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/Spiolto			
Name of active ingredient: Tiotropium bromide + Olodaterol			
Report date: 03 Sep 2020	**Study number :** 1237-0093	**Version/Revision:** Version 01	**Version/Revision date:** NA
Title of study:	Effectiveness and Safety of Maintenance Treatment with Combination of Tiotropium and Olodaterol in Comparison to Maintenance Treatment with a Combination of Inhaled Corticosteroids and Long-acting β2 Agonists in COPD patients		
Keywords:	*COPD, COPD exacerbation, pneumonia, ICS/LABA, tiotropium, olodaterol*		
Rationale and background:	The treatment of COPD increasingly involves multiple therapies, including long-acting bronchodilators (LAMAs and LABAs) and inhaled corticosteroids (ICS). The use of ICS has increased disproportionately with respect to COPD treatment guidelines and may be appropriate only in a subset of these users [P15-12888; P16-12287]. A recent population- based observational study showed no difference in exacerbation risk for COPD patients with B-Eosinophils below 4% if treated either with LAMA or LABA/ICS [P18-09975], but this data have yet to be confirmed in population based studies in real world conditions.		
Research question and objectives:	The primary objective is to compare the effectiveness of maintenance therapy initiation with the combination treatment Tiotropium and Olodaterol (Olo+Tio) compared with LABA/ICS combination in COPD as the time to the first COPD exacerbation. Secondary objectives are to compare patients treated with Tio+Olo and patients treated with LABA/ICS combination: (1) Time to community acquired pneumonia, (2) time to escalation to triple therapy (3) time to an adverse outcome including exacerbation, escalation to triple therapy, or pneumonia, and (4) healthcare utilization outcomes and an analysis of all- cause and COPD-specific cost overall and by care setting. Additionally, the study investigated effect modification by circulating eosinophil levels and exacerbation history on the safety		

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	and effectiveness of Tio+Olo compared with any LABA/ICS. Analyses were repeated in sub-groups of patients under high or low risk of exacerbation based on previous history of exacerbations in the year preceding cohort entry (with high exacerbation history defined as either 1+ hospitalization or 2+ exacerbations in emergency department or outpatients settings [R05-1384]), as well as based on circulating eosinophils (cut-off: B-Eos 300 cells/uL [P18-09975]) overall and among those with low history of exacerbation.		
Study design:	A claims-based incident new-user cohort design was used, with confounding controlled via fine stratification and reweighting of exposure propensity scores.		
Setting:	The HealthCore Integrated Research Database^{SM} (HIRD)		
Subjects and study size, including dropouts:	In this cohort study, administrative data from the HealthCore Integrated Research Database (January 2013 – March 2019) were used to identify and compare new users of Tio+Olo with new users of LABA/ICS combination therapy with respect to safety and effectiveness. Patients in each cohort were required to have at least one prescription for a fixed dose combination (FDC) inhaler of Tio+Olo or LABA/ICS, with the first prescription defined as the index date. Those with less than one year of continuous health plan eligibility prior to the index date; no pre-index diagnosis of COPD; age <40 years at the index date; pre-index diagnosis of asthma, lunch cancer, interstitial lung disease, or lung transplant; or pre- index use of Tio+Olo, LABA/ICS, or LABA/LAMA/ICS in free or fixed form were excluded. Patients were followed from the index date until the earliest of a switch in treatment, addition of either an ICS for the Tio+Olo group or of LAMA to the LABA/ICS group, discontinuation of COPD treatment, the end of the study period, the end of continuous health plan eligibility, or (for main analyses) one year after cohort entry. To assess whether results differed within subgroups, all analyses were conducted for the total population, as		

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	well as in sub-groups of patients under high- or low risk of exacerbation based on (1) previous history of exacerbations in the year preceding cohort entry (cut-off: 1+ hospitalization or 2+ exacerbations in emergency department or outpatients settings [R05-1384], (2) circulating eosinophils (cut-off B-Eos 300 cells/uL [P18- 09975]), and (3) as an exploratory analysis, a combination of exacerbation history and circulating eosinophils.		
Analyses:	Hazard ratios and their 95% CI from proportional hazards models were then used to assess differences in the risk of COPD exacerbation, pneumonia, escalation to triple therapy, or a composite of those outcomes with confounding controlled via fine stratification and reweighting of an exposure propensity score.		
Results:	There were 2,684 Tio+Olo and 59,301 LABA/ICS users meeting all study criteria. Users of Tio+Olo and LABA/ICS were similar in terms of age, but Tio+Olo users were slightly more often male and residing in the Southern region of the US. No Tio+Olo users had index dates prior to 2015. Tio+Olo users more often had LAMA monotherapy at baseline, and fewer had baseline COPD exacerbations. Tio+Olo users had lower risk of exacerbation than LABA/ICS users (aHR 0.76, 0.68-0.85). Tio+Olo users also had lower rates of exacerbation pneumonia than LABA/ICS users (aHR 0.74, 0.57-0.97). This protective effect may be limited to those with low exacerbation history (aHR 0.66, 0.45-0.96), noting a numerical but non-significant decrease in risk among those with high exacerbation history (aHR 0.80, 0.55-1.17). Stratification by circulating eosinophil levels did not show an association, but produced small cell sizes with <10 events in the Tio+Olo group for each stratum and imprecise estimates. Escalation to triple therapy was dramatically less common in Tio+Olo than LABA/ICS users, with an aHR of 0.23 (0.19-0.27) that was similar across exacerbation history and circulating eosinophil		

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	strata. An alternative definition of escalation to triple therapy yielded similar results (aHR 0.22, 0.19-0.26). When considering COPD exacerbation, community acquired pneumonia, and escalation to triple therapy as a composite, Tio+Olo users had lower rates of events than LABA/ICS users (aHR 0.46, 0.42-0.51 based on pre- specified definitions and 0.45, 0.41-0.49 based on revised definitions). Healthcare utilization was higher for Tio+Olo than LABA/ICS users.		
Discussion:	In this study, patients newly initiating Tio+Olo appeared to have a lower risk of exacerbation, community acquired pneumonia, and escalation to triple therapy during treatment when compared to similar patients who instead initiated therapy with LABA/ICS. Differences in subgroup varied by outcome.		
Names and affiliations of principal investigators	[redacted]		