Evaluation of Time-to-First COPD Exacerbation in Patients Diagnosed With COPD Initiating Maintenance Therapy With Inhaled Fixed-Dose Combinations of LAMA/LABA or ICS/LABA Within a Large US Health Insurer Database

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Background

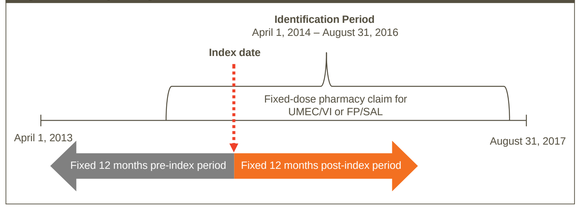
- Inhaled corticosteroid (ICS) with long-acting β_2-agonist (LABA) combination therapies are commonly prescribed across all Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity groups.[1-3]
  - Current 2019 GOLD guidelines only recommend ICS/LABA as initial maintenance therapy for GOLD group D patients with high levels of blood eosinophils (≥300 μL).[4]
  - Long-acting muscarinic antagonist (LAMA)/LABAs are recommended as initial maintenance therapy for highly symptomatic GOLD group B and GOLD group D patients.[4]
- Recent data from randomized controlled trials suggest that a LAMA/LABA combination therapy can significantly improve lung function and reduce exacerbation rates compared with ICS/LABA.[5,6]
- Exacerbation rates in patients with chronic obstructive pulmonary disease (COPD) initiating LAMA/LABA versus ICS/LABA have not previously been compared using real-world data.
- This real-world study compared the use of the LAMA/LABA umeclidinium/vilanterol (UMEC/VI; 62.5/25 mcg) and the ICS/LABA fluticasone propionate/salmeterol (FP/SAL; 250/50 mcg) as initial maintenance therapy in patients diagnosed with COPD.
- The primary objective of the study (previously published) was to evaluate medication adherence, measured by proportion of days covered.[7]
- A secondary objective (the focus of this poster) was to evaluate the time-to-first COPD exacerbation among patients initiating UMEC/VI versus FP/SAL.

Methods

Study design

- A retrospective observational study in a population diagnosed with COPD enrolled in either commercial or Medicare Advantage with Part D (MAPD) health plans. Data from the Optum Research Database were utilized for this study.
- Patients aged ≥40 years who initiated once-daily UMEC/VI (62.5/25 mcg) or twice-daily FP/SAL (250/50 mcg) between April 1, 2014 and August 31, 2016 were identified. The index date was the first fill date for UMEC/VI or FP/SAL (**Figure 1**).

Figure 1. Study design



- Patients had 12 months of pre- and post-index continuous enrollment and at least one medical claim containing a COPD diagnosis code in any position during the pre-index period.
- Exclusion criteria included an asthma diagnosis in the pre-index period or on the index date; ICS-, LABA-, LAMA-containing therapy during the pre-index period; missing demographic information; or pharmacy fills for both UMEC/VI and FP/SAL, multiple-inhaler triple therapy, a non-index therapy, or a COPD exacerbation on the index date.
- Exacerbations were defined as moderate (an outpatient or emergency department visit with a primary diagnosis of COPD and a COPD-guideline recommended antibiotic or systemic corticosteroid within ±5 days of each other) or severe (hospitalization with a primary diagnosis of COPD).
- Time-to-first moderate/severe exacerbation was evaluated in intent-to-treat (ITT) and on-treatment (sensitivity) analyses. For the on-treatment analysis, patients were censored at the time of discontinuation, at the time of a pharmacy fill for a non-index controller medication, or the end of the 12-month post-index period, whichever occurred first.

Statistical analysis

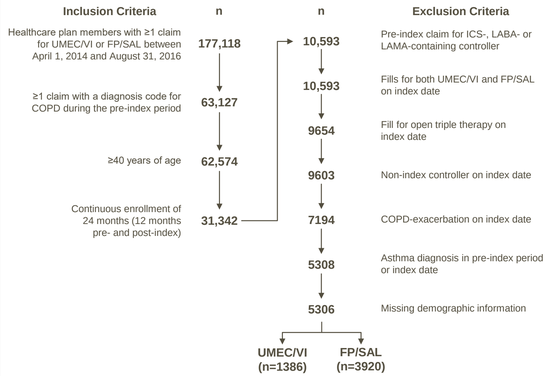
- Inverse probability of treatment weighting (IPTW) of pre-index characteristics was used to control for possible confounding of the association between study outcomes and index treatment.
- Kaplan–Meier and weighted Cox proportional hazards regression was performed to model the incidence of a first COPD exacerbation. Variables that were not balanced following IPTW (standardized difference >0.10 or *P*-value <0.05) were included in the multivariable adjusted model.

Results

Study population

- A total of 1386 and 3920 UMEC/VI and FP/SAL initiators, respectively, met all study selection criteria (**Figure 2**).

Figure 2. Patient identification and attrition



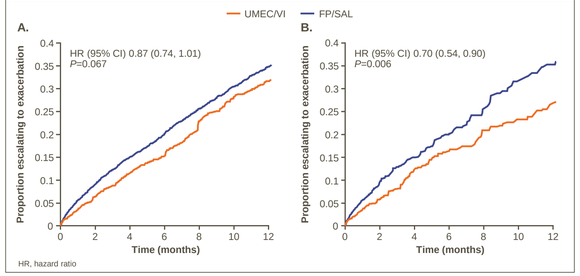
- Following IPTW, most pre-index characteristics were adequately balanced between treatment groups (**Table 1**), although some variables remained unbalanced (methylxanthines use, short-acting muscarinic antagonist [SAMA] nebulized use, SAMA/short-acting β_2-agonist [SABA] combination inhaled units [categorized], all-cause inpatient costs [categorized] and all-cause other medical costs [categorized]).
- The post-IPTW mean (standard deviation [SD]) age was 69.2 (10.6) years, 51.4% were female, and 73.2% were MAPD enrollees. Approximately a third of patients experienced a COPD exacerbation in the pre-index period.

Table 1. Demographics and pre-index clinical characteristics pre-and post-IPTW

Demographics	Pre-IPTW				Post-IPTW			
	UMEC/VI (N=1386)	FP/SAL (N=3920)	Std. diff. (%)	*P*-value	UMEC/VI (N=1386)	FP/SAL (N=3920)	Std. diff. (%)	*P*-value
Age, 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
Female, %	45.31	53.62	−16.68	<0.001	50.99	51.50	−1.02	0.823
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
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
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)	5077.14 (3743.13)	5316.92 (3632.34)	−6.50	0.036	5358.00 (3964.69)	5225.13 (3620.08)	3.50	0.496
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
Count of COPD exacerbations, mean (SD)	0.47 (0.80)	0.41 (0.76)	6.95	0.028	0.46 (0.78)	0.43 (0.77)	4.61	0.281
≥1 moderate/severe COPD exacerbation, %	33.19	30.26	6.31	0.042	32.83	31.15	3.61	0.409
≥1 moderate COPD exacerbation, %	27.49	23.75	8.57	0.006	27.05	24.73	5.30	0.222
≥1 severe COPD exacerbation, %	8.37	8.62	−0.91	0.772	9.25	8.63	2.17	0.621
COPD medication in pre-index period								
SABA, %	49.13	54.52	−10.79	<0.001	54.00	53.37	1.27	0.780
Systemic corticosteroids, %	48.56	47.88	1.35	0.666	47.63	48.06	−0.87	0.849
COPD-related healthcare resource utilization and costs								
Total medical costs ($), mean (SD)	1302 (5387)	1966 (9399)	−8.66	0.001	1467 (5806)	1950 (9434)	−6.17	0.114
Inpatient costs ($), mean (SD)	916 (5182)	1597 (9136)	−9.17	<0.001	1107 (5566)	1538 (9173)	−5.67	0.141
Ambulatory visits, %	77.78	63.37	32.02	<0.001	70.35	67.41	6.35	0.197
ER visits, %	8.59	8.01	2.09	0.501	8.62	8.30	1.15	0.781
Inpatient stays, %	6.13	6.96	−3.36	0.289	7.16	6.81	1.37	0.763

ER, emergency room; Std. diff., standard difference

Figure 3. Kaplan–Meier and weighted Cox proportional hazards regression of time-to-first moderate/severe COPD exacerbation in the UMEC/VI and FP/SAL cohorts. (A) ITT and (B) on-treatment sensitivity analyses



HR, hazard ratio

Incidence of first ITT exacerbation

- In the ITT analysis, the incidence rate for a moderate/severe exacerbation per 100 person-days was 0.105 for UMEC/VI and 0.121 for FP/SAL.
  - The adjusted hazard ratio (HR) of a moderate/severe exacerbation in the UMEC/VI cohort was 0.87 (95% confidence interval [CI]: 0.74, 1.01; *P*=0.067) compared with the FP/SAL cohort, which was directionally in favor of UMEC/VI but not statistically significant (**Figure 3A**).
- The incidence rate for a severe COPD exacerbation per 100 person-days was 0.008 for UMEC/VI and 0.009 for FP/SAL.

Incidence of first on-treatment exacerbation (sensitivity analysis)

- In the on-treatment sensitivity analysis, the mean (SD) post-index duration of treatment was 102 (96) and 74 (71) days for UMEC/VI and FP/SAL initiators, respectively.
- The incidence rate for a moderate/severe exacerbation per 100 person-days was 0.098 for UMEC/VI and 0.148 for FP/SAL.
  - The on-treatment adjusted HR was 0.70 (95% CI: 0.54, 0.90; *P*=0.006); the UMEC/VI cohort had a significant 30% reduced risk of having a first moderate/severe exacerbation compared with the FP/SAL cohort (**Figure 3B**).
- The incidence rate for a severe COPD exacerbation per 100 person-days was 0.027 for UMEC/VI and 0.044 for FP/SAL.
  - The on-treatment adjusted HR for a severe COPD exacerbation in the UMEC/VI cohort was 0.65 (95% CI: 0.42, 1.02; *P*=0.063) compared with the FP/SAL cohort, which was directionally in favor of UMEC/VI but not statistically significant.

Limitations

- Limitations of this study include those frequently associated with claims studies, such as the reliance on diagnosis codes, and a potential survivor bias resulting from the requirement for patients to have been enrolled for 12 months post index.

Conclusions

- This real-world study found that patients with COPD who initiated treatment with UMEC/VI versus FP/SAL had a numerically lower risk of a first exacerbation. Patients who remained on-treatment had a significant 30% reduced risk of a first exacerbation with UMEC/VI versus FP/SAL.
- These findings may support the use of LAMA/LABA as a first-line therapy in symptomatic patients.

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Disclosures

- CM, BH, RR, and RHS are employees of GlaxoSmithKline (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.

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