1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiriva			
Name of active ingredient: Tiotropium bromide			
Report date: 1 October 2018	**Study number:** 0205-0538	**Version/Revision:** 1.0	**Version/Revision date:** Version 1.0, 1 October 2018
Title of study:	Comparative effectiveness of combination therapies in COPD		
Keywords:	Long-acting bronchodilators; Inhaled corticosteroids; COPD; Pharmacoepidemiology; Comparative effectiveness; Cohort study; Safety		
Rationale and background:	The treatment of COPD increasingly involves multiple therapies, including long-acting bronchodilators (LAMAs and LABAs) and inhaled corticosteroids (ICS), with combinations of these drugs now formulated into single inhalers. While most trials of the combination treatments have been conducted against the respective mono components or placebo, the head-to-head trials of double combinations versus other double combinations that have been performed to date reported inconsistent findings. In addition, these trials represent a limited view of the patients who could potentially use these treatments, with many exclusion criteria applied during the screening and run-in periods. Thus, we conducted a real-world study of this question in a population of patients representative of clinical practice.		
Research question and objectives:	**Primary objective**: To assess the effectiveness of maintenance treatment of COPD with the combination of the LAMA tiotropium with a LABA (LABA-TIO) compared with the combination of a LABA with ICS (LABA-ICS) on the time to COPD exacerbation. **Secondary objective:** To compare the effectiveness on the rate of exacerbation and the safety on the incidence of community acquired pneumonia for LABA and tiotropium with LABA and ICS.		
Study design:	Population-based propensity score-matched incident new-user cohort study.		

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Setting:	General practice setting (United Kingdom)		
Subjects and study size, including dropouts:	The base cohort included 56,460 patients with COPD, new users of tiotropium, LABA or ICS between 1 January 2002 and 31 December 2015, aged 55 years or older. The study cohort included 1,977 initiators of LABA-TIO (mean age 71.8 years) who were matched on propensity score and time to 1,977 initiators of LABA-ICS.		
Variables and data sources:	The exposures were based on prescriptions for the two long-acting bronchodilators under study, namely LABA and tiotropium, and for ICS. The primary outcome event was the first COPD exacerbation to occur after cohort entry, defined as a hospitalization for COPD (severe exacerbation) or the prescription of an oral corticosteroid, namely prednisolone (moderate exacerbation). Secondary outcomes were the rate of COPD exacerbations and occurrence of the first hospitalization for community-acquired pneumonia over the one-year follow-up. Covariates included demographics, lifestyle variables, cardiovascular and other co-morbidity (e.g. asthma), co-medications, and measures of COPD severity.		
Results:	The hazard ratio of a moderate or severe COPD exacerbation associated with LABA-TIO relative to LABA-ICS from the as-treated analysis was 1.04 (95% CI: 0.90-1.19), while for severe exacerbation the hazard ratio was 0.94 (95% CI: 0.65-1.35). The rate ratio of the frequency of moderate or severe COPD exacerbations associated with LABA-TIO relative to LABA-ICS was 1.06 (95% CI: 0.92-1.25). The as-treated hazard ratio of a severe pneumonia associated		

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	with LABA-TIO relative to LABA-ICS was 0.66 (95% CI: 0.41-1.05). The on-treatment hazard ratio of a severe pneumonia associated with LABA-TIO relative to any current ICS use during follow-up was 0.66 (95% CI: 0.47-0.91). Results remained generally constant after sensitivity analyses.		
Discussion:	This real world setting study of the treatment of COPD suggests that the combination of a long-acting beta$_2$-agonist (LABA) and tiotropium (TIO) use (both without ICS) has similar effectiveness as the combination of LABA and ICS on the incidence and frequency of COPD exacerbations. On the other hand, the initiation of LABA-TIO tended to reduce the risk of pneumonia compared with LABA-ICS.		
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