Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Stiolto Respimat			
Name of active ingredient: Tiotropium bromide/olodaterol			
Report date: 14 September 2022	**Study number:** 1237-0113	**Version/Revision:** 2.0	**Version/Revision date:** 14 September 2022
Title of study:	Health Care Resource Utilization, Cost and Other Outcomes of Patients Diagnosed with COPD Initiating Tiotropium Bromide/Olodaterol vs. Fluticasone Furoate/Umeclidinium/Vilanterol		
Keywords:	COPD; COPD exacerbation; LAMA/LABA; Triple therapy; healthcare resource utilization and costs; pneumonia		
Rationale and background:	The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 report recommends dual therapy with long-acting muscarinic antagonists (LAMAs) plus long-acting beta$_2$ agonists (LABAs) for patients with chronic obstructive pulmonary disease (COPD) who have persistent symptoms and/or exacerbations on LAMA or LABA monotherapy. Consideration of escalation to triple therapy (TT; LAMA+LABA+inhaled corticosteroids [ICS]) is recommended in case of further exacerbation and after assessing the risks/benefits, including the increased risk of pneumonia with ICS treatment. A blood eosinophil count >300 cells/µL and exacerbation history together can be used to identify patients with the greatest likelihood of treatment benefit with ICS. Despite these recommendations, evidence suggests TT is not prescribed according to guidelines across all COPD severities, including those at low exacerbation risk. This deviation from GOLD recommendations may have economic and clinical consequences. Following the approval of FF/UMEC/VI FDC TT in late 2017 for the long-term maintenance treatment of COPD, this study attempts to fill the existing real-world evidence gap by comparing tiotropium bromide/olodaterol (TIO/OLO) vs. fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI). We aim to understand the clinical and economic implications of prescribing FDC TT vs. TIO/OLO in clinical practice.		
Research question and objectives:	The purpose of this study was to estimate disease-related and all-cause burden and clinical outcomes of interest following initiation of COPD maintenance therapy with TIO/OLO or FF/UMEC/VI.		

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The specific primary objectives for this project were:

- To compare disease related and all-cause HCRU among patients newly treated with TIO/OLO compared with patients newly treated with FF/UMEC/VI
- To compare disease-related and all-cause medical and total (medical & pharmacy) health care costs among patients newly treated with TIO/OLO compared with patients newly treated with FF/UMEC/VI
- To compare pneumonia outcomes among patients newly treated with TIO/OLO compared with patients newly treated with FF/UMEC/VI
- To compare COPD exacerbations following initiation of TIO/OLO or FF/UMEC/VI

The specific secondary objective for this project is:

- To compare 30-day all-cause hospital readmissions following initiation of TIO/OLO or FF/UMEC/VI

The study objectives were assessed within each of the following populations of TIO/OLO and FF/UMEC/VI initiators:

- Overall population of initiators (i.e., initiators who met study selection criteria)
- Maintenance naïve (patients with no baseline maintenance medication [no free or fixed dose combination (FDC) LAMA, LABA, or ICS])
- No exacerbation (patients with no baseline exacerbation)
- No exacerbation or 1 exacerbation not leading to hospitalization (i.e., baseline GOLD A/B)
- ≥2 exacerbations not leading to hospitalization or ≥1 exacerbation leading to hospitalization [i.e., baseline GOLD C/D])

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	Additionally, HCRU, costs, COPD exacerbations, and pneumonia outcomes following initiation of TIO/OLO or FF/UMEC/VI were assessed among subgroups of patients with ≥1 eosinophil lab in the following groups: • Baseline blood eosinophil count ≤300 cells/µL • Baseline blood eosinophil count >300 cells/µL		
Study design:	This was a non-interventional study using existing data from commercial enrollees and Medicare Advantage with Part D beneficiaries diagnosed with COPD who initiated treatment with TIO/OLO or FF/UMEC/VI. The study period was from 01 June 2014 through 31 December 2019. Stratified propensity score matching (PSM), using an exact match on some variables and a propensity score match on the others, were used to control for possible confounding of the association between the outcomes (e.g., health care resource utilization) and treatment with TIO/OLO or FF/UMEC/VI. Descriptive analyses were performed before and after propensity score matching. Following the matching procedure, descriptive and multivariable analyses were performed.		
Setting:	COPD patients initiating treatment with TIO/OLO or FF/UMEC/VI between 15 June 2015 through 30 November 2019 were eligible for inclusion in the study. Study periods were defined as follows: • **Baseline period:** The 12 months prior to and including the index date (index date–364 through index date) was used to assess baseline patient and clinical characteristics. The index pharmacy claims were excluded from the baseline period and included in the follow-up period. • **Follow-up period:** The variable period starting on the day after the index date, with a minimum of 30-days duration (index date+1 through index date+30) up to a maximum of 12 months duration (index date+1 through index date+365) was used to assess HCRU, costs, exacerbation and pneumonia outcomes.		

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	Patients were censored at the earliest of the following: discontinuation of the index medication, switch to a non-index regimen, disenrollment from the health plan, 12-months following the index date, or the end of the study period.
Subjects and study size, including dropouts:	All patients in the [redacted] Database meeting the study selection criteria were included in this study. Overall 16,338 patients met the study selection criteria and were included in the study population. Approximately 40% of the study population initiated TIO/OLO (n=6,681) and 60% initiated FF/UMEC/VI (n=9,657). The number of TIO/OLO and FF/UMEC/VI initiators before and after matching in each of the populations of interest is noted below.

	Pre-match		Post-match	
Study Population	**TIO/OLO**	**FF/UMEC/VI**	**TIO/OLO**	**FF/UMEC/VI**
Maintenance Naïve	3928	4168	3025	3025
GOLD A/B	4838	5730	3884	3884
GOLD C/D	1843	3927	1774	1774
No Baseline Exacerbation	3369	3453	2552	2552
Overall	6681	9657	5658	5658

In the overall study population 3,867 patients had ⩾1 EOS lab result in the six months prior to the index date through 15 days after the index date; of these, 81.9% (N=3,168) had an eosinophil count ⩽300 cells/µL, and 18.1% (N=699) had an eosinophil count >300 cells/µL. Among the EOS >300 cells/µL subgroup there were 277 TIO/OLO and 422 FF/UMEC/VI pre-match initiators and 202 matched pairs. Among the EOS ⩽300 cells/µL subgroup there were 1,372 TIO/OLO and 1,796 FF/UMEC/VI pre-match initiators and 1,098 matched pairs.

Variables and data sources:	**Data source:** The [redacted] Database, a fully de-identified and HIPAA compliant claims database that comprises medical and pharmacy claims data (including linked enrollment) from 1993-present. **Exposure:** Initiation with TIO/OLO or FF/UMEC/VI

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	Outcomes: All-cause and disease-related health care resource utilization, COPD or pneumonia-attributable health care resource utilization; all-cause and disease-related health care costs; COPD or pneumonia-attributable health care costs; COPD exacerbation, pneumonia diagnosis, pneumonia-related hospitalization, COPD exacerbation and/or pneumonia diagnosis, 30-day all-cause hospital readmission following COPD-related hospitalization discharge. **Clinical and demographic covariates:** Quan-Charlson comorbidity score; Elixhauser score; COPD Severity Score; comorbid conditions; oxygen therapy; baseline respiratory medications; index provider specialty; pulmonologist visit within 30 days of index date; spirometry testing; early adopter of index medication; evidence of tobacco use; index year; seasonality; age; gender; race/ethnicity; insurance type; plan type; geographic region; resource scarce area.		
Results:	Balance between TIO/OLO and FF/UMEC/VI cohorts improved considerably after matching for all populations except the EOS >300 cells/µL subgroup, which varied from other populations in having small patient counts. Substantial imbalances between cohorts that remained after matching in the EOS >300 cells/µL subgroup included but were not limited to the following baseline measures: age group, gender, index year, provider specialty, select baseline comorbidities, rescue medication use, all-cause utilization, COPD or pneumonia-attributable utilization/costs, and reason for end of index treatment. <u>Primary objectives</u> Follow-up all-cause health care resource utilization was generally similar between the TIO/OLO and FF/UMEC/VI cohorts. The population annualized count of pharmacy fills was significantly greater for the TIO/OLO cohort in the overall (59.4 vs 57.1, p=0.021), maintenance naïve (60.4 vs 57.2, p=0.017), and GOLD C/D (72.0 vs 65.4, p<0.001) populations, compared with the FF/UMEC/VI cohort. The population annualized count of ER visits was significantly lower among TIO/OLO initiators compared with FF/UMEC/VI initiators in the maintenance naïve (1.3 vs 1.5, p=0.041) and GOLD A/B (1.0 vs		

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1.1, p=0.019) populations and in the EOS ≤300 cells/µL subgroup (1.2 vs 1.7, p=0.002). Despite relatively similar all-cause utilization between TIO/OLO and FF/UMEC/VI initiators, population annualized total (medical + pharmacy) all-cause costs were significantly lower among TIO/OLO initiators compared with FF/UMEC/VI initiators in the maintenance naïve ($28,514; 95% CI: $26,762 - $30,267 vs $33,031; 95% CI: $30,765 - $35,297, p=0.002), GOLD A/B (23,309; 95% CI: $22,083 - $24,536 vs $26,244; 95% CI: $24,853 -$27,635, p=0.002), and overall populations (27,104; 95% CI: $25,871 - $28,336 vs $30,435; 95% CI: $29,019 - $31,850), p<0.001). All-cause pharmacy costs were also significantly lower among TIO/OLO initiators compared with FF/UMEC/VI initiators in the maintenance naive, GOLD A/B, overall, and no exacerbation history population. The population annualized all-cause medical costs were similar between the study cohorts among all populations.

Population annualized COPD and/or pneumonia-related ambulatory (9.0 vs 9.9, p=0.017), inpatient (0.4 vs 0.5, p=0.036), and other utilization (4.4 vs 4.9, p=0.001) was lower among TIO/OLO initiators compared with FF/UMEC/VI initiators in the overall population. COPD and/or pneumonia-related utilization in the other populations was generally similar between cohorts, with the following exceptions: TIO/OLO initiators had lower population annualized inpatient (maintenance naïve [0.42 vs 0.50, p=0.029], GOLD A/B [0.27 vs 0.33, p=0.022]), other (maintenance naïve, GOLD A/B, no exacerbation history), emergency room (EOS ≤300 cells/µL), and ambulatory (GOLD A/B, EOS >300 cells/µL) visits, and more pharmacy fills (GOLD C/D) compared with FF/UMEC/VI initiators. COPD and/or pneumonia-related population annualized pharmacy costs were consistently lower among TIO/OLO initiators compared with FF/UMEC/VI initiators in all populations. Population annualized total (medical + pharmacy) COPD and/or pneumonia-related costs were significantly lower among TIO/OLO vs. FF/UMEC/VI initiators, in all populations except GOLD C/D and EOS ≤300 cells/µL. Additionally, COPD and/or pneumonia-related population annualized medical costs

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were significantly lower among TIO/OLO initiators compared with FF/UMEC/VI initiators in the maintenance naïve population ($10,254; 95% CI: $9,040 - $11,468 vs $12,390; 95% CI: $10,830 - $13,951, p=0.031), and COPD and/or pneumonia-related population annualized emergency room costs were significantly lower among TIO/OLO initiators compared with FF/UMEC/VI initiators in the GOLD A/B ($303 vs $390, p=0.031) and EOS ≤300 cells/µL populations ($370 vs $538, p=0.034). Population annualized COPD and/or pneumonia-attributable cost results were consistent with the findings for COPD and/or pneumonia-related costs, with lower total (medical + pharmacy) and pharmacy costs among TIO/OLO initiators compared with FF/UMEC/VI initiators except for total costs in the GOLD C/D and EOS ≤300 cells/µL populations where there was no difference.

Adjusted COPD and/or pneumonia-related total (medical + pharmacy) costs were significantly higher among FF/UMEC/VI initiators compared with TIO/OLO initiators in the maintenance naive (cost ratio [CR]: 1.30; 95% CI: 1.16 – 1.50), p<0.001), GOLD A/B (CR: 1.25; 95% CI: 1.13 – 1.38, p<0.001), no baseline exacerbation (CR: 1.21; 95% CI: 1.09 – 1.36, p<0.001), and overall populations (CR: 1.22; 95% CI: 1.12 – 1.32, p<0.001). Adjusted COPD and/or pneumonia-related medical costs were significantly higher among FF/UMEC/VI initiators compared with TIO/OLO initiators in the maintenance naive (CR: 1.24; 95% CI: 1.03 – 1.48, p=0.021) and overall populations (CR: 1.14; 95% CI: 1.0 – 1.29, p=0.042). Adjusted COPD and/or pneumonia-related pharmacy costs were significantly higher among FF/UMEC/VI initiators compared with TIO/OLO initiators in all populations.

Pneumonia-related utilization in the follow-up was generally similar between the study cohorts in each of the populations; there were no difference in population annualized ambulatory, ER, or other utilization between TIO/OLO and FF/UMEC/VI initiators. The population annualized count of pneumonia-related inpatient stays was lower among TIO/OLO initiators compared to FF/UMEC/VI initiators in the maintenance naïve (0.12 vs 0.17, p=0.017), overall (0.12 vs 0.15, p=0.024), and EOS >300 cells/µL populations (0.06 vs 0.20, p=0.046).

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	There were no differences in population annualized pneumonia-related total (medical + pharmacy), medical, or pharmacy costs between TIO/OLO and FF/UMEC/VI initiators. The incidence of pneumonia diagnosis was similar between TIO/OLO and FF/UMEC/VI cohorts, except the no exacerbation history population where the incidence of pneumonia was lower among TIO/OLO initiators. Among GOLD C/D patients, the incidence of any exacerbation was higher for TIO/OLO vs. FF/UMEC/VI initiators in both unadjusted and adjusted analysis, and the population annualized exacerbation count was likewise higher for TIO/OLO vs. FF/UMEC/VI initiators (1.8 vs 1.6, p=0.013). The adjusted risk of any exacerbation was lower among FF/UMEC/VI initiators compared with TIO/OLO initiators (HR: 0.87 (95% CI: 0.78 - 0.98) p=0.020). While no significant differences between cohorts were observed in unadjusted incidence of exacerbations or population annualized exacerbation count among the overall population, adjusted risk of any exacerbation was lower among FF/UMEC/VI initiators compared with TIO/OLO initiators (HR: 0.925; 95% CI: 0.857 - 0.999, p=0.047). In the other study populations, there were no differences in incidence of or population annualized exacerbations between TIO/OLO and FF/UMEC/VI. <u>Secondary objective</u> In the overall study population, there were 191 and 400 eligible follow-up COPD hospitalizations, with 17 (8.9%) and 61 (15.3%) readmissions for TIO/OLO and FF/UMEC/VI initiators, respectively. The adjusted odds of readmission were not significantly different between FF/UMEC/VI and TIO/OLO (OR 1.5, 95% CI: 0.8 – 2.8 p=0.162).
Discussion:	Real-world data suggest that initiating maintenance treatment with TIO/OLO rather than FF/UMEC/VI is a more effective cost of care decision, especially among maintenance naïve, GOLD A/B, and no exacerbation history populations. Moreover, there was no difference in exacerbation outcomes, with the exception of the GOLD C/D and overall populations. GOLD C/D patients had higher incidence of

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	exacerbations with TIO/OLO, that was counterbalanced by reduced pneumonia incidence. No baseline exacerbation patients had lower incidence of pneumonia diagnosis with TIO/OLO vs. FF/UMEC/VI. Readmission after COPD hospitalization did not differ between patients on TIO/OLO and FF/UMEC/VI maintenance therapy and are likely impacted by other factors. Real-world data support the ATS guidelines and GOLD recommendations for treating symptomatic COPD patients with LAMA/LABA and treating patients with a history of exacerbations or more severely symptomatic COPD with TT.		
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