Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat® 28 puffs/ Spiolto® Respimat® 60 puffs			
Name of active ingredient: Tiotropium + olodaterol fixed-dose combination solution for inhalation - RESPIMAT			
Report date: 11 July 2019	**Study number:** 1237.34	**Version/Revision:** Ver.1.0	**Version/Revision date:** Not applicable
Title of study:	Post Marketing Surveillance (PMS) on long-term use of tiotropium + olodaterol fixed dose combination (Tio + Olo FDC) 5 µg/5 µg in patients with chronic obstructive pulmonary disease (COPD) (chronic bronchitis, emphysema) in Japan		
Keywords:			
Rationale and background:	The number of patients exposed to Tio + Olo fixed dose combination (FDC) 5 µg/5 µg was limited in clinical trials. In addition, the clinical trial setting had some limitations compared to the real-world setting, such as inclusion/exclusion criteria defined patient's background and restriction of concomitant medications. In addition, post-approval execution of PMS was requested by Japanese Pharmaceutical Affairs Law in order to accumulate safety and efficacy data for re-examination.		
Research question and objectives:	The study objective was to assess the long-term safety and effectiveness of Tio + Olo FDC 5 µg/5 µg in patients with COPD (chronic bronchitis, emphysema) in real-world setting.		
Study design:	No interventional cohort study with follow up of 52 weeks. (Observational)		
Setting:	Number of study sites: 199 sites Duration of observation: 52 weeks or until discontinuation of administration Registration period: August 2016 to August 2017 Study period: August 2016 to November 2018		
Subjects and study size, including dropouts:	Number of patients registered: 1335 <u>Inclusion criteria</u> · Patients who had been diagnosed with COPD (chronic bronchitis, emphysema) by physician and need to be treated co-administration of		

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	a long-acting inhalational anticholinergic and a long-acting inhalational β2-agonist to relief of various symptoms associated with the obstructive impairment of airways · Patients who were prescribed Tio + Olo FDC 5 µg/5 µg for the first time Exclusion criteria · Patients who had been registered once in this study (i.e., re-entry of patients was not allowed). · Patients who were participating or registry in a clinical trial. · Patients who had a contraindication to Tio + Olo FDC 5 µg/5 µg defined in the package insert for Tio + Olo FDC 5 µg/5 µg.		
Variables and data sources:	**Variables:** Safety All adverse events (AEs) occurring between first drug intakes till 21 days after last drug intake during observation period were analysed. · Adverse Drug Reactions (ADRs) (primary outcome) · AEs leading to death · AEs leading to discontinuation of the Tio + Olo FDC 5 µg/5 µg treatment · Serious Adverse Events (SAEs) · Priority survey items: Cardiovascular AEs, Anticholinergic-related AEs, β2 agonist-related AEs Effectiveness · COPD Assessment Test™ (CAT) at 12 weeks (Secondary outcome) · Patient's global rating (PGR) · Physicians' global assessment · Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV_1) · CAT at 24 weeks and 52 weeks (or discontinuation)		

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	Other Baseline characteristics: · Demographics · Duration of COPD · COPD status (severity [i.e., GOLD stage]) · Tio + Olo FDC 5 µg/5 µg administration status · Medical history/baseline conditions · Previous/concomitant therapies · Concomitant/past medications (start/stop date, dosage, unknown) - COPD (chronic bronchitis, emphysema) medications (inhaled corticosteroid [ICS], long acting β2 agonist [LABA], long acting muscarinic antagonist [LAMA], other, unknown) - Other medications (start/stop date, dosage, unknown) · CAT · FVC and FEV_1 (if the data was available at sites with information of pulmonary medication [i.e., pre-dose or post-dose]) · Pregnancy **Data sources:** Patients' data were collected by electronic Case Report Form (eCRF) on Electronic Data Capture system		
Results:	Disposition of patients In this PMS, 1335 patients were registered at 199 study sites and 1308 patients were entered as treated with Spiolto® Respimat® puffs. Case report forms (CRFs) were collected from 1308 patients. The safety set included 1273 patients (97.32%) and the effectiveness set included 1255 patients (95.95%). More than half of the patients (987 patients, 77.53%) received the treatment over 24 weeks (discontinued: 364 patients, 27.83% of treated 1308 patients).		

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Baseline patient characteristics

In the safety set (N=1273), the majority of patients were male (1067 patients, 83.82%) and aged ≥65 years (1082 patients, 85.00%). Mean age of patients (mean ± SD) was 73.3 ± 9.1 years (range, 38 to 101). COPD duration (mean ± SD) was 3.260 ± 4.192 years in 963 patients. Most patients were smoker (210 patients, 16.50%) or ex-smoker (858 patients, 67.40%). Total CAT score (mean ± SD) was 15.5 ± 8.5 in 698 patients, FVC was 2.666 ± 0.870 L in 865 patients, FEV_1 [L] was 1.515 ± 0.646 L in 870 patients, and FEV_1 [%] was 59.973 ± 23.030% in 829 patients.

Primary outcome (Safety set)

In the safety set (N = 1273), at least one ADR was reported in 50 patients (3.93%). The most frequently reported ADR (Preferred term, hereinafter PT) was thirst (7 patients, 0.55%), followed by cough (5 patients, 0.39%), dysuria and dysphonia (4 patients each, 0.31%), palpitations and dyspnoea (3 patients each, 0.24%), constipation, hypoaesthesia oral, upper respiratory tract infection, and throat irritation (2 patients each, 0.16%). ADRs other than the above were all reported in 1 patient.

A fatal ADR was reported in 1 patient (0.08%), which was sudden death. Other serious ADRs (excluding the fatal ADR) were reported in 4 patients (0.31%), which included angina pectoris, cardiac failure, ileus, and dementia (1 patient each, 0.08%).

Safety summary (Safety set)

The ADRs including important identified and potential risks stated in the Japanese Risk Management Plan (J-RMP) were evaluated in the PMS.

In the safety set (N = 1273), fatal AEs were reported in 38 patients (2.99%). The most frequently reported fatal AEs (PT) were chronic obstructive pulmonary disease (7 patients, 0.55%), followed by death, pneumonia, and malignant neoplasm progression (4 patients each, 0.31%), and interstitial lung disease and pneumonia aspiration (3 patients each, 0.24%). Other than the above, fatal AEs were all reported in n≤2 patients.

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At least one SAE was reported in 94 patients (7.38%). The most frequently reported SAEs (PT) were pneumonia and chronic obstructive pulmonary disease (12 patients each, 0.94%), pneumothorax (7 patients, 0.55%), malignant neoplasm progression (6 patients, 0.47%), cardiac failure (5 patients, 0.39%), death and pneumonia aspiration (4 patients each, 0.31%).

Seventy-five patients (5.89%) discontinued Spiolto® Respimat® puffs due to AEs. The most frequently reported AE (PT) leading to discontinuation of treatment was chronic obstructive pulmonary disease (7 patients, 0.55%), followed by pneumonia (6 patients, 0.47%), cough (5 patients, 0.39%), thirst and pneumonia aspiration (4 patients each, 0.31%), palpitations, malignant neoplasm progression, dysuria, dysphonia, and interstitial lung disease (3 patients each, 0.24%).

At least one AE categorised into priority survey items was reported in 29 patients (2.28%): Cardiovascular AEs occurred in 13 patients (1.02%), anticholinergic-related AEs occurred in 11 patients (0.86%), and β2 agonist-related events occurred in 10 patients (0.79%).

Secondary outcome (Effectiveness set)

Total CAT score (mean ± SD) was 15.5 ± 8.5 at baseline and decreased to 11.7 ± 7.9 at Week 12. Change of CAT score (mean ± SD) from baseline was −3.7 ± 7.1 at Week 12 (95% CI [-4.3, -3.1]). Total CAT score shows preferable decreased after treatment and remained low at Week 12.

Further outcomes (Effectiveness set)

- PGR at each visit

The percentages of "Very much better" and "Much better" in PGR increased from Week 4 to Week 52, represented as 4.88% to 8.78 and 25.39% to 32.15%, respectively, while those of "No change" decreased from 31.65% to 25.62%. In by-visit assessment, the highest percentage during the period from Week 4 to Week 12 was "A little better" (32.10-35.33%), and that at Week 52 was "Much better" (32.15%). More than half

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	of patients assessed either one of "Very much better", "Much better", or "A littler better" throughout the investigated period. · Physician's global assessment at each visit The percentage of "Improved" in the Physician's global assessment was consistently high throughout the investigated period, showing slight increase over time (61.62% at Week 12, 62.77% at Week 24, and 65.58% at Week 52). Overall, no marked changed was noted in each assessment variable. · FVC and FEV_1 FVC at baseline (mean) was 2.722 L and change from baseline (mean ± SD) was 0.103 ± 0.431 L at Week 12, 0.123 ± 0.470 L at Week 24, and 0.115 ± 0.481 L at Week 52. FEV_1 [L] at baseline (mean) was 1.526 L and change from baseline (mean ± SD) was 0.107 ± 0.320 L at Week 12, 0.090 ± 0.299 L at Week 24, and 0.083 ± 0.328 L at Week 52. FEV_1 [%] at baseline (mean) was 59.901% and change from baseline (mean ± SD) was 3.926 ± 11.855% at Week 12, 3.060 ± 11.925% at Week 24, and 2.884 ± 12.482% at Week 52. · CAT at 24 weeks and 52 weeks Total CAT score (mean ± SD) was 15.5 ± 8.5 at baseline and decreased to 11.1 ± 8.3 at Week 24 and 10.6 ± 8.1 at Week 52. Change of CAT score (mean ± SD) from baseline was −4.0 ± 8.1 at Week 24 and −4.2 ± 8.2 at Week 52. Total CAT score decreased after treatment and remained low throughout the investigated period.		

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Discussion:	As for ADRs, 50 patients of all were reported (3.93%). There was no notable trend was found in the incidence rate of ADRs. Most ADRs reported in the PMS were the same as those listed in Japanese package insert of Spiolto® Respimat® puffs, suggesting no remarkable changes were found on the safety profiles from the time of Spiolto® Respimat® puffs approval on 28 September 2015. Total CAT score shows preferable decreased (improved) after treatment and remained low at Week 12. The results for total CAT score at 12 weeks (also 24 and 52 weeks) showed consistent effectiveness profile for long-term use of Spiolto® Respimat® puffs, as shown in the results from clinical trials at the time of Spiolto® Respimat® puffs approval on 28 September 2015. Overall, the PMS results raised no new concerns on the safety and effectiveness profile of Spiolto® Respimat® puffs in long-term daily use in Japanese patients with COPD.		
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