Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Stiolto/Spiolto			
Name of active ingredient: Tiotropium bromide + Olodaterol			
Report date: 06 December 2022	**Study number:** 1237-0121	**Version/Revision:** Original	**Version/Revision date:**
Title of study:	Comparison of Exacerbation Risk and Health Outcomes in Maintenance Treatment Naïve COPD patients using Stiolto vs. Trelegy.		
Keywords:	COPD; COPD exacerbation; LAMA/LABA; Triple therapy; pneumonia		
Rationale and background:	Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality throughout the world. COPD has risen to become the third leading cause of death in the United States (US). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 report and the American Thoracic Society 2020 report recommends dual bronchodilator therapy (DBT) with long-acting muscarinic antagonists (LAMAs) plus long-acting beta2-agonists (LABAs) for patients with 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 (⩾2 moderate exacerbations or 1 severe exacerbation) and after assessing the risks/benefits. An important consideration is the trade-off between preventing exacerbations and the increased risk of pneumonia associated with addition of ICSs. There are recommendations to restrict TT use further, to only patients who are likely to respond to ICS (such as ⩾2 moderate exacerbations or 1 severe exacerbation in the previous year, to those with asthma- COPD overlap or elevated blood eosinophils). We intended to conduct an observational study in a real-world clinical practice setting because there is a clear unmet need for better evidence on specific patient populations upon which to base (Fixed Dose Combination) FDC TT treatment recommendations. We assessed the effectiveness of Trelegy Ellipta, a FDC TT and compared it with Stiolto, a FDC DBT in patients who are maintenance treatment naïve and measured the incidence of COPD		

	exacerbation, the incidence of community acquired pneumonia, health care resource utilization (HCRU) and associated HCRU costs.
Research question and objectives:	The goal of this study was to investigate the risk of COPD exacerbations, community acquired pneumonia, and health care utilization in maintenance treatment naïve patients treated as first line therapy with Fixed Dose Combination (FDC) of Tiotropium + Olodaterol (Stiolto, 5/5 mcg), in comparison to maintenance treatment naïve patients treated with first line therapy, FDC of Fluticasone Furoate + Umeclidinium + Vilanterol (Trelegy, 100/62.5/25 mcg). Primary objective: • characterize the COPD patient population who are maintenance treatment naïve and initiated Trelegy or Stiolto as the first line therapy; • compare the effectiveness of Stiolto (new treatment initiation) with Trelegy (new treatment initiation) for time to the first COPD exacerbation (moderate/severe) in COPD patients who are maintenance treatment naïve; • compare COPD exacerbations following initiation of Stiolto (new treatment initiation) with initiation of Trelegy (new treatment initiation). Secondary objectives: • compare Stiolto (new treatment initiation) with Trelegy (new treatment initiation) for time to the first hospitalization of community acquired pneumonia in COPD patients who are maintenance treatment naïve; • assess differences between Stiolto vs Trelegy in, "all-cause" and "COPD and/or pneumonia-related", HCRU and HCRU cost.
Study design:	This was a non-interventional, retrospective, observational, new user design, real world study of Commercial Insurance and Medicare beneficiaries, using administrative claims data for the period of 15th September 2016 through 31st March 2020. Propensity score matching (PSM) technique (1:1 matching using nearest neighbor matching approach) was used to develop matched cohorts of patients between Stiolto and Trelegy initiators. Descriptive analyses were performed before and after propensity score matching. Balance after PSM was assessed by calculating the standardized mean differences (SMD) between the matched cohorts. Following the matching procedure, descriptive and multivariable analyses were performed.

Setting:	Patients initiating Stiolto, or Trelegy were identified using pharmacy claims. The date of the first prescription claim was defined as the index date. Inclusion Criteria: 1. At least one pharmacy claim for Stiolto Respimat or Trelegy Ellipta between 15 September 2017 and 31st March 2020. 2. ≥40 years of age. 3. Two medical claims (at least one claim on index date or before in the baseline period) with an ICD-9/10 diagnosis code(s) for COPD in any position during the study period (baseline + post index date). 4. At least one year of continuous health plan enrollment prior to the index date (to allow a baseline period for the covariates and characterizing the study population). Exclusion Criteria: 1. Two or more medical claims of asthma, cystic fibrosis, lung cancer, or interstitial lung disease in any position on separate dates of service during the study period. 2. LAMA monotherapy, LABA monotherapy, ICS monotherapy, free or FDC of ICS+LABA, LAMA+LABA, ICS+LABA+LAMA, biologics therapy within six months prior to index date. 3. Pharmacy claims for multiple index medications on the index date.
Subjects and study size, including dropouts:	The cohort sizes before and after propensity score matching are included below. **Pre-match** Stiolto: 3996 Trelegy: 5121 **Post-match** Stiolto: 2951 Trelegy: 2951
Variables and data sources:	Data source: We utilized medical and pharmacy claim records for COPD patients included in the [redacted] database (previously named [redacted]). This database contains administrative insurance data and enrolment information derived from approximately 150 million commercially insured and Medicare lives. This longitudinal database allows documentation and analysis of the patient journey from diagnosis to intervention and follow-up. It is nationally representative covering 90% of US hospitals and compliant with

	current HIPAA (Health Insurance Portability and Accountability Act) regulations. Exposure: Initiation with Stiolto or Trelegy Outcomes: Moderate-or-severe exacerbations, pneumonia related hospitalizations and encounters, all-cause and disease-related health care resource utilization.
Results:	Stiolto was also associated with lower risk of exacerbation as shown by the Cox PH regression (HR: 0.882, 0.773-1.007, p=0.064) but this association was not statistically significant at alpha=0.05. The annualized rate of exacerbation was 0.28 per patient-year for the Stiolto group, which was significantly lower compared to the Trelegy group (0.32 per patient-year, p=0.032). Among patients with no (0) or 1 baseline exacerbations, the Stiolto group had significantly lower exacerbation rate per patient-year compared to the Trelegy group (0.27 vs. 0.31, p=0.016). Similarly in the subgroups of 0/1 exacerbations ((HR: 0.896, 0.782-1.027, p=0.114)) or ≥2 exacerbations ((HR: 0.728, 0.413-1.284, p=0.273). Kaplan-Meier (KM) curve analysis also showed a lower probability of exacerbation for the Stiolto group, and it was significant at Wilcoxon p=0.045, but not significant at the Log-rank p=0.063. Secondary Endpoints: Cox PH regression analysis showed no statistically significant differences between the two cohorts for time to first pneumonia hospitalization (diagnosis in any position, HR: 1.014, CI: (0.741, 1.386), p=0.932). KM curve analysis showed no statistically significant differences between the two cohorts for time to first pneumonia hospitalization (diagnosis in any position, Wilcoxon p=0.896, Log Rank p=0.932). Similar results were noted when looking at time to pneumonia diagnosis (any position, any encounter). No statistically significant difference was noted for the KM curves (p=0.603). When looking at the composite end point of exacerbation or pneumonia related hospitalization (primary diagnosis), a significantly lower proportion of the Stiolto cohort had the event (14% vs. 17% in Trelegy, p=0.008). The Stiolto cohort showed a lower risk of the event but was not statistically significant (HR: 0.887, 0.779-1.01, p=0.069). KM curve analysis showed that Stiolto group had a lower probability of event over time (Wilcoxon p=0.048, Log-Rank p=0.069). There were no significant differences in the population annualized rates of all-cause or COPD and/or pneumonia-related HCRU between cohorts.

	Regression analysis showed that Trelegy was associated with a statistically significant 11% increase in total (medical + pharmacy) COPD and/or pneumonia-related cost (1.117 (CI:1.027, 1.215), p=0.01), with predicted means of $8,099 for Trelegy and $7,230 for Stiolto, and a statistically significant 11% increase in total (medical + pharmacy) COPD-related cost (1.115 (CI:1.024, 1.213), p=0.012) with predicted means of $7,981 for Trelegy and $7,140 for Stiolto. There was no significant difference in COPD and/or pneumonia-related medical costs (0.968 (CI:0.847, 1.107), p=0.636) with predicted means of $5,632 and $5,648 for Trelegy and Stiolto, respectively. Trelegy was associated with a statistically significant, 53% increase in COPD-related pharmacy cost (1.533 (CI:1.429, 1.644), p<0.0001), with predicted means $2,467 (Trelegy) and $1,582 (Stiolto).
Discussion	Our study is unique in its objective of and design for assessing the outcomes in a population of treatment-naïve matched patient population who initiated Stiolto vs. Trelegy. There was no difference observed in the risk of COPD exacerbation, however, Trelegy patients incurred severe or moderate COPD exacerbations at a greater rate per patient-year, compared with the Stiolto group. Additionally, Stiolto was associated with significantly lower COPD and/or pneumonia-related total and pharmacy costs. Our study results are corroborated with existing literature, for example, a study conducted using the managed care Medicare database found that only 8.3% of dual therapy initiators experienced severe exacerbations compared with 15.5% of triple therapy initiators (P=0.014). Our study showed that risk of exacerbation was not significantly different between the two groups, similar to results reported by Quint et al. (2021) that showed that triple therapy was not associated with added benefits over dual therapy in terms of risk reduction.
Marketing Authorisation Holder(s):	[redacted]
Names and affiliations of principal investigators:	[redacted]

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