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Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiriva® HandiHaler®, Respimat®			
Name of active ingredient: Tiotropium Bromide Monohydrate			
Report date: 15 Feb 2021	Study number: 0205-0542	Version/Revision: 1	Version/Revision date:

Title of study:	Non-interventional study to compare effectiveness of long-acting muscarinic antagonists (LAMA) to fixed dose combination of inhaled corticosteroid and long-acting beta agonists (ICS/LABA) in patients with chronic obstructive pulmonary disease (COPD) based on existing data
Keywords:	COPD, Big data analysis, Tiotropium, ICS containing therapy, LAMA
Rationale and background:	Even though Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines limit the use of inhaled corticosteroid (ICS) to a small portion of chronic obstructive lung disease (COPD) patients, ICS is overprescribed in clinical practice regardless of COPD severity and exacerbation. Thus, a timely review on the impact of long-term treatment with ICS with cumulated data is needed at this point.
Research question and objectives:	The purpose of this study is to compare the occurrence of several outcomes after initiation of ICS/LABA therapy with their occurrence after initiation of LAMA therapy in COPD patients to compare the real-world effectiveness and safety of ICS/LABA versus LAMA in South Korea. The primary objectives are to compare the incidence of pneumonia, frequencies of COPD exacerbations, the time to initiating triple combination therapy in COPD patients initiating LAMA or ICS/LABA. The secondary objectives are to compare healthcare resource utilization (HCRU) and costs, and the incidence of all-cause death, lung cancer, tuberculosis (TB), and non-tuberculosis mycobacteria (NTM) lung disease in COPD patients initiating LAMA or ICS/LABA
Study design:	This study was a retrospective cohort study, using Korean national health insurance claims data from 01 January 2002 to 30 April 2016.
Setting:	This study consisted of the baseline period of 36-months, the selection period of 124-months (01 January 2005 to 30 April 2015), and the observational period of 136-months. The follow-up period for each endpoint was ended when 1) study endpoint occurred, 2) patients discontinued the index drug (i.e. LAMA or ICS/LAB), 3) patients died, or 4) study period ended, whichever occurred first. The index date was defined as the first prescription date of LAMA or ICS/LABA with COPD diagnosis during the selection period. .
Subjects and study size, including dropouts:	COPD patient aged ≥55 years with a prescription of LAMA or ICS/LABA during the selection period and received LAMA or ICS/LABA more than twice within 12 months from the index date were identified for the study. Patients who had a history of using long-acting bronchodilator including ipratropium bromide, LTRA, ICS, LABA/LAMA FDC, LAMA, or ICD/LABA during the baseline period of 12 months, or who were diagnosed with lung cancer, idiopathic pulmonary fibrosis (IPF), interstitial lung disease (ILD), or undergoing lung transplantation during the baseline period of 36 months were also excluded from the study. Further, patients with <80% MPR in the first 12 month from the index date were also excluded in order to enrol patients with good adherence.

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	In addition, patients who are prescribed with ICS, LABA, and LAMA as triple combination therapy within 30 days from the index date were further excluded. The enrolled patients were categorized as LAM group or ICS/LABA group according to the index drug prescribed on the index date. Study size was estimated using the national health insurance database (NHID). According to the NHID, approximately 200,000 patients per year were treated for COPD defined using diagnostic code and received prescriptions with COPD medications such as LAMA, LABA, ICS + LABA, SAMA, SABA, SAMA + SABA, PDE-4, systemic beta agonist, theophylline. Among them, it was estimated that 26% (n=52,000) and 37% (n=74,000) of COPD patients were treated with LAMA and ICS/LABA, respectively. However, it was expected that the number of eligible patients for this study would be smaller than the estimated sample size, since patients with good adherence were only enrolled in this study and also propensity score (PS) matching would be considered.
Variables and data sources:	The primary outcomes were pneumonia, COPD exacerbations, and time to initiating triple combination therapy from the index date, and the secondary outcomes were the healthcare utilization (HCRU), all-cause mortality, lung cancer, tuberculosis (TB), and non-tuberculosis mycobacteria (NTM). This study used Korea National Health Insurance Claim Database (NHID) from National Health Insurance Service (NHIS) and mortality data from the Bureau of Statistics from 01 January 2005 to 30 April.
Results:	After matching with propensity scores, a total of 4,888 patients were selected for this study. The mean (SD) age of LAMA group (N=2,444) was 69.57 (7.85) whereas ICS/LABA group (N=2,444) was 69.73 (7.91) after matching. Among LAMA group, 1,854 (75.86%) was male and 590 (24.14%) was female. Similarly, 1,822 (74.55%) was male and 622 (25.45%) was female in ICS/LABA group. ICS/LABA group showed significantly higher risks for pneumonia events (overall hazard ratio [HR] 1.475, 95% confidence interval [CI] 1.308-1.663; inpatient HR 1.517, 95% CI 1.314-1.751; outpatient HR 1.358, 95% CI 1.187-1.554) , COPD exacerbations (overall HR 1.145, 95% CI 1.059-1.237; moderate exacerbations HR 1.151, 95% CI 1.057-1.253; severe exacerbations HR 1.166, 95% CI 1.022-1.330) , and escalation to triple combination (HR 1.601, 95% CI 1.404-1.826) compared to LAMA group, whereas no significant difference between study groups were observed for lung cancer, pneumonia-related or all-cause mortality, TB, and NTM. LAMA significantly delayed the time to initiation of triple combination therapy (LAMA 450.44±510.56; ICS/LABA 358.12±418.70), and patients of LAMA group spent less on medical care on average than those on ICS/LABA group.
Discussion:	This study results based on the large population suggests that LAMA may be the effective treatment option for COPD patients, especially when compared to ICS/LABA. As this study assesses only patients with good adherence rate (i.e. ≥80% MPR), findings in this study warrants further studies including the non-adherent population and these limitations should be considered when interpreting the study results.
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