period (Supplementary Figure 2). A total of 2091 patients had 12 months of follow-up data (exploratory objectives only).

Baseline Patient Sociodemographic and Clinical Characteristics

Baseline demographic and clinical characteristics are reported in Table 1. Mean (standard deviation [SD]) age was 75.3 (9.7) years, and 77.1% of patients were male. The majority of patients (92.8%) recorded an asthma diagnosis in the 24 months prior to index, with 68.4% receiving current asthma treatment (≥1 pharmacy claim for either ICS, ICS/LABA, or a leukotriene receptor agonist in the same calendar month, observed within 12 months prior to index). Overall, the most commonly prescribed MITT medications immediately prior to switching were LAMA+ICS/LABA

Table 1 Baseline Demographics and Clinical Characteristics

	Full study cohort (N=2365)
Age at index, years, mean (SD)	75.3 (9.7)
Male sex, n (%)	1824 (77.1)
Hospital size (number of beds), n (%)	
<200	330 (14.0)
200–499	1463 (61.9)
500+	572 (24.2)
Asthma status 24 months prior to index, n (%)	
Current asthma	2195 (92.8)
Not current asthma	170 (7.2)
Asthma status >24 months prior to index, n (%)	
Historical asthma	2168 (91.7)
No historical asthma	197 (8.3)

(*Continued*)

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Table 1 (Continued).

	Full study cohort (N=2365)
Asthma status with current treatment of ICS, ICS/LABA, or LTRA in the 12 months prior to index, n (%)	
Asthma with current treatment	1617 (68.4)
Not asthma with current treatment	748 (31.6)
Comorbidities, n (%)	
Anxiety	1 (0.0)
Bronchiectasis	89 (3.8)
Cancer	626 (26.5)
Cerebrovascular disease	484 (20.5)
Chronic bronchitis	1140 (48.2)
Connective tissue disease	479 (20.3)
Dementia-cognitive impairment	127 (5.4)
Depression	133 (5.6)
Diabetes	955 (40.4)
GERD	1409 (59.6)
Heart failure	910 (38.5)
Hypertension	1463 (61.9)
Lung cancer	173 (7.3)
Myocardial infarction	152 (6.4)
Osteoporosis	388 (16.4)
Peptic ulcer	972 (41.1)
Peripheral vascular disease	362 (15.3)
Stroke	282 (11.9)
Rheumatoid arthritis/osteoarthritis	679 (28.7)
Outpatient pneumonia	574 (24.3)
Inpatient pneumonia	808 (34.2)
Baseline CCI, mean (SD)	2.3 (1.7)
MITT therapy immediately prior to index, n (%)	
LABA+LAMA+ICS/LABA	1 (0.0)
LAMA+ICS/LABA	1774 (75.0)
LAMA+LAMA/LABA+ICS/LABA	14 (0.6)
LAMA/LABA+ICS/LABA	81 (3.4)
ICS+LABA+LAMA	3 (0.1)
ICS+LAMA+ICS/LABA	17 (0.7)
ICS+LAMA+LAMA/LABA	6 (0.3)
ICS+LAMA+LAMA/LABA+ICS/LABA	1 (0.0)
ICS+LAMA/LABA	462 (19.5)
ICS+LAMA/LABA+ICS/LABA	6 (0.3)

Abbreviations: CCI, Quan–Charlson Comorbidity Index; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β2 agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; MITT, multiple-inhaler triple therapy; SD, standard deviation.

(75.0%), ICS+LAMA/LABA (19.5%), and LAMA/LABA+ICS/LABA (3.4%). Clinical characteristics during the 12–15 months prior to index were similar to those observed for 0–3 months prior to index (Table 2). In the 12–15 months prior to index, patients had a mean (SD) baseline Quan–Charlson Comorbidity Index of 1.8 (1.4), and the most commonly reported comorbidities were hypertension (60.1%), gastroesophageal reflux disease (57.7%), and chronic bronchitis (47.0%) (Table 2). The majority of patients had five or more baseline comorbidities (60.6%).

Table 2 Patient Clinical Characteristics and Treatment Use at Baseline for Variables Reported Within 12–15 and 0–3 months Prior to Index Date

	12–15 months prior to switch from MITT to FF/UMEC/VI (N=2365)	0–3 months prior to switch from MITT to FF/UMEC/VI (N=2365)
BMI, kg/m^2		
n	199	320
Mean (SD)	22.4 (4.5)	22.1 (4.4)
Median (range)	21.9 (13.5, 45.7)	21.5 (12.4, 46.3)
IQR	19.3, 24.9	19.0, 24.4
Home oxygen therapy, n (%)		
Not received home oxygen therapy	2121 (89.7)	2061 (87.1)
Received home oxygen therapy	244 (10.3)	304 (12.9)
Smoking history (Brinkman Index), n (%)		
No history of smoking	60 (2.5)	84 (3.6)
History of smoking	1357 (57.4)	1333 (56.4)
Unknown	948 (40.1)	948 (40.1)
Baseline activities of daily living (Barthel Index)		
n	196	311
Mean (SD)	95.9 (12.4)	93.3 (15.8)
Median (range)	100.0 (20.0, 100.0)	100.0 (10.0, 100.0)
IQR	100.0, 100.0	100.0, 100.0
Baseline absolute eosinophil count, cells/μL		
n	59	84
Mean (SD)	377.6 (420.9)	438.7 (504.5)
Median (range)	206.0 (0.0, 1839.6)	237.7 (0.0, 2314.1)
IQR	129.3, 475.2	144.2, 502.9
Comorbidities, n (%)		
Anxiety	1 (0.0)	1 (0.0)
Bronchiectasis	86 (3.6)	89 (3.8)
Cancer	602 (25.5)	626 (26.5)
Cerebrovascular disease	472 (20.0)	484 (20.5)
Chronic bronchitis	1112 (47.0)	1140 (48.2)
Connective tissue disease	463 (19.6)	479 (20.3)
Dementia-cognitive impairment	124 (5.2)	127 (5.4)
Depression	88 (3.7)	101 (4.3)
Diabetes	936 (39.6)	955 (40.4)
GERD	1365 (57.7)	1409 (59.6)
Heart failure	888 (37.5)	910 (38.5)
Hypertension	1421 (60.1)	1463 (61.9)
Lung cancer	170 (7.2)	173 (7.3)
Myocardial infarction	150 (6.3)	152 (6.4)
Osteoporosis	376 (15.9)	388 (16.4)
Peptic ulcer	949 (40.1)	972 (41.1)
Peripheral vascular disease	352 (14.9)	362 (15.3)
Stroke	274 (11.6)	282 (11.9)
Rheumatoid arthritis/osteoarthritis	654 (27.7)	679 (28.7)
Outpatient pneumonia	51 (2.2)	118 (5.0)
Inpatient pneumonia	193 (8.2)	283 (12.0)

(*Continued*)

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Table 2 (Continued).

	12–15 months prior to switch from MITT to FF/UMEC/VI (N=2365)	0–3 months prior to switch from MITT to FF/UMEC/VI (N=2365)
Number of comorbidities[a]		
Mean (SD)	5.5 (3.0)	5.7 (2.8)
Median (range)	5.0 (0.0, 16.0)	5.0 (0.0, 16.0)
IQR	3.0, 8.0	3.0, 8.0
Baseline CCI		
Mean (SD)	1.8 (1.4)	2.0 (1.5)
Median (range)	1.0 (0.0, 13.0)	1.0 (0.0, 13.0)
IQR	1.0, 3.0	1.0, 3.0
Respiratory class within baseline, n (%)		
SABA	391 (16.5)	405 (17.1)
SAMA	1 (0.0)	3 (0.1)
ICS	65 (2.7)	111 (4.7)
ICS/LAMA	12 (0.5)	6 (0.3)
ICS/LABA	457 (19.3)	431 (18.2)
LABA	16 (0.7)	10 (0.4)
LAMA	344 (14.5)	451 (19.1)
LAMA/LABA	250 (10.6)	188 (7.9)
ICS/LABA/LAMA	1749 (74.0)	2283 (96.5)
Transdermal LABA	62 (2.6)	67 (2.8)
LTRA	666 (28.2)	668 (28.2)
SCS	381 (16.1)	417 (17.6)
Biologics	32 (1.4)	48 (2.0)
Home oxygen/mechanical ventilation	260 (11.0)	312 (13.2)
None	190 (8.0)	1 (0.0)
Number of treatment strategies		
Mean (SD)	2.3 (1.1)	2.0 (1.2)
Median (range)	2.0 (0.0, 7.0)	2.0 (0.0, 7.0)
IQR	1.0, 3.0	1.0, 3.0

Notes: [a]Includes asthma.

Abbreviations: BMI, body mass index; CCI, Quan–Charlson Comorbidity Index; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β2 agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor agonist; MITT, multiple-inhaler triple therapy; SABA, short-acting β2 agonist; SAMA, short-acting muscarinic antagonist; SCS, systemic corticosteroid; SD, standard deviation.

COPD Exacerbations

Numbers and incidence rates of COPD exacerbations experienced in the 6 months pre- and post-switch to FF/UMEC/VI in the overall population and among patients who had ≥1 exacerbations while receiving MITT are shown in Supplementary Table 1.

In the 6 months post-switch from MITT to FF/UMEC/VI, there was a statistically significant decrease in the proportion of patients who experienced ≥1 overall COPD exacerbation (11.2% to 8.8%; p=0.0014) and ≥1 severe COPD exacerbation (4.6% to 3.2%; p=0.0069) compared with the 6 months pre-switch (Figure 2). There was a similar proportion of patients who experienced ≥1 moderate COPD exacerbation pre-switch and post-switch (6.9% to 6.2%; p=0.2394) (Figure 2); however, statistical significance was not achieved.

Rates of overall and moderate COPD exacerbations were numerically lower following a switch to FF/UMEC/VI versus pre-switch (RR: 0.86, 95% CI: 0.74–1.00; p=0.0528, and RR: 0.95, 95% CI: 0.79–1.13; p=0.5796, respectively). There was a significant reduction in severe exacerbations post-switch compared with pre-switch (RR: 0.68, 95% CI: 0.51–0.90; p=0.0084) (Figure 3).

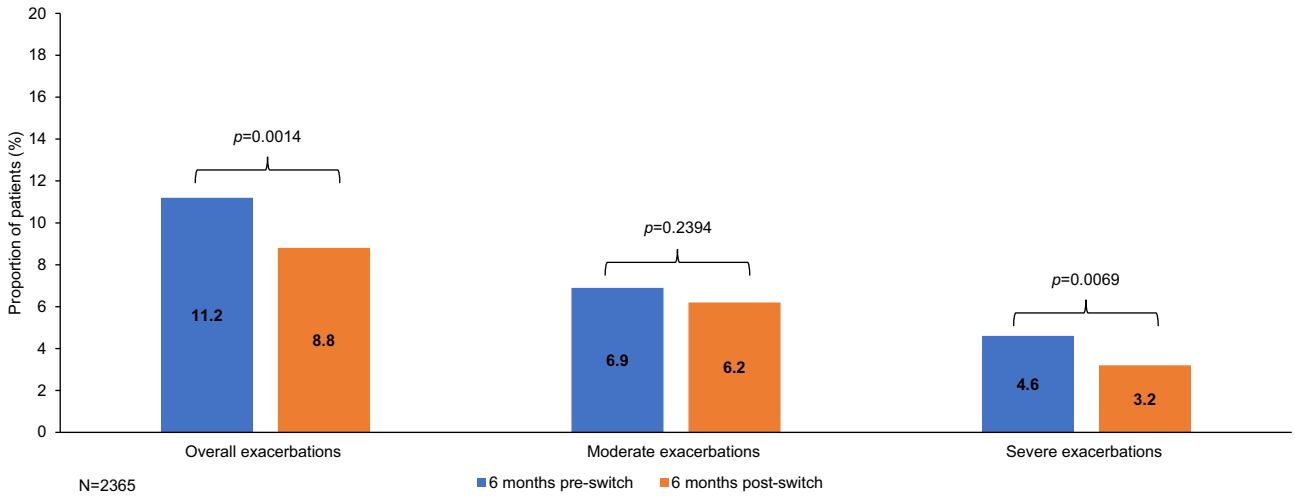

Figure 2 Proportion of patients with ≥1 overall, moderate, and severe COPD exacerbation in the 6 months pre- and post-switch from MITT to FF/UMEC/VI (N=2365).
Abbreviations: COPD, chronic obstructive pulmonary disease; FF/UMEC/VI, fluticasone furoate/umeclidinium bromide/vilanterol; MITT, multiple-inhaler triple therapy.

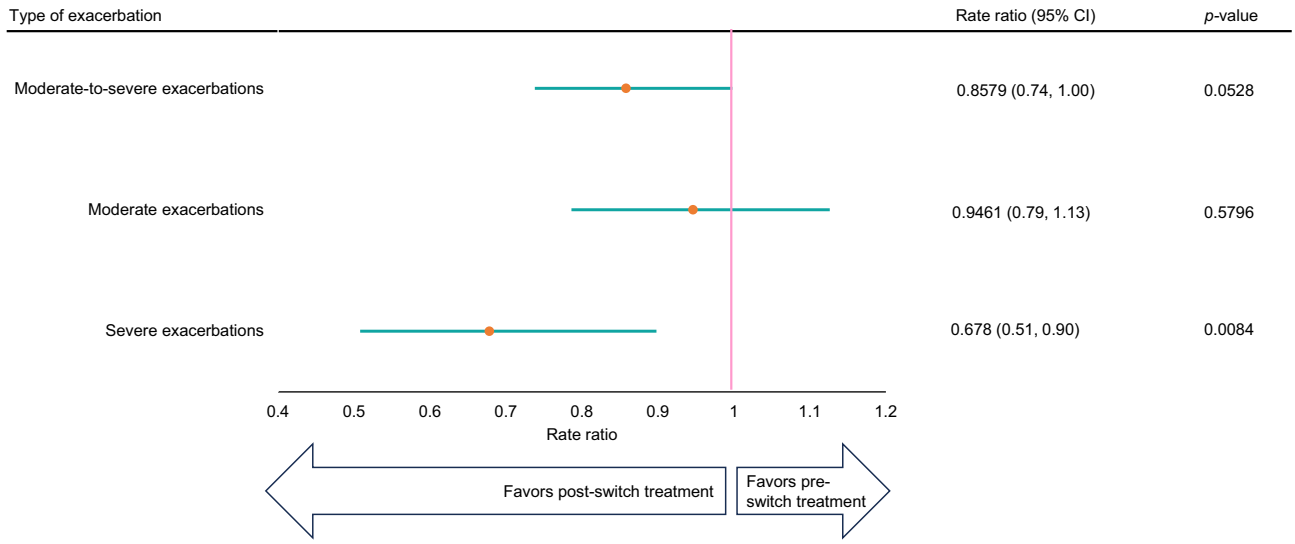

Figure 3 COPD exacerbation rate in the 6 months pre- and post-switch from MITT to FF/UMEC/VI.
Notes: Rate ratio <1 indicates lower risk post-switch.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FF/UMEC/VI, fluticasone furoate/umeclidinium bromide/vilanterol; MITT, multiple-inhaler triple therapy.

Among the cohort of patients who had ≥1 overall exacerbation while receiving MITT, rates of COPD exacerbation were significantly lower in the 6 months post- versus pre-switch (overall, RR: 0.48, 95% CI: 0.40–0.57; $p<0.0001$; moderate, RR: 0.61, 95% CI: 0.50–0.75; $p<0.0001$; severe, RR: 0.20, 95% CI: 0.13–0.32; $p<0.0001$) (Figure 4).

In the 12 months following a switch to FF/UMEC/VI (n=2091), the proportions of patients experiencing overall, moderate, and severe COPD exacerbations were significantly reduced compared with the 12 months pre-switch (17.4% to 12.6%; $p<0.0001$; 11.3% to 8.8%; $p=0.0013$; and 7.2% to 4.9%; $p=0.0007$, respectively) (Figure 5).

Sensitivity Analyses

When using different lengths of permissible gaps (30, 60, and 90 days), and when removing the 28 days prior to the treatment switch, there were minimal changes in the proportion of patients who experienced ≥1 COPD exacerbation pre- versus post-switch (Supplementary Figures 3–6). Similar RRs were observed for overall and moderate COPD

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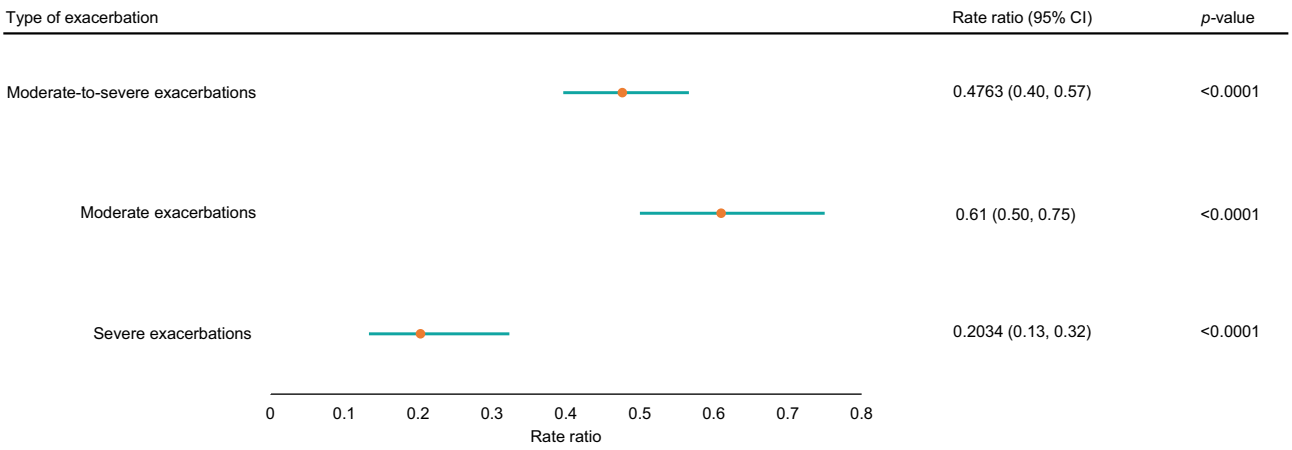

Figure 4 COPD exacerbation rate in the 6 months pre- and post-switch to FF/UMEC/VI among patients who experienced ≥1 exacerbation while receiving MITT.
Notes: Rate ratio <1 indicates lower risk post-switch.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FF/UMEC/VI, fluticasone furoate/umeclidinium bromide/vilanterol; MITT, multiple-inhaler triple therapy.

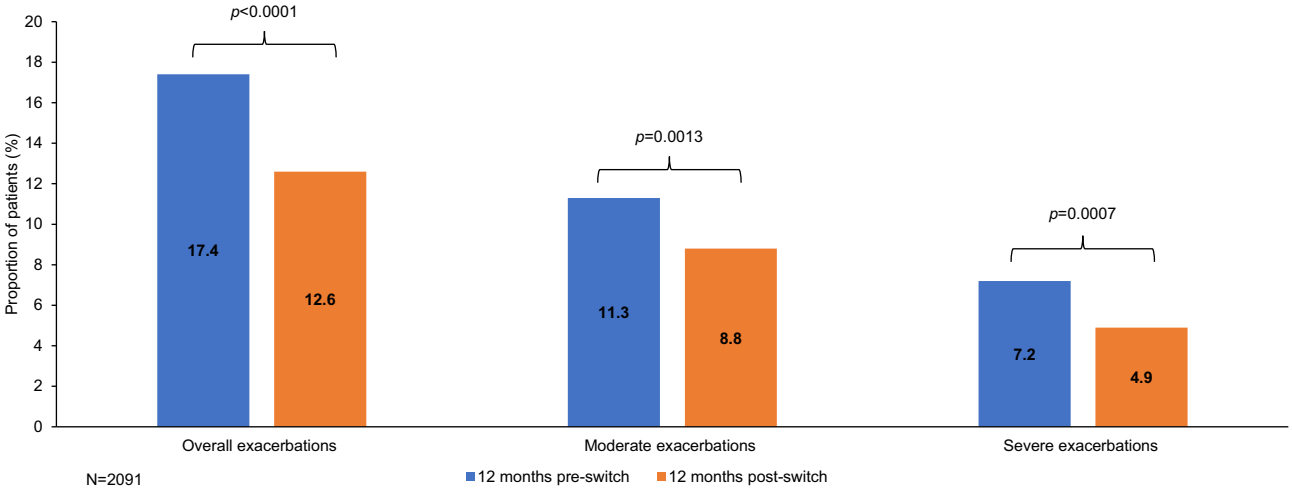

Figure 5 Proportion of patients with overall, moderate, or severe COPD exacerbations in the 12 months pre- and post-switch from MITT to FF/UMEC/VI (N=2091).
Abbreviations: COPD, chronic obstructive pulmonary disease; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; MITT, multiple-inhaler triple therapy.

exacerbations, whereas numerically higher RRs were observed for severe COPD exacerbations (Supplementary Figures 7–9).COPD exacerbation rates for when the 28 days prior to the treatment switch were removed are reported in Supplementary Figure 10.

Medication Adherence

Mean PDC was significantly higher in the 6 months post-switch compared to pre-switch (mean [SD] PDC: 0.83 [0.25] versus 0.80 [0.26]; $p<0.0001$). There was a small, numerical increase in mean PDC in the 12 months post-switch compared to pre-switch (mean [SD] PDC: 0.77 [0.29] versus 0.76 [0.29]; $p=0.1376$) (Table 3).

All-Cause and COPD-Related Direct Medical Costs

COPD-related hospitalization costs decreased numerically in the 6 months post-switch (Table 4). Total all-cause and COPD-related total costs were significantly higher ($p<0.0001$) following a switch, which is thought to have been driven by an increase in outpatient costs. Similar results were observed when assessing total direct medical costs in the 12 months pre- and post-switch.

Table 3 Medication Adherence (Continuous PDC) Among Patients in the 6 and 12 months Pre- and Post-Switch from MITT to FF/UMEC/VI (Exploratory Analysis)

Cumulative PDC	6 months pre-switch	6 months post-switch	*p*-value
n	2365	2365	<0.0001
Mean (SD)	0.80 (0.26)	0.83 (0.25)	
Median (range)	0.93 (0.01, 1.00)	0.97 (0.08, 1.00)	
IQR	0.67, 1.00	0.79, 1.00	
Cumulative PDC	**12 months pre-switch**	**12 months post-switch**	***p*-value**
n	2091	2091	0.1376
Mean (SD)	0.76 (0.29)	0.77 (0.29)	
Median (range)	0.89 (0.01, 1.00)	0.91 (0.04, 1.00)	
IQR	0.62, 0.98	0.67, 0.99	

Abbreviations: FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; IQR, interquartile range; MITT, multiple-inhaler triple therapy; PDC, proportion of days covered; SD, standard deviation.

Discussion

In this Japanese real-world study of patients who switched from MITT to single-inhaler FF/UMEC/VI, the proportion of patients who experienced COPD exacerbations was consistently lower in the 6 and 12 months post-switch compared with pre-switch. Switching from MITT to FF/UMEC/VI resulted in a significantly lower rate of severe exacerbations in the 6 months post-switch compared with the 6 months pre-switch.

These findings build upon the INTREPID trial, which showed improved health benefits with single-inhaler FF/UMEC/VI versus MITT,[14] as well as previous real-world studies conducted in the US[17] and the UK[18] that reported a significant reduction in COPD exacerbations following a switch from MITT to SITT. The benefits of FF/UMEC/VI have also been demonstrated in a network meta-analysis, in which FF/UMEC/VI demonstrated statistically significant improvements in the annualized rate of combined moderate or severe exacerbations at 24 weeks post-index compared with MITT among patients with COPD.[21]

This study also demonstrates significant reductions in exacerbations in the 6 months post-switch among patients who experienced ≥1 exacerbation while receiving MITT. A similar study in the UK reported higher RRs for COPD exacerbations at 12 months post-switch compared with 6 months post-switch among patients with prior COPD exacerbations while receiving MITT, suggesting a benefit of early initiation of FF/UMEC/VI.[18] Prompt initiation of SITT following moderate or severe COPD exacerbation has previously been shown to reduce the rate and time to subsequent exacerbations,[22–24] including among Japanese patients.[25] Further studies are required to determine the impact of early versus delayed initiation of SITT in patients experiencing COPD exacerbations while receiving MITT, as this current study did not evaluate exacerbation rate beyond 6 months in this subgroup of patients.

The continual use sensitivity analysis showed minimal change in the proportion of patients who experienced a COPD exacerbation when comparing pre- and post-switch periods at 6 months across each permissible treatment gap (30, 60, and 90 days). This sensitivity analysis was performed as the inclusion of continual MITT use in the primary analysis would introduce bias toward a more adherent MITT and/or FF/UMEC/VI population, which may have affected the comparison of clinical outcomes.

The findings from our study suggest that switching to FF/UMEC/VI can provide a greater clinical benefit to MITT users, reflecting the results of a study that assessed the clinical effectiveness of SITT initiation in patients with moderate-to-severe COPD in Japan.[26] In that study, significantly improved pulmonary function was observed among patients with severe symptoms who received FF/UMEC/VI after their initial therapy. Response to FF/UMEC/VI was rapid, with improvements observed within 1 month of initiating therapy.

The apparent benefits of early treatment with FF/UMEC/VI may be in part due to increased adherence to once-daily, single-inhaler therapy. We found that adherence to therapy (assessed via PDC) was significantly higher in the 6 months post-switch to SITT versus pre-switch MITT use. Our findings support those from another real-world study in Japan,

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Table 4 All-Cause and COPD-Related Medical Costs in the 6 and 12 months Pre- and Post-Switch from MITT to FF/UMEC/VI (Exploratory Analysis)

	6 months pre-switch (N=2365)	6 months post-switch (N=2365)	*p*-value	12 months pre-switch (n=2091)	12 months post-switch (n=2091)	*p*-value
Outpatient costs (¥), PPPY						
All-cause Mean (SD) Median (IQR)	482,050.7 (805,691.0) 266,136.9 (166,719.2, 484,838.5)	593,400.3 (914,528.9) 323,964.0 (206,956.6, 600,444.6)	<0.0001	483,936.3 (717,998.6) 280,550.4 (184,046.8, 467,607.5)	569,097.2 (869,786.3) 305,451.3 (194,118.4, 568,290.5)	<0.0001
COPD-related Mean (SD) Median (IQR)	430,497.3 (719,115.8) 236,171.9 (139,008.8, 425,114.3)	562,925.6 (886,955.7) 303,781.2 (194,595.5, 551,539.4)	<0.0001	408,274 (571,772.9) 237,194.5 (148,310.4, 401,506.3)	534,423.4 (822,491.6) 284,014 (183,252.9, 531,849.0)	<0.0001
Hospitalisation costs (¥), PPPY						
All-cause Mean (SD) Median (IQR)	122,697.4 (416,392.5) 0 (0, 0)	102,277.6 (380,968.3) 0 (0, 0)	0.0477	104,283.3 (295,965.5) 0 (0, 97,615.5)	97,684.3 (289,983.1) 0 (0, 0)	0.415
COPD-related Mean (SD) Median (IQR)	99,166.5 (371,434.3) 0 (0, 0)	93,717.5 (369,032.5) 0 (0, 0)	0.5664	77,828.4 (243,542.5) 0 (0, 0)	84,865.6 (264,119.3) 0 (0, 0)	0.321
Total medical costs (¥), PPPY						
All-cause Mean (SD) Median (IQR)	604,748.1 (936,148.1) 305,763.8 (183,636.1, 662,802.7)	695,677.9 (1,027,369.1) 353,559.6 (215,626.8, 763,486.9)	<0.0001	588,219.6 (807,113.0) 325,633.8 (205,831.3, 646,937.4)	666,781.5 (960,917.8) 342,033.9 (204,898.8, 767,847.7)	<0.0001
COPD-related Mean (SD) Median (IQR)	529,663.8 (823,485.9) 264,623.6 (155,879.9, 579,549.8)	656,643.1 (990,007.9) 326,896.5 (201,898.3, 692,519.8)	<0.0001	486,102.4 (644,437.6) 269,987.8 (161,855.5, 512,706.7)	619,289 (897,211.1) 311,988.8 (190,830.0, 698,845.8)	<0.0001

Abbreviations: COPD, chronic obstructive pulmonary disease; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; IQR, interquartile range; MITT, multiple-inhaler triple therapy; PPPY, per-patient-per-year; SD, standard deviation.

which reported increased adherence at 6, 12, and 18 months following switch from MITT to FF/UMEC/VI SITT.[27] In the same study, patients newly initiating SITT also had greater medication adherence and persistence compared with those initiating a MITT regimen. Adherence and persistence to therapy are crucial for achieving optimal clinical outcomes;[6–9] however, real-world evidence suggests that adherence to MITT is low, with one study reporting a mean PDC of only 0.37 at 12 months in patients with COPD.[11] In a cross-sectional study of Japanese patients, 21.8% of patients with COPD showed poor adherence to inhaled therapy.[28] Once-daily treatment with SITT presents an opportunity to improve poor treatment adherence and persistence by removing barriers such as complexity, dosing frequency, number and variety of medications, and ease of inhaler use.[29]

Although this study demonstrated the clinical benefits of switching from MITT to FF/UMEC/VI, COPD-related total medical costs were higher in the 6 and 12 months post- versus pre-switch. The increase in total costs following a switch to FF/UMEC/VI is thought to be mainly due to an increase in outpatient costs; however, the details are unclear. Regarding the increase in outpatient costs, it is worth noting the prevalence of outliers leading to a positive skew in data, which is demonstrated by the higher mean in comparison to the median. Further investigation is required to determine the full economic impact of switching from MITT to FF/UMEC/VI.

Of note, the majority of patients in our study (92.8%) had a current asthma diagnosis in addition to COPD, which is similar to the population of patients observed in other studies from Japan.[25] Patients with comorbid asthma were not excluded from this study in order to reflect the real-world population and ensure a sufficient sample size of patients. Asthma was defined based on ICD-10 codes only, regardless of treatment use. Patients who had only one asthma diagnosis code during the 24–36 months prior to index date were also included, which could have potentially over-estimated the number of patients with comorbid asthma. JRS guidelines recommend the addition of ICS maintenance therapy for patients with COPD based on asthmatic features, blood eosinophil count, and exacerbation frequency.[10] This may result in the total number of patients escalated to triple therapy in Japan being lower than in studies conducted in countries whose guidance is in alignment with GOLD recommendations.

This study spanned the COVID-19 pandemic period; therefore, the potential impact of the pandemic on the clinical profiles of the patients included in this study was considered. A feasibility assessment in the MDV database for a previous GSK study found that the number of patients with COPD in Japan who also had disease codes for COVID-19 was small. Therefore, the COVID-19 pandemic is not expected to have greatly impacted the results of this study. However, there is still the potential that bias may have been introduced; for example, there may have been less visits to the hospital during the pandemic or exacerbations may not have been as well recorded during this period. Additionally, diagnoses for COVID-19 may have been underestimated, particularly at the start of the pandemic. Feasibility and/or sub-group analyses may be helpful for other studies conducted during the period of the COVID-19 pandemic to assess its impact on study conduct and outcomes.

Overall, the findings from this study may suggest that the introduction of FF/UMEC/VI to the treatment of patients receiving MITT is an opportunity to reduce the frequency of COPD exacerbations in the future. This reflects a key goal outlined in the GOLD 2024 strategy (to minimize the negative impact of the current exacerbation and prevent the development of subsequent events).[2]

Several limitations of this study should be considered. Firstly, patients were required to have ≥6 months of follow-up data following indexing to be eligible for inclusion in the study cohort, which introduced an element of survivorship bias. Mortality was therefore not assessed in this study. Although this may have impacted the generalizability of the study findings, this design aspect was implemented to ensure sufficient observation time to assess the study endpoints. Diagnosis (ICD-10) codes were only captured at monthly intervals, ie an exact date was not recorded. Therefore, it is not possible to explicitly link diagnoses to disease-related outpatient visits, hospitalizations, and pharmacy claims captured within the MDV database, and instead a diagnosis observed within the same calendar month was used as a proxy measure. This may have introduced misclassification bias when determining COPD-related healthcare service provision; however, this was primarily relevant when observing exacerbation rates and was mitigated through the definition of COPD exacerbations including a pharmacy claim for a systemic corticosteroid and an antibiotic within the same calendar month. As is common for retrospective database analyses in COPD, there was potential for misdiagnosis of COPD as asthma and vice versa, and we cannot know for certain that COPD MITT medications were

not prescribed to treat asthma, for which they are also indicated. Other limitations of retrospective database analyses which apply to this study include the possible introduction of bias (selection, misclassification and survivorship) and difficulties establishing causality. Medication adherence was measured via PDC, by which patients are considered to be "covered" for days in which they have a valid days' supply from a pharmacy claim of triple therapy (or overlapping components of MITT). This method is a proxy measure of adherence and may have resulted in an overestimation of actual adherence. However, as the purpose of this study was to compare adherence, the pre- versus post-switch comparison should not be affected, as any potential estimation would affect pre- and post-switch adherence results. Confounding by indication may be a limitation of this study when comparing before and after a treatment switch from MITT to FF/UMEC/VI. However, measures were taken to reduce this impact, such as excluding continual treatment use pre- and post-switch in the primary analysis. Future studies should consider assessing exacerbation rates beyond 6 months post-switch, to help inform suitable long-term management of COPD, as well as assessing objective measures such as spirometry and oxygen saturation prior to the index date. However, it is worth noting the limited availability of these data in EHR databases.

Conclusions

In the primary analysis conducted in this study, significantly lower rates of severe exacerbations and numerically lower rates of overall and moderate exacerbations were observed in Japanese patients with COPD following a switch from MITT to once-daily single-inhaler FF/UMEC/VI. The impact of switching to FF/UMEC/VI was especially evident in patients with prior COPD exacerbations. Medication adherence improved in the 6 months following switch from MITT to FF/UMEC/VI. These results support evidence form the INTREPID trial and may be used to inform clinical guidance and the optimum management strategy for patients with COPD in Japan.

Abbreviations

CI, confidence interval; COPD, chronic obstructive pulmonary disease; DPC, Diagnosis Procedures Combination; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICD-10, International Classification of Diseases, Tenth Revision; ICS, inhaled corticosteroid; JRS, Japanese Respiratory Society; LABA, long-acting β2 agonist; LAMA, long-acting muscarinic antagonist; MDV, Medical Data Vision Co. Ltd; MITT, multiple-inhaler triple therapy; PDC, proportion of days covered; RR, rate ratio; SD, standard deviation; SITT, single-inhaler triple therapy; UK, United Kingdom; US, United States.

Data Sharing Statement

The data analyzed in this publication are derived from the MDV database (Tokyo, Japan; https://www.mdv.co.jp/). Authors had access to the study data for the purposes of this work only. The interpretation and conclusions contained in this study are those of the authors alone. Data were accessed through an existing GSK license to address the prespecified research questions only. Therefore, the data cannot be broadly disclosed or made publicly available at this time. Access to the database can be requested via the website.

Ethics Approval and Informed Consent

This study complied with all applicable laws regarding subject privacy, Declaration of Helsinki. No direct subject contact or primary collection of individual human subject data has occurred in this study. This study used existing, fully de-identified data and the subject(s) cannot be identified, directly or through identifiers. Study results were in tabular form and aggregate analyses that omits subject identification; therefore, informed consent, ethics committee or Institutional Review Board approval were not required.

Consent for Publication

Not applicable.

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Author Contributions

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

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Disclosure

Gema Requena and Akiko Mizukami were employees of, and/or held financial equities in, GSK at the time of study. Masao Yarita, Kenichi Hashimoto, and Stephen G Noorduyn are employees of, and/or hold financial equities in, GSK. Stephen G Noorduyn is also a PhD candidate at McMaster University. Lucinda J Camidge, Alexander Ford, Thomas Jennison, and Olivia S Massey are employees of Adelphi Real World. Adelphi Real World received funding from GSK to conduct the study only. The authors report no other conflicts of interest in this work.

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