Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiriva			
Name of active ingredient: Tiotropium bromide			
Report date: 24 April 2019	**Study number:** 1237-0078	**Version/Revision:** 1.0	**Version/Revision date:** Version 1.0, 24 April 2019

Title of study:	Comparative effectiveness of triple therapy in COPD: A new-user cohort study
Keywords:	Long-acting bronchodilators; Inhaled corticosteroids; COPD; Pharmacoepidemiology; Comparative effectiveness; Cohort study; Safety
Rationale and background:	The treatment of COPD involves multiple therapies, including long-acting bronchodilators (LAMAs and LABAs) and inhaled corticosteroids (ICS), with dual and triple combinations of these drugs now formulated into single inhalers. The recent TRIBUTE trial and IMPACT trials compared triple therapy with a dual long-acting bronchodilator regimen (LABA-LAMA), the recommended step-up in COPD treatment. These trials, however, have methodological issues related to the deleterious effect of withdrawal of maintenance treatment at randomization, the inclusion of patients with asthma and the use of run-in periods. Moreover, they represent a limited view of the patients who could potentially use these treatments, so that real-world studies of patients who are representative of clinical practice are important. As many of these drugs have been in use in separate inhalers for many years, including their combined use, an observational study of the comparative effectiveness of triple therapy is feasible and can provide useful data on the relative benefits of different combinations in the treatment of COPD. The intended audience is prescribers and payers. The results from the study will be published in the scientific literature.
Research question and objectives:	To assess the effectiveness of maintenance treatment of COPD with the LABA-LAMA-ICS combination compared with a LABA-LAMA combination on the risk of COPD exacerbation and the safety on the incidence of community acquired pneumonia.
Study design:	Incident new-user cohort design with high-dimensional propensity scores to match the two comparison groups.

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Setting:	General practice setting - United Kingdom's Clinical Practice Research Datalink (CPRD)		
Subjects and study size, including dropouts:	The base cohort included all patients in the CPRD with a diagnosis of COPD who received at least one prescription for a LABA, LAMA, or an ICS from 1 January 2002 until 31 December 2015. Patients were 55 years of age or older on the date of this initial prescription and patients with a diagnosis of asthma at any time prior to the study cohort entry date were excluded. The primary study cohort included patients with their first concurrent prescriptions of a LAMA and LABA (no ICS) as two inhalers on the same day. These patients were matched on high-dimensional propensity score with patients initiating treatment with LABA-LAMA-ICS combination as three or two inhalers on the same day. Subjects were followed for up to one year from the cohort entry date, the date of death, 31 December 2016, or the end of coverage in the practice, whichever occured first.		
Variables and data sources:	United Kingdom's Clinical Practice Research Datalink (CPRD), part of which is linked with the Hospital Episodes Statistics (HES) database.		
Results:	The source data included 669,626 patients with a prescription for LABA, LAMA or ICS between January 1, 2002 and December 31, 2015, from CPRD practices linked to the HES database. After exclusions related to age, COPD diagnosis, and asthma, the base cohort included 56,460 eligible subjects of initiators of these treatments. After matching, the study cohort included 6,921 initiators of LAMA-LABA-ICS matched to 1,932 initiators of LAMA-LABA. The adjusted hazard ratio (HR) of a moderate or severe COPD exacerbation associated with LAMA-LABA-ICS initiation compared with LAMA-LABA initiation was 0.97 (95% CI: 0.87-1.09). However, for patients with blood eosinophils >6% (as a percent of the white blood cell count), the HR was 0.66 (95% CI: 0.46-0.94) and for patients with two or more prior exacerbations it was 0.83 (95% CI: 0.70-0.98). The incidence of severe pneumonia requiring hospitalization was increased with LAMA-LABA-ICS initiation (HR 1.46; 95% CI: 1.03-2.07).		

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Discussion:	In a real world setting of COPD treatment, the triple combination of LAMA, LABA and ICS inhalers is generally as effective as combining LAMA and LABA inhalers in preventing COPD exacerbations. However, with the exception of patients with significant eosinophilia or frequent exacerbators, a LAMA-LABA combination without ICS may be preferable because it is associated with fewer severe pneumonias.		
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