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ORIGINAL RESEARCH

Real-world effectiveness of umeclidinium/vilanterol versus fluticasone propionate/salmeterol as initial maintenance therapy for chronic obstructive pulmonary disease (COPD): a retrospective cohort study

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Background and objective: Retrospective claims data in patients with chronic obstructive pulmonary disease (COPD) initiating maintenance therapy with inhaled fixed-dose combinations of long-acting muscarinic antagonist/long-acting β_2-agonist (LAMA/LABA) versus inhaled corticosteroid (ICS)/LABA have not been reported.

Methods: Retrospective observational study in a COPD-diagnosed population of commercial and Medicare Advantage with Part D (MAPD) enrollees aged ≥40 years from a US health insurer database. Patients initiated umeclidinium/vilanterol (UMEC/VI [62.5/25 µg]) or fluticasone propionate/salmeterol (FP/SAL [250/50 µg]) between April 1, 2014 and August 31, 2016 (index date) and had 12 months continuous enrollment pre- and post-index. Exclusion criteria included an asthma diagnosis in the pre-index period/index date; ICS-, LABA-, or LAMA-containing therapy during the pre-index period; or pharmacy fills for both UMEC/VI and FP/SAL, multiple-inhaler triple therapy, a non-index therapy, or COPD exacerbation on the index date. Adherence (proportion of days covered [PDC] ≥80%) was modeled using weighted logistic regression following inverse probability of treatment weighting (IPTW). Weighted Kaplan–Meier and Cox proportional hazards regression following IPTW were performed for incidence of COPD exacerbation and escalation to multiple-inhaler triple therapy.

Results: The study population included 5306 patients (1386 initiating UMEC/VI and 3920 initiating FP/SAL). Adjusted odds of adherence were 2.00 times greater among UMEC/VI than FP/SAL initiators (95% confidence interval [CI]: 1.62–2.46; $P<0.001$). The adjusted hazard ratio (HR) for first exacerbation was 0.87 (95% CI: 0.74–1.01; $P=0.067$) among UMEC/VI versus FP/SAL initiators. UMEC/VI initiators had 35% lower adjusted risk of escalation to multiple-inhaler triple therapy (HR 0.65; 95% CI: 0.47–0.89; $P=0.008$) versus FP/SAL. On-treatment, UMEC/VI initiators had an adjusted 30% reduced risk of a first moderate/severe COPD exacerbation (HR 0.70; 95% CI: 0.54–0.90; $P=0.006$).

Conclusion: Patients with COPD initiating UMEC/VI had higher adherence and longer time before escalation to multiple-inhaler triple therapy than FP/SAL initiators.

Keywords: COPD, LAMA/LABA, ICS/LABA, real-world effectiveness, retrospective cohort

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Plain language summary

Chronic obstructive pulmonary disease (COPD) is a respiratory disease that commonly causes breathlessness. Despite recommendations, many patients diagnosed with COPD begin treatment

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with an inhaled medication that contains corticosteroids (ICS) in combination with a long-acting β_2-agonist (LABA) bronchodilator. Several studies have demonstrated that treatment with a different combination of medications, a long-acting muscarinic antagonist (LAMA) bronchodilator and a LABA, may be more effective at improving a person's ability to breathe and their quality of life, while reducing flare-ups (exacerbations) of their disease.

This study compared the effectiveness of the LAMA/LABA combination umeclidinium/vilanterol (UMEC/VI) with the ICS/LABA combination fluticasone propionate/salmeterol (FP/SAL) in patients who were initiating treatment with these medications. During the following year, patients who started treatment with UMEC/VI took their medication on a more consistent basis than those starting treatment with FP/SAL. Patients initiating UMEC/VI or FP/SAL had a similar time-to-first moderate/severe COPD exacerbation, but while on treatment, UMEC/VI initiators had a lower risk of an exacerbation compared with FP/SAL initiators. Patients who initiated UMEC/VI remained on the treatment for longer before they increased their medication to a combination of ICS+LABA+LAMA (multiple-inhaler triple therapy). These results suggest that for patients diagnosed with COPD, initiating treatment with a LAMA/LABA combination may provide benefits compared with initiating treatment with an ICS/LABA combination in a routine-care setting.

Introduction

Bronchodilation with a long-acting muscarinic antagonist (LAMA), a long-acting β_2-agonist (LABA), or a combination of the two is the foundation of chronic obstructive pulmonary disease (COPD) treatment.[1] The combination of LAMA and LABA bronchodilators has been shown to improve lung function and patient-reported outcomes when compared with either component alone and may reduce COPD-related exacerbations.[2,3] Evidence suggests that a combination of bronchodilator therapy with an inhaled corticosteroid (ICS) is beneficial in certain populations of patients diagnosed with COPD, such as those at high risk of exacerbations.[4–7] However, there is evidence that LAMA/LABA significantly improves lung function, including a greater improvement in trough forced expiratory volume in one second, reduces the rate of moderate/severe exacerbations, reduces rescue medication use, and lowers adverse event incidence, including lower risk of pneumonia, when compared with an ICS/LABA.[8–12]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document includes treatment recommendations for patients diagnosed with COPD based on assessment of symptom burden and exacerbation risk.[13] In the 2019 GOLD report, ICS/LABA is no longer recommended as the preferred initial maintenance therapy (IMT) for most patients diagnosed with COPD, although ICS/LABA continues to be a recommended treatment option for patients with COPD and a history of asthma, reflecting a shift toward a personalized treatment approach. LAMA/LABA is indicated as the preferred initiation option for GOLD Group B patients with severe breathlessness and for patients with a high symptom burden and exacerbation risk (GOLD Group D).[13] Despite this, ICS/LABA continues to be commonly prescribed across all severity groups.[14–17] Furthermore, the proportion of patients diagnosed with COPD initiating maintenance therapy with ICS/LABA is likely to increase following the introduction of a bioequivalent generic of the ICS/LABA fluticasone propionate/salmeterol (FP/SAL).[18] The preferential access given to generics on healthcare plans may lead to symptomatic patients who do not have a history of COPD exacerbation undergoing treatment that includes an unnecessary ICS component before they try a LAMA/LABA combination. Although clinical trials have compared the head-to-head efficacy and safety of ICS/LABA with LAMA/LABA,[8–12,19,20] there has not been a real-world study comparing the use of ICS/LABA with LAMA/LABA as IMT in patients diagnosed with COPD. This study aimed to address this knowledge gap by comparing the once-daily LAMA/LABA combination umeclidinium/vilanterol (UMEC/VI) with twice-daily FP/SAL for patients diagnosed with COPD in a large US health insurer database. This study focused on patients who were ICS-, LABA- and LAMA-naïve in the 12 months prior to initiating once-daily UMEC/VI or twice-daily FP/SAL, which complements the data that are available from LAMA/LABA versus ICS/LABA clinical trials.[8,9] The primary objective was to evaluate medication adherence, with secondary objectives to evaluate the incidence of first COPD exacerbation and escalation to multiple-inhaler triple therapy among maintenance-naïve patients initiating treatment with UMEC/VI compared with FP/SAL.

Methods

Study design

This was a retrospective observational cohort study (study number 207969 [HO-17–18426]) of patients diagnosed with COPD enrolled in commercial or Medicare Advantage with Part D (MAPD) health plans using claims from within the Optum Research Database (ORD) between April 01, 2013 and

August 31, 2017 (Figure 1). Patients had not received maintenance therapy for COPD 12 months prior to initiation of UMEC/VI (62.5/25 µg) or FP/SAL (250/50 µg) between April 01, 2014 and August 31, 2016 (index date set as the first fill date), had 12 months of continuous enrollment before (pre-index) and after (post-index) the index date, were at least 40 years of age as of the year of the index date, and had at least one medical claim containing a COPD diagnosis code in any position during the pre-index period were identified. Exclusion criteria included asthma diagnosis in the pre-index period or on index date; ICS-, LABA-, or LAMA-containing therapy during the pre-index period; or any of the following on the index date: pharmacy fills for both UMEC/VI and FP/SAL, multiple-inhaler triple therapy, a non-index therapy, or COPD exacerbation.

Endpoints

Patient demographic and clinical characteristics were assessed during the pre-index period, and medication adherence, incidence of first COPD exacerbation, and incidence of multiple-inhaler triple therapy were assessed during the post-index period. The primary endpoint, medication adherence, was defined as the proportion of days covered (PDC) ≥80%. PDC was calculated by dividing the number of days with available index medication (based on filled prescriptions) by the number of days between the index prescription claim and the end of the observation period. Medication adherence was corrected for inpatient stays with the assumption that the medication was provided by the facility during hospitalization. Overlapping pharmacy fills for the index medication were corrected for.

A moderate COPD exacerbation was defined as an outpatient or emergency department visit with a primary diagnosis indicating a COPD-related exacerbation and an administration or prescription fill for a COPD-guideline recommended antibiotic or systemic corticosteroid within ±5 days. A severe exacerbation was defined as a hospitalization with a primary diagnosis indicating a COPD-related exacerbation. Exacerbations occurring within 14 days of each other were considered a single exacerbation episode and classified according to the highest severity contributing event. The end date of the exacerbation episode was defined as the last observed exacerbation event date (or discharge date if an inpatient event) plus 14 days.

Multiple-inhaler triple therapy was defined as at least one day of overlapping days' supply of ICS, LABA, and LAMA.

Statistical analysis

PDC was calculated from the index date until the earliest occurrence of either a pharmacy fill for a non-index maintenance medication or the end of the 12-month post-index period. Intent-to-treat (ITT) analyses, with no censoring during the 12-month post-index period, were used to evaluate the secondary endpoints of incidence of first exacerbation (moderate/severe), incidence of first severe exacerbation, and incidence of multiple-inhaler triple therapy. An on-treatment sensitivity analysis was performed for the incidence of first COPD exacerbation. In the on-treatment sensitivity analysis, patients were censored at the time of discontinuation of the index medication (defined as a gap of 45 days from the index date for a retail pharmacy fill and 115 days for a mail order pharmacy fill), at the time of a pharmacy fill for a non-index maintenance medication, or at the end of the 12-month post-index period, whichever occurred first.

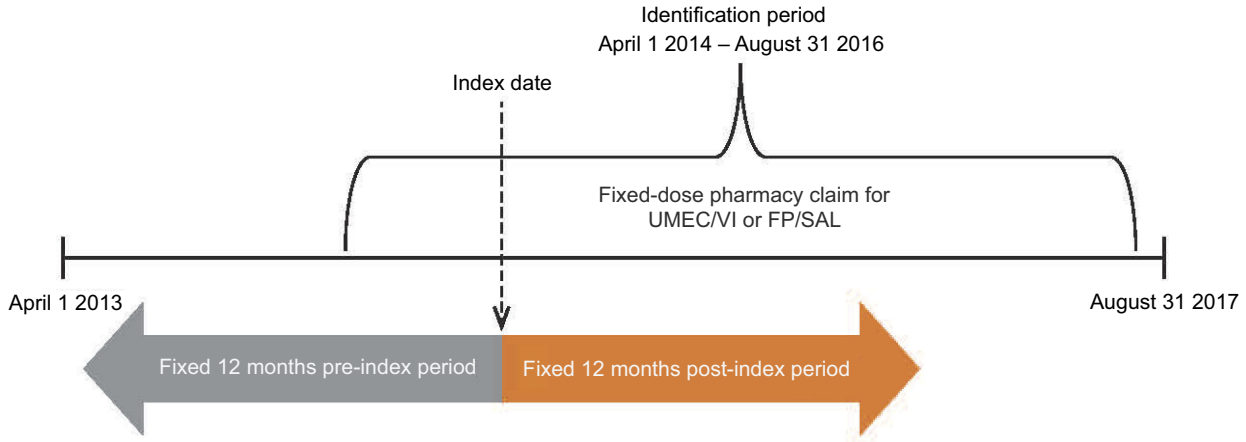

Figure 1 Study design.
Abbreviations: FP/SAL, fluticasone propionate/salmeterol; UMEC/VI, umeclidinium/vilanterol.

Inverse probability of treatment weighting (IPTW) was used to control for possible confounding of the association between the outcomes and index treatment. Weights were estimated using logistic regression with treatment cohort as the outcome and possible predictors of treatment initiation as independent variables (Table S1). The weights for each treatment cohort are the inverse fitted probability of being in that cohort, for a given covariate pattern. Weights were standardized to account for the marginal probability of being in the UMEC/VI and FP/SAL treatment cohorts.

Pre-index characteristics were stratified by treatment cohort and analyzed descriptively prior to and following IPTW. Post-index outcomes were analyzed descriptively and with multivariable modeling on the weighted sample. Adjusted treatment effects were estimated in the weighted sample; 1) without additional covariate adjustment and 2) with additional adjustment for pre-index variables with a post-IPTW standardized difference >10% or a *P*-value ($P<0.05$). The following pre-index variables were included as covariates in the multivariable-adjusted regression models estimating the association between treatment cohort and medication adherence, incidence of first exacerbation, and incidence of multiple-inhaler triple therapy: methylxanthines use, short-acting muscarinic antagonist (SAMA) nebulized use, SAMA/short-acting β_2-agonist (SABA) combination inhaled units (categorized), all-cause inpatient cost (categorized), and all-cause other medical cost (categorized). Medication adherence was modeled using weighted logistic regression with a robust variance estimator. Kaplan–Meier analysis was used to calculate the incidence of first COPD exacerbation and incidence of multiple-inhaler triple therapy. Weighted Cox proportional hazards regression with robust variance estimator was used to model the incidence of first COPD exacerbation and the incidence of multiple-inhaler triple therapy. To test the proportional hazards assumption a proportional hazards test (log[time] with Schoenfeld residuals) was conducted.

Results

Study population

A total of 5306 patients were included in the study population, comprising 1386 initiating UMEC/VI and 3920 initiating FP/SAL (Figure 2). Pre-IPTW differences in patients initiating UMEC/VI versus FP/SAL were observed across multiple variables (Table 1). For instance, UMEC/VI initiators were significantly younger (mean [standard deviation, SD]: 68.5 [10.5] vs 69.5 [10.5] years; $P=0.003$), more likely to be male (54.7% vs 46.4%; $P<0.001$) and were less likely to be enrolled in an MAPD health plan (66.4% vs 75.9%; $P<0.001$). A higher proportion of UMEC/VI initiators had a COPD exacerbation (33.2% vs 30.3%; $P=0.042$) in the pre-index period compared with FP/SAL initiators. Following IPTW, pre-index characteristics were adequately balanced between treatment groups. Indicators of disease severity, including Charlson Comorbidity Score, Chronic Disease Score, COPD Severity Score and the proportion of moderate/severe exacerbations in the pre-index period, were also balanced following IPTW. The variables that were not balanced (methylxanthines use, SAMA nebulized use, SAMA/SABA combination inhaled units (categorized), all-cause inpatient cost (categorized), all-cause other medical cost (categorized)) were included in multivariable-adjusted models for each study endpoint.

Medication adherence

The mean (SD) PDC was significantly higher among the UMEC/VI cohort versus the FP/SAL cohort (UMEC/VI: 0.50 [0.33]; FP/SAL: 0.39 [0.32]; $P<0.001$) during a mean (SD) post-index period of 332 (87) and 311 (109) days for the UMEC/VI and FP/SAL cohorts, respectively (Figure 3A). A significantly higher percentage of patients initiating UMEC/VI had a PDC ≥80% than those initiating FP/SAL (29.1% vs 17.0%, respectively; $P<0.001$) (Figure 3B). The adjusted odds of a PDC ≥80% were 2.00 (95% confidence interval [CI]: 1.62–2.46; $P<0.001$) times greater in patients initiating UMEC/VI compared with FP/SAL.

Incidence of and time to first COPD exacerbation

ITT analysis

In the ITT analysis, the incidence rate of a first moderate/severe COPD exacerbation was 0.105 per 100 patient-days for patients initiating UMEC/VI and 0.121 per 100 patient-days for patients initiating FP/SAL during the 12 months post-index period (IRR 0.87; 95% CI: 0.74–1.02; $P=0.079$). There were no significant differences in the time to first moderate/severe or severe COPD exacerbation between cohorts ($P=0.092$ and $P=0.531$, respectively) (Figure 4A). The multivariable-adjusted HR for a moderate/severe exacerbation in the UMEC/VI versus FP/SAL cohorts was 0.87 (95% CI: 0.74–1.01; $P=0.067$). The incidence rate of a first severe (hospitalized) exacerbation was 0.008 per 100 patient-days and 0.009 per 100 patient-days for the UMEC/VI and FP/SAL cohorts, respectively

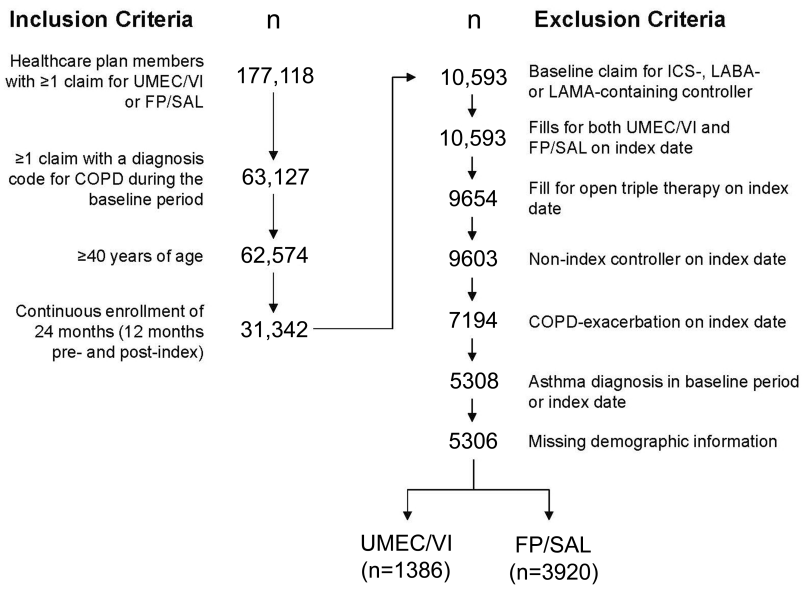

Figure 2 Patient identification and attrition.
Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; FP/SAL, fluticasone propionate/salmeterol; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; UMEC/VI, umeclidinium/vilanterol.

(IRR 0.84; 95% CI: 0.53–1.32; *P*=0.447). The multivariable-adjusted hazard ratio for a severe exacerbation in the UMEC/VI versus FP/SAL cohorts was 0.83 (95% CI: 0.53–1.30; *P*=0.418).

On-treatment sensitivity analysis

In the on-treatment sensitivity analysis of the incidence rate of first COPD exacerbation, the mean (SD) post-index duration of treatment was 102 (96) and 74 (71) days for UMEC/VI and FP/SAL initiators, respectively. The on-treatment incidence rates of a first moderate/severe exacerbation were 0.098 and 0.148 per 100 patient-days for UMEC/VI and FP/SAL cohorts, respectively (IRR 0.66; 95% CI: 0.51–0.85; *P*=0.002) (Figure 4B). The UMEC/VI cohort had a 30% lower adjusted risk of a first moderate/severe COPD exacerbation compared with the FP/SAL cohort (adjusted HR 0.70 [95% CI: 0.54–0.90]; *P*=0.006). The incidence rate of a first severe COPD exacerbation was 0.027 per 100 patient-days for the UMEC/VI cohort and 0.044 per 100 patient-days for the FP/SAL cohort (IRR 0.61; 95% CI: 0.39–0.97; *P*=0.035). However, the risk of a severe exacerbation in the UMEC/VI cohort versus the FP/SAL cohort was similar (adjusted HR 0.65 [95% CI: 0.42–1.02]; *P*=0.063).

Incidence of and time to multiple-inhaler triple therapy

In the ITT analysis, the incidence rate for initiation of multiple-inhaler triple therapy was 0.018 and 0.027 per 100 patient-days in patients initiating UMEC/VI and FP/SAL, respectively (IRR 0.65 [95% CI: 0.47–0.90], *P*=0.010). UMEC/VI initiators had a statistically significant 35% lower adjusted risk of progression to multiple-inhaler triple therapy over the 12-month post-index period compared with FP/SAL initiators (adjusted HR 0.65 [95% CI: 0.47–0.89; *P*=0.008]) (Figure 5).

While the Kaplan–Meier curves for the cohorts do not cross during the 365-day follow-up period (Figure 5), a proportional hazards test (log[time] with Schoenfeld residuals) demonstrated that there was variation over the 365-day post-index period (*P*=0.005). The adjusted rate of triple therapy initiation was found to be significantly lower among the UMEC/VI cohort compared with the FP/SAL cohort during the first 90 days (HR 0.41, 95% CI: 0.25–0.67; *P*≤0.001); this direction continued from days 91–365 but was no longer significant (HR 0.88, 95% CI: 0.58–1.33; *P*=0.539; Table S2). An analysis also was performed with HRs at monthly intervals where the incidence of triple therapy initiation was significantly lower for UMEC/VI compared with FP/SAL in the first, third, and twelfth months. The variability in HR was partly due to low numbers of events within each month (Table S3).

Discussion

In this retrospective observational claims-based study, patients initiating maintenance therapy with UMEC/VI

Table 1 Pre-index patient demographics and clinical characteristics before and after inverse probability of treatment weighting

Demographics	Pre-IPTW				Post-IPTW			
	UMEC/VI (N=1386)	FP/SAL (N=3920)	Standard difference (%)	*P*-value	UMEC/VI (N=1386)	FP/SAL (N=3920)	Standard difference (%)	*P*-value
Age, years, mean (SD)	68.52 (10.48)	69.49 (10.49)	−9.30	0.003	69.47 (10.59)	69.15 (10.53)	3.04	0.497
Male, %	54.69	46.38	16.68	<0.001	49.01	48.50	1.02	0.823
Geographic region, %								
Northeast	14.43	17.70	−8.92	0.005	17.23	16.88	0.95	0.845
Midwest	26.77	31.63	−10.72	<0.001	30.62	30.29	0.72	0.878
South	51.37	41.10	20.72	<0.001	42.28	43.73	−2.93	0.510
West	7.43	9.57	−7.66	0.017	9.86	9.10	2.60	0.620
Insurance type, %								
Commercial	33.62	24.06	21.23	<0.001	26.94	26.76	0.40	0.920
MAPD	66.38	75.94	−21.23	<0.001	73.06	73.24	−0.40	0.920
Charlson comorbidity score								
Mean (SD)	2.16 (1.66)	2.33 (1.78)	−10.07	0.001	2.31 (1.77)	2.30 (1.78)	0.42	0.928
Chronic disease score								
Mean (SD)	5,077.14 (3,743.13)	5,316.92 (3,632.34)	−6.50	0.036	5,358.00 (3,964.69)	5,225.13 (3,620.08)	3.50	0.496
Median	4,272.00	4,636.00			4,596.00	4,596.00		
COPD severity score								
Mean (SD)	23.86 (5.27)	24.04 (5.80)	−3.15	0.301	24.21 (4.97)	23.98 (6.03)	4.06	0.267
Median	23.37	23.31			24.18	23.29		
Moderate/severe COPD exacerbations pre-index, %	33.19	30.26	6.31	0.042	32.83	31.15	3.61	0.409
COPD-related healthcare resource utilization								
Ambulatory visits, %	77.78	63.37	32.02	<0.001	70.35	67.41	6.35	0.197
ED visits, %	8.59	8.01	2.09	0.501	8.62	8.30	1.15	0.781
Inpatient visits, %	6.13	6.96	−3.36	0.289	7.16	6.81	1.37	0.763

(*Continued*)

Table 1 (Continued).

Demographics	Pre-IPTW				Post-IPTW			
	UMEC/VI (N=1386)	**FP/SAL (N=3920)**	**Standard difference (%)**	***P*-value**	**UMEC/VI (N=1386)**	**FP/SAL (N=3920)**	**Standard difference (%)**	***P*-value**
Medical costs ($), mean (SD)	1,301.96 (5,387.25)	1,965.51 (9,398.59)	−8.66	0.001	1,466.79 (5,806.35)	1,950.14 (9,434.29)	−6.17	0.114
All-cause healthcare costs, mean (SD)	16,195.32 (26,647.25)	18,232.19 (32,821.94)	−6.81	0.022	16,556.59 (25,056.32)	18,130.01 (33,271.90)	−5.34	0.128
COPD medications, %								
Systemic corticosteroids	48.56	47.88	1.35	0.666	47.63	48.06	−0.87	0.849
SAMA	2.09	2.93	−5.38	0.098	2.55	2.87	−2.02	0.645
SABA	49.13	54.52	−10.79	<0.001	54.00	53.37	1.27	0.780
SAMA/SABA combination	13.85	17.02	−8.76	0.006	17.04	16.21	2.21	0.662

Abbreviations: CDS, chronic disease score; COPD, chronic obstructive pulmonary disease; ED, emergency department; FP/SAL, fluticasone propionate/salmeterol; IPTW, inverse probability of treatment weighting; MAPD, Medicare advantage plan D; SD, standard deviation; PDE-4, phosphodiesterase-4; SABA, short-acting β_2-antagonist; SAMA, short-acting muscarinic antagonist; UMEC/VI, umeclidinium/vilanterol.

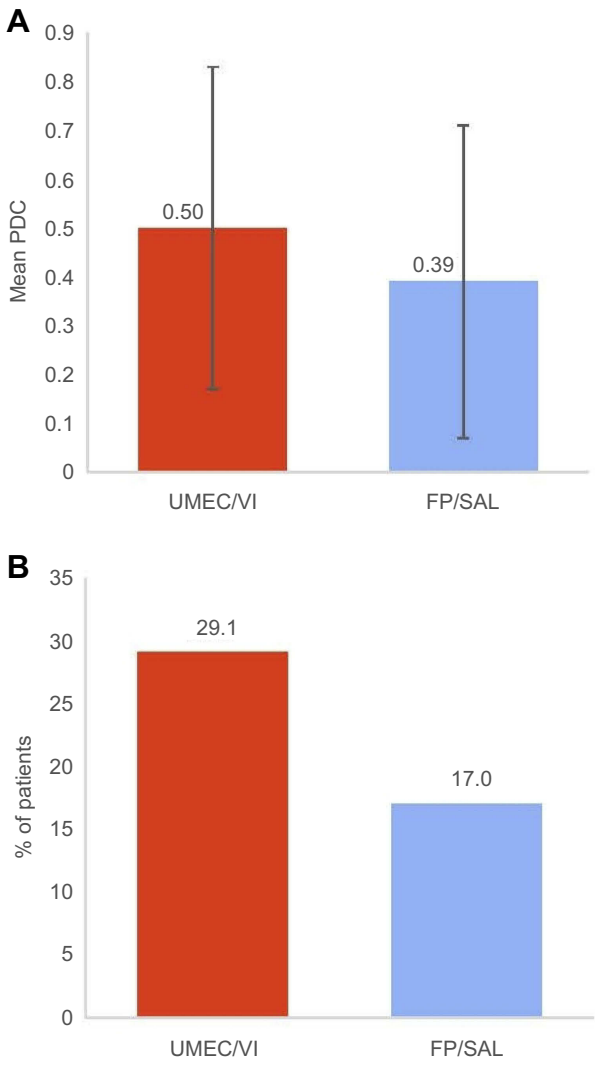

Figure 3 Medication adherence. (**A**) Mean PDC. (**B**) Percentage of patients achieving PDC≥80.
Note: Error bars indicate the standard deviation.
Abbreviations: FP/SAL, fluticasone propionate/salmeterol; PDC, proportion of days covered; UMEC/VI, umeclidinium/vilanterol.

had significantly greater medication adherence and slower escalation to multiple-inhaler triple therapy compared with patients initiating FP/SAL, and a reduced rate of moderate/severe exacerbations in the on-treatment sensitivity analysis. Recent clinical evidence suggests that the LAMA/LABA medication class improves lung function and protects against exacerbations in low-risk patients compared with ICS/LABA as maintenance therapy in patients diagnosed with COPD with or without a history of exacerbations.[8–11,19,20] However, studies focusing on the relative effectiveness of LAMA/LABA and ICS/LABA using real-world data have been scarce, with the limited data available arising from patients that were switched from twice-daily ICS/LABA to LAMA/LABA.[21]

This study presents the first analysis of LAMA/LABA medication adherence in a US population. The need to improve medication adherence in patients diagnosed with COPD has been previously acknowledged, with COPD known to have a particularly low rate of adherence across medical conditions, potentially due to improper inhaler use and the complexity of medication regimens.[22,23] Medication adherence has also been associated with dosing frequency in a retrospective study that compared real-world use of inhaled medications for patients with COPD, which reported a consistent trend of declining PDC as the frequency of dosing increased; the PDC for once-daily, twice-daily, 3 times daily, and 4 times daily was 43.3%, 37.0%, 30.2%, and 23.0%, respectively.[24] A retrospective claims data analysis compared medication adherence in patients with COPD initiating therapy on the once-daily LABA tiotropium or twice-daily FP/SAL and examined the association between adherence and respiratory-related costs and found good adherence was associated with 37.1% lower medical costs and 53.4% lower inpatient costs than poor adherence.[25] Moreover, a retrospective cross-sectional analysis that investigated the association of COPD maintenance medication adherence with hospitalization and Medicare spending in the US found that patients with good adherence (PDC ≥80%) exhibited 10% lower hospitalization rates and lower total Medicare spending (-$2,185) than patients with poor adherence (PDC <80%; after adjusting for covariates).[26]

In this study, there were no significant differences in the risk of a moderate/severe or severe COPD exacerbation between treatment groups in the ITT analyses; however, in the on-treatment sensitivity analysis patients initiating UMEC/VI had a significantly reduced risk of a first moderate/severe exacerbation compared with patients initiating FP/SAL. These results are consistent with a randomized, retrospective analysis that evaluated the impact of adherence to inhaled medication (including FP/SAL) in patients with COPD for 3 years and found a 44% lower rate of COPD exacerbations requiring hospital admission in patients with good versus poor adherence.[27] The evidence therefore suggests that remaining on treatment is key to reducing the risk of a first moderate/severe COPD exacerbation, which should be emphasized by providers to patients, since the GOLD strategy document outlines LAMA/LABA use as IMT for patients with a low risk of exacerbations but experiencing dyspnea symptoms.[27] The reduced rate of exacerbations in patients taking UMEC/VI versus FP/SAL may have been partly

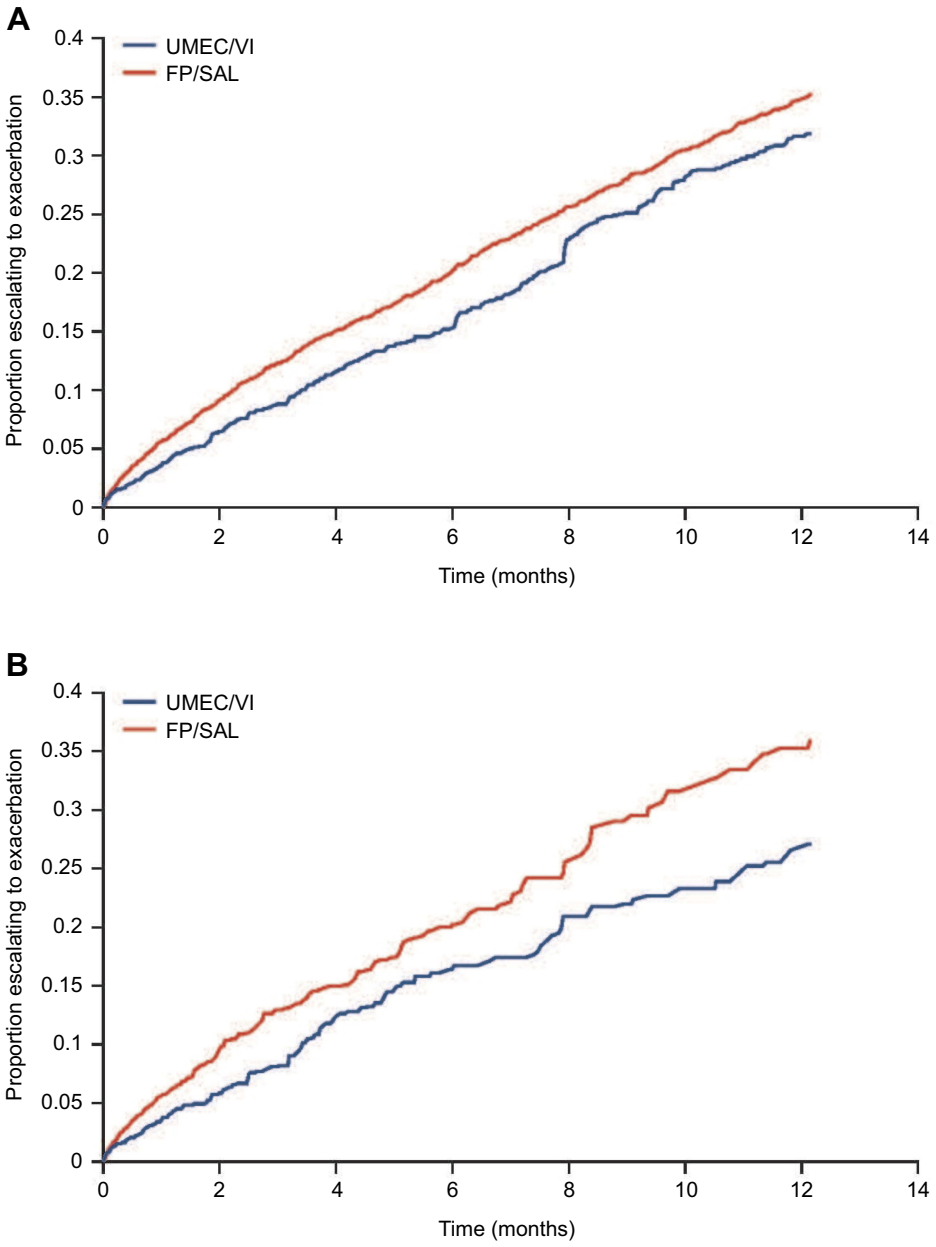

Figure 4 Kaplan–Meier curves for incidence of moderate/severe exacerbations. (**A**) Intent-to-treat analysis. (**B**) On-treatment sensitivity analysis.
Abbreviations: FP/SAL, fluticasone propionate/salmeterol; UMEC/VI, umeclidinium/vilanterol.

due to the reduction of symptoms in these patients, as symptom severity and exacerbation frequency are known to positively correlate.[28] Unfortunately, as this was a claims-based study, patient-reported outcomes could not be used to assess impacts on symptoms, meaning that this relationship could not be directly explored.

Escalation in therapy to multiple-inhaler triple therapy has been examined previously in retrospective observational studies that used administrative medical and pharmacy retrospective claims-data medical and pharmacy data. One such study reported that patients diagnosed with COPD receiving UMEC/VI had a slower rate of escalation to multiple-inhaler triple therapy than those receiving tiotropium alone.[30] This correlates with the results of this study, where patients initiating dual bronchodilator LAMA/LABA escalated to multiple-inhaler triple therapy at a slower rate than patients receiving mono bronchodilator ICS/LABA. This difference in the rate of escalation to multiple-inhaler triple therapy was seen only in the first 90 days of the post-index period. This highlights that the difference in escalation to multiple-inhaler triple therapy could be due to a more appropriate choice of

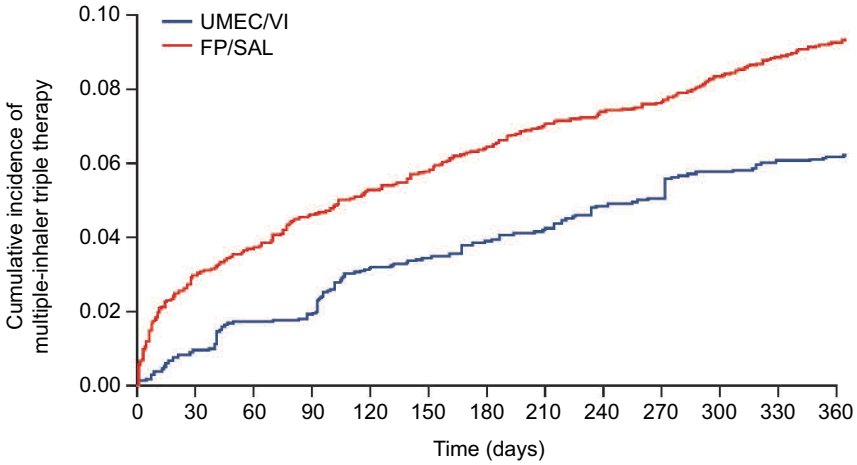

Figure 5 Kaplan–Meier curve for incidence of multiple-inhaler triple therapy.
Abbreviations: FP/SAL, fluticasone propionate/salmeterol; UMEC/VI, umeclidinium/vilanterol.

treatment for symptomatic patients or a better delivery device leading to improved drug adherence with UMEC/VI versus FP/SAL.

The findings from this study support and are consistent with results from randomized controlled trials (RCTs).[10–12,19] Two recent meta-analyses including data from 10 RCTs have shown that LAMA/LABA therapy demonstrates significant improvements in lung function, reduced exacerbation risk and rescue medication use and a lower risk of pneumonia relative to ICS/LABA.[8,9] Specifically, UMEC/VI has demonstrated significant and clinically meaningful improvements in lung function versus FP/SAL in patients diagnosed with stable COPD.[10] Furthermore, the relative risk of COPD exacerbations has been previously reported to be reduced in patients taking LAMA/LABA versus those on twice-daily ICS/LABA.[12,19] The LANTERN study found that patients receiving the LAMA/LABA indacaterol-glycopyrronium had a longer time-to-first exacerbation than those taking FP/SAL in a population at low risk of exacerbations.[19] Together, the results from RCTs and retrospective observational studies provide support for initiating maintenance therapy with LAMA/LABA rather than ICS/LABA in patients with low exacerbation risk, per the GOLD guidelines. UMEC/VI use appears to be associated with greater effectiveness on-treatment, combined with slightly greater levels of adherence compared with the more commonly chosen ICS/LABA IMT options used by physicians.[14–17] However, maintenance therapy with an ICS component has been demonstrated to improve patient outcomes in certain subpopulations of patients with COPD, such as those with a high symptom burden or high risk of exacerbations.[4–7]

Limitations of this study include those frequently associated with claims studies. For instance, the presence of a COPD diagnosis code in the claims does not necessarily mean that the patient has COPD[31] and the underlying reasons for patient progression to MITT are unknown. Furthermore, medication use was based on observed pharmacy dispensing and was not a direct measure of drug taking. Similarly, it is possible that the improved adherence of the UMEC/VI cohort compared with the FP/SAL cohort may be due to the once-daily dose schedule of UMEC/VI versus the twice-daily dose schedule of FP/SAL. It must also be noted that adherence in both cohorts was low (UMEC/VI: 50%; FP/SAL: 39%). In addition, whereas the progression to MITT from FP/SAL only requires the addition of a LAMA component, switching from UMEC/VI to MITT may be more difficult as there are no ICS monotherapy treatments approved for use in COPD. However, our study defined MITT as any combination of LAMA, LABA, and ICS used concurrently to capture real-world patterns of care. It is also possible that the lack of randomization to treatment could have introduced confounding in this analysis; however, IPTW was used to control for confounding, and multivariable modeling used to further adjust for remaining imbalances. The presented findings may also have been affected by a potential survivor bias arising from the requirement of patients to have been continuously enrolled for at least 12 months following the initiation of treatment, potentially

excluding patients diagnosed with severe or advanced COPD that may not have survived. Furthermore, the on-treatment analyses may have excluded patients that later resumed their index medication. Similarly, some patients may have been censored that were taking their index medication but were not taking this as prescribed, possibly due to rescue medication use. If a longer discontinuation gap of 60 days had been used instead of 45 days, fewer patients may have been censored.

Conclusion

This retrospective observational claims-based real-world study found that initiators of UMEC/VI had significantly better adherence to their medication and were less likely to escalate to multiple-inhaler triple therapy than FP/SAL initiators. In the ITT primary analysis, patients initiating UMEC/VI had a similar incidence rate of moderate/severe exacerbation compared with FP/SAL; however, UMEC/VI initiators had a lower rate of moderate/severe exacerbation compared with FP/SAL initiators in the on-treatment sensitivity analysis. Together, these data suggest that, compared with FP/SAL, initiating maintenance therapy with UMEC/VI may have a positive impact on patient outcomes.

Abbreviations

AHRQ, Agency for Healthcare Research and Quality; CDS, chronic disease score; COPD, chronic obstructive pulmonary disease; CI, confidence interval; CTR, COPD treatment ratio; ED, emergency department; FP/SAL, fluticasone propionate/salmeterol; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; ICS, inhaled corticosteroids; IMT, initial maintenance therapy; IPTW, Inverse probability of treatment weighting; IRR, incidence rate ratios; ITT, intent-to-treat; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MAPD, Medicare Advantage with Part D; OCS, oral corticosteroid; ORD, Optum Research Database; PDC, proportion of days covered; PDE-4, phosphodiesterase-4; RCT, randomized controlled trial; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation; UMEC/VI, umeclidinium/vilanterol.

Data sharing statement

Information on GSK's data sharing commitments and requesting access to anonymized individual participant data and associated documents from GSK sponsored studies can be found at www.clinicalstudydatarequest.com. The data reported in this publication are contained in a database owned by Optum and contains proprietary elements. Therefore, it cannot be broadly disclosed or made publicly available at this time. The disclosure of this data to third-party clients assumes certain data security and privacy protocols are in place and that the third-party client has executed Optum's standard license agreement which includes restrictive covenants governing the use of the data.

Ethics approval and informed consent

This study utilized de-identified retrospective claims data, and as such, this study does not require institutional review board review and approval or informed consent procedures. This study is in scope for GlaxoSmithKline (GSK)'s policy 408 for reporting and disclosure.

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Author contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval for the version to be published. All authors take complete responsibility for the integrity of the data and accuracy of the data analysis. CM, BH, RHS and RR were involved in the conception/design of the study and analysis/interpretation of data. LGSB and LS were involved

in the conception/design of the study, acquisition of data and analysis/interpretation of data. EK, LL, and JT were involved in acquisition of data and analysis/interpretation of data.

Disclosure

CM, BH, RR, and RHS are employees of GSK and hold stocks/shares in GSK. LGSB, EK, LL, and JT are employees of Optum and LS was an employee of Optum at the time of the study, which was contracted by GSK to conduct the study. Employees of Optum were not paid for manuscript development. The authors report no other conflicts of interest in this work.

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Supplementary materials

Table S1 Variables included in inverse probability of treatment weighting model

Variable category	Variable
Demographics	Index month/year (categorical) Age in years (categorical) Gender Region Health plan type Business line (commercial or MAPD) Pharmacy plan type: Enhanced alternative, Employer group
Clinical characteristics and comorbidities	COPD severity score Charlson comorbidity index (categorical) AHRQ-defined comorbidities • Hypertension • Other lower respiratory disease • Disorders of lipid metabolism • Diseases of the heart • Diseases of the urinary system • Other connectivity tissue disease • Non-traumatic joint disorder • Respiratory infection • Screening and history of mental health and substance abuse
COPD exacerbation	COPD exacerbation (moderate/severe) Severe COPD exacerbation
Respiratory medication use	SAMA units (categorical) SAMA/SABA inhaled units (categorical) Count of SABA fills (categorical) CTR (categorical) CTR non-missing flag Methylxanthines use SAMA/SABA use Index fill ≥90-day fill OCS use
All-cause and COPD-related healthcare utilization and costs	All-cause ambulatory count (categorical) All-cause inpatient count (categorical) All-cause medical costs (categorical) COPD-related ambulatory cost (categorical) Index prescription patient-paid costs (categorical) COPD-related inpatient stay

Abbreviations: AHRQ, agency for healthcare research and quality; COPD, chronic obstructive pulmonary disease; CTR, COPD treatment ratio; MAPD, medicare advantage Part D; OCS, oral corticosteroids; SABA, short-acting β_2-antagonist; SAMA, short-acting muscarinic agonist.

Table S2 Post-inverse probability of treatment weighting post-index time to first occurrence of multiple-inhaler triple therapy (intent-to-treat) – proportional hazard model, first 90 days and 91—365 days

Independent variables	Hazard ratio (95% CI)	*P*-value
UMEC/VI vs FP/SAL over time		
First 90 days	0.408 (0.247, 0.674)	<0.001
91—365 days	0.878 (0.580, 1.329)	0.539
Baseline medication units		
Methylxanthines units	1.093 (0.362, 3.304)	0.874
SAMA nebulized units	0.526 (0.167, 1.662)	0.274
SAMA/SABA combination inhaled units		
1	reference	–
2—5	1.109 (0.438, 2.808)	0.828
6—10	1.805 (0.399, 8.163)	0.443
10+	2.106 (0.631, 7.027)	0.226
0	1.155 (0.563, 2.371)	0.694
All cause inpatient costs, %		
≤50	reference	–
>50–≤75	1.381 (0.430, 4.436)	0.587
>75	1.239 (0.975, 1.574)	0.080
All cause other medical costs, %		
≤25	reference	–
>25–≤50	1.009 (0.750, 1.359)	0.950
>50–≤75	1.111 (0.809, 1.527)	0.514
>75	1.152 (0.867, 1.530)	0.331

Abbreviations: CI, confidence interval; FP/SAL, fluticasone propionate/salmeterol; SABA, short-acting β_2-antagonist; SAMA, short-acting muscarinic-antagonist; UMEC/VI, umeclidinium/vilanterol.

Table S3 Secondary outcome: post-inverse probability of treatment weighting post-index time to first occurrence of multiple-inhaler triple therapy (intent-to-treat) – proportional hazard model, monthly time increments

Independent variables	Hazard ratio (95% CI)	*P*-value
UMEC/VI vs FP/SAL over time, days		
1–30	0.314 (0.188, 0.521)	<0.001
31–60	1.020 (0.346, 3.003)	0.971
61–90	0.222 (0.057, 0.861)	0.030
91–120	1.859 (0.858, 4.028)	0.116
121–150	0.493 (0.177, 1.372)	0.176
151–180	0.669 (0.200, 2.233)	0.513
181–210	0.509 (0.186, 1.397)	0.190
211–240	1.737 (0.638, 4.735)	0.280
241–270	0.772 (0.221, 2.693)	0.684
271–300	1.027 (0.219, 4.812)	0.973
301–330	0.550 (0.189, 1.602)	0.273
331–365	0.274 (0.090, 0.830)	0.022
Baseline medication units		
Methylxanthines units	1.093 (0.362, 3.302)	0.874
SAMA nebulized units	0.526 (0.167, 1.662)	0.274
SAMA/SABA combination inhaled units		
1	reference	–
2—5	1.108 (0.438, 2.807)	0.828
6—10	1.806 (0.398, 8.194)	0.444
10+	2.105 (0.632, 7.015)	0.226
0	1.155 (0.563, 2.371)	0.694
All cause inpatient costs, %		
≤50	reference	–
>50–≤75	1.383 (0.430, 4.449)	0.586
>75	1.238 (0.975, 1.574)	0.080
All-cause other medical costs		
0%≤ Other medical cost ≤ 25%	reference	–
25%< Other medical cost ≤ 50%	1.010 (0.750, 1.359)	0.950
50%< Other medical cost ≤ 75%	1.112 (0.809, 1.527)	0.514
75%< Other medical cost	1.152 (0.867, 1.530)	0.330

Abbreviations: CI, confidence interval; FP/SAL, fluticasone propionate/salmeterol; SABA, short-acting beta antagonist; SAMA, short-acting muscarinic-antagonist; UMEC/VI, umeclidinium/vilanterol.