1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Striverdi, Respimat			
Name of active ingredient: Olodaterol			
Report date: 15 Sep 2020	**Study number:** 1222.54	**Version/Revision:** 2.0	**Version/Revision date:** 13 Oct 2020
Title of study:	Cohort study of cardiovascular events in patients with chronic obstructive pulmonary disease initiating olodaterol or other long-acting beta2-agonists		
Keywords:	Chronic obstructive pulmonary disease, atrial fibrillation or flutter, ventricular fibrillation, cardiac arrest, ventricular tachycardia, acute myocardial infarction, serious acute coronary heart disease, unstable angina, all-cause mortality		
Rationale and background:	Inhaled long-acting beta2-agonist (LABA) drugs are used in chronic obstructive pulmonary disease (COPD) to relieve bronchial constriction and associated symptoms. At present, formoterol, salmeterol, indacaterol and vilanterol are the main LABAs approved for COPD treatment. The clinical long-term safety experience of the LABA olodaterol at the time of regulatory approval was based on four phase 3 randomised, placebo-controlled, parallel-group studies, two of which included formoterol as an active comparator in addition to placebo. No imbalances were detected in this study pool with regards to any cardiovascular effect during the 48-week study period. This was further supported by a recent study in which treatment with olodaterol or formoterol was not associated with arrhythmias or a persistent increase in heart rate as assessed by Holter ECG in patients with COPD. Nevertheless, cardiac arrhythmia and myocardial ischaemia are known class effects of LABAs and have been included as potential important risks in the risk management plan for olodaterol. Within the Decentralised Procedure for Striverdi Respimat, the health authorities of the European Union/European Economic Area Member States requested that a post-authorisation safety study (PASS) to gather additional data on safety in long-term use beyond 1 year of olodaterol be included in the risk management plan. The results of this study were intended to provide insight into the absolute and relative frequency of cardiac arrhythmias and myocardial ischaemia events of interest in comparison to alternative LABA therapies for COPD.		

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Research question and objectives:	Primary objectives: • Examine the risk of selected cardiac arrhythmias in patients with COPD exposed to olodaterol compared with the risk in patients exposed to other long-acting beta2-agonists (LABAs) • Examine the risk of acute myocardial infarction (AMI) and other serious ischaemic heart disease events, including unstable angina, in patients with COPD exposed to olodaterol compared with the risk in patients exposed to other LABAs Secondary objective: • Examine the risk of all-cause mortality in patients with COPD exposed to olodaterol compared with the risk in patients exposed to other LABAs		
Study design:	This was an observational cohort study.		
Setting:	The study was conducted by using data on drug prescriptions and disease occurrence routinely collected on an ongoing basis for large, population-based automated health care databases in Denmark. Diagnoses, including COPD, were identified in the Danish National Patient Registry, which contains inpatient and outpatient hospital clinic diagnoses. Dispensings were obtained from the Danish Prescription Database. Information on cause of death was obtained from the Danish Register of Causes of Death. The study period started 01 March 2014 and ended 31 January 2019.		
Subjects and study size, including dropouts:	Patients in each cohort were required to have a prior COPD diagnosis recorded in the inpatient or outpatient hospital setting, aged 40 years or older who were new users of olodaterol or of any LABA other than olodaterol and who had no dispensing of the same LABA in the 180 days before the cohort entry date and at least 1 year of enrolment in the electronic database. Patients in the olodaterol cohort were matched 1:4 to users of other LABA, by age, sex, and calendar year. An approach using exposure propensity scores was utilised to remove measured confounding by adjusting the analysis for observed covariates. The 2.5th tails of the distribution of the propensity scores were trimmed. The study size needed was that estimated to achieve the number of person-years of olodaterol necessary to obtain an 80% probability that the upper bound of the 95% confidence interval of the incidence rate ratio was below		

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	2.5 (3.0 for ventricular tachycardia), assuming a minimum ratio of 1 exposed (olodaterol) patient to 4 unexposed (any other LABA) patients, a two-sided alpha level of 0.05, and a range of expected incidence rates of each study endpoint. The estimated minimum number of olodaterol-exposed person-years needed ranged from 100 person-years for all-cause mortality to 8,380 person-years for ventricular tachycardia.		
Variables and data sources:	Exposures: olodaterol and other LABA monotherapy or in free or fixed-dose combination with long-acting muscarinic antagonist (LAMA). The exposure window considered only the first episode of continuous use, defined as the time comprising consecutive dispensings separated by 14 days or less. Primary outcomes • Incidence of atrial fibrillation or flutter • Incidence of hospitalisation for ventricular tachycardia, including ventricular fibrillation/flutter and cardiac arrest • Incidence of supraventricular tachycardia (other than atrial fibrillation/flutter) • Incidence of hospitalisation for acute myocardial infarction • Incidence of hospitalisation for serious acute coronary heart disease, including unstable angina Secondary outcomes • Mortality from all causes Exposures of interest were (1) olodaterol and (2) any other LABA. The following covariates were of interest: • Sociodemographics, such as age, sex, and proxies for smoking (i.e., drugs used in nicotine dependence) • Severity of COPD defined by patterns of use of bronchodilators, antibiotic use for lower respiratory tract infection, courses of systemic corticosteroids, diagnosis of COPD exacerbation, pneumonia, or acute bronchitis with or without hospitalisation, oxygen therapy, nebuliser therapy, and diagnosis of emphysema. • History of comorbidities, such as cardiovascular diseases, hypertension,		

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	diabetes, hyperlipidemia, chronic kidney disease, liver disease, osteoporosis, and malignancies. • Other relevant variables, such as hospitalisations and history of COPD exacerbations with or without hospitalisation, and proxies for frailty were not considered initially in the protocol but were added in a post hoc analysis. • Comedications in the 180 days before the index date, such as respiratory medications, cardiovascular medications, lipid-lowering medications, blood glucose–lowering medications, anticoagulants and antiplatelet agents, antibiotics, and antineoplastic agents. Data on race, ethnicity, and lifestyle factors, such as smoking, were not available. Data sources where these variables were assessed are described under Section 9.2. The adjusted incidence rates and IRRs and IRDs and their 95% CIs were estimated using Poisson regression models, including the propensity score as one variable with categories represented by the propensity score strata and variables that were not balanced after matching and trimming.
Results:	The study population included 14,239 users of olodaterol and 51,167 users (19,458 unique users) of other LABA. Most users were users of fixed-dose combinations of LABA/LAMA (92% in olodaterol cohort and 63% in other LABA cohort). Prior use of LABA was more frequent among users of olodaterol than among users of other LABA (58% vs. 37%). The mean duration of the first episode of continuous use was less than 5 months in both cohorts, and it was more than 12 months for less than 8% of the patients. Mean age was around 72.7 years (SD, 10) and 54% were females in both cohorts. Users of olodaterol had more severe COPD and a higher frequency of prior use of respiratory medications. Hospitalisations and history of COPD exacerbations with or without hospitalisation were more frequent among users of olodaterol than among users of other LABA. The adjusted IRRs (adjusted for quintiles of propensity score and LAMA use at baseline) were 1.20 (95% CI, 0.98-1.47) for atrial fibrillation or flutter, 1.83 (95% CI, 0.90 −−3.74) for supraventricular tachycardia, 1.30 (95% CI, 0.71- 2.36) for ventricular tachycardia, 1.22 (95% CI, 0.79-1.87)

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	for acute myocardial infarction, and 1.00 (95% CI, 0.64- 1.56) for serious acute coronary heart disease. The adjusted IRR for all-cause mortality was 1.63 (95% CI, 1.44- 1.84; adjusted for propensity score quintiles and LAMA use at index date), and it was attenuated to 1.40 (95% CI, 1.24-1.59) when additional variables were included in the model (number of hospitalisations in the 180 days before index date, number of COPD hospitalisations in the 90 days before index date, number of COPD exacerbations in the 180 days before index date, and history of lung cancer). Given the differences between the two cohorts in important baseline characteristics and treatment patterns, the risk of all-cause mortality was further assessed among a population that would potentially be more similar at baseline (i.e., post hoc analyses were performed among users of fixed-dose combinations of LABA/LAMA who were LABA naïve at cohort entry). Among these patients, the crude IRR for all-cause mortality was 1.83 (95% CI, 1.53-2.18) that was attenuated to an adjusted IRR of 1.48 (95% CI, 1.23-1.78) when additional factors were included in the propensity score model and in the outcome model when variables remained unbalanced. However, inspection of baseline characteristics showed that patients in the olodaterol/tiotropium cohort still had more severe COPD and a higher proportion of recent hospitalisations and exacerbations. The study population was further restricted to those without prior hospitalisations for COPD in the last 90 days, which was the characteristic with the biggest difference between study cohorts at baseline and was a major confounder. In this population, the crude IRR for all-cause mortality was 1.45 (95% CI, 1.13-1.86), and the adjusted IRR was 1.26 (95% CI, 0.97-1.64) when adjusting the outcome model for the remaining imbalances. No adverse events were reported, based on Guideline on Good Pharmacovigilance Practices (GVP) from the European Medicines Agency (EMA).		
Discussion:	The results of this study showed that use of olodaterol was not associated with an increased risk of ischaemic or arrhythmia events. Analysis suggest that findings related to an increase risk of death are likely due to non-comparability of the study populations, channelling bias, and residual		

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	confounding. Both the matched cohort study design and propensity score methodology aimed to create comparable treatment cohorts for the incidence analyses. However, for relevant variables not included in the initial protocol-specified analysis, comparability was not completely achieved: descriptive analysis showed that olodaterol was preferentially prescribed to sicker patients who had more severe COPD. Nonetheless, for the primary outcomes most of the main confounders were controlled, although residual or uncontrolled confounding cannot be ruled out. Compared with use of "other LABA," use of olodaterol was associated with an increased risk of all-cause mortality. However, this association was apparently a result, in large part, of differences in the baseline characteristics of the populations stemming from preferential prescribing. Furthermore, the analyses suggest that residual confounding due to unmeasured variables biased the estimate of all-cause mortality away from the null value. Large, randomised, long-term clinical studies have not shown increased mortality with olodaterol. Post hoc analysis of the current data indicated that channelling of the drug to sicker patients in ways that could not be completely be identified may explain the observed association. Adjustment for measured covariates demonstrated substantial confounding of the observed association between olodaterol and all-cause mortality. Bias analysis showed that residual (i.e., unmeasured) confounding could readily account for much of the association that remained after adjustment.		
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