Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiriva® 2.5 µg Respimat® 60 puffs			
Name of active ingredient: Tiotropium			
Report date: 6 June 2018	**Study number:** 205.525	**Version/Revision:** Version 1.0	**Version/Revision date:** Not applicable
Title of study:	Specific Use-Result Surveillance of Spiriva Respimat in Asthmatics (patients with severe persistent asthma)		
Keywords:			
Rationale and background:	In Japan, post-approval execution of post-marketing surveillance (PMS) is requested by the Japanese Pharmaceutical Affairs Law (J-PAL) in order to accumulate safety and effectiveness data for re-examination. This is a regulatory required PMS to investigate the safety and effectiveness of Spiriva® 2.5 µg Respimat® 60 puffs in patients with severe persistent asthma under real-world use.		
Research question and objectives:	The objective of this PMS was to investigate the safety and effectiveness of Spiriva Respimat in patients with severe persistent asthma under real-world use.		
Study design:	Non-interventional, observational study based on new data collection		
Setting:	Planned number of subjects: 360 Comparator product: Not applicable Duration of treatment: 52 weeks		
Subjects and study size, including dropouts:	340 (safety set) Inclusion criteria: · Patients diagnosed with severe persistent bronchial asthma patient aged ≥ 15 years · Patients who are naive to Spiriva Respimat and receive Spiriva Respimat for the first time for treatment of bronchial asthma on top of at least ICS treatment.		
Variables and data sources:	<u>Variables</u> Demographics Medical history/baseline conditions Previous/concomitant therapies Pulmonary function test (peak expiratory flow rate, forced expiratory volume in 1 second, forced vital capacity), if available Asthma severity and asthma control status, if available		

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	ACQ 6 score, if available Spiriva Respimat administration Adverse event Safety laboratory test (if corresponding AEs are reported) <u>Outcomes</u> ・ Primary Outcome; safety The absolute and relative (%) frequency or patients with suspected ADRs. ・ Secondary Outcome; effectiveness Change from baseline in asthma control status at Week 52. ・ Further Outcomes; effectiveness - Change from baseline in PEFR at Week 52 - Change from baseline in FEV1 at Week 52 - Change from baseline in FVC at Week 52 - ACQ 6 score at Week 52 <u>Data sources</u> Patient's data was gathered by electronic Case Report Form on EDC. <u>Main statistical methods</u> This was a non-interventional, observational study to collect new real-world data (i.e., data under routine medical practice) on safety and effectiveness of Spiriva Respimat treatment in patients. Analyses were descriptive in nature. Due to the nature of the observational study, no confirmatory statistical testing was foreseen in this study. The analysis of outcome events included all patients had registered in the study and receiving the Spiriva Respimat treatment. All outcome events were based on reported AE data which was handled according to BI standards. Several interim analyses had been performed for the purpose of creating periodic safety update reports to the local authority (every 6 to 12 months depending on the time from the approval).		
Results:	A total of 359 patients were registered in 50 study sites of Japan. CRFs were collected from 352 patients. The safety set included 340 patients;		

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excluding 12 patients who had no visit after registration. One adverse event was reported from the 12 patients excluded from the safety set. The efficacy set included 308 patients; excluding 32 patients who had no effectiveness data.

Demographic and Baseline Characteristics

Of 340 patients in the safety set, 157 (46.18%) patients were male and 183 (53.82%) patients were female. The mean age was 60.5 ± 15.0 [SD] years, 340 (100.00%) patients were diagnosed severe persistent asthma. 8 (2.35%) patients had concomitant ischemic heart disease, 6 (1.76%) patients had concomitant angina pectoris, 1 (0.29%) patient had concomitant myocardial infarction, 6 (1.76%) patients had concomitant cardiac failure, 7 (2.06%) patients had concomitant cardiac arrhythmia, 2 (0.59%) patients had concomitant renal failure and 13 (3.82%) patients had concomitant COPD. Total of 327 (96.18%) patients had previous medication and 332 (97.65%) patients had concomitant use of any medication.

Treatment Exposure

In overall treatments, the mean duration of Spiriva Respimat treatment was 274.6 ± 152.7 [SD] days, ranged from 5 to 630 days. The average total exposure dose was 1372.82 ± 763.28 [SD] µg ranging from 25.0 to 3150.0 µg. In the safety set, 127 patients [37.4 % (127/340 patients)] were discontinued.

Safety

Of 340 patients included in the safety set, 53 patients had any AEs. 19 patients had 21 ADRs. The incidence of ADRs was 5.59% (the incidence of ADRs was 9.11% (35/384 patients) in the Japanese package insert).

Of 14 SAEs reported from 10 patients, no SAEs related to Spiriva Respimat (serious ADRs) were reported. A fatal AE was reported for a male patient aged 90 years, and the cause of death was asthma bronchial aggravated resulting from cardiorespiratory depression associated with aging. The event was considered to be not related to Spiriva Respimat.

For AEs defined as ‘important identified risks of Spiriva Respimat’ in the

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Japanese RMP, one patient reported 1 event of anaphylactic reaction, which was considered to be not related to Spiriva Respimat.

For AEs defined as 'important potential risks of Spiriva Respimat' in the Japanese RMP, arrhythmia (1 patient, 1 event) and palpitations (1 patient, 1 event) were reported in the surveillance. The arrhythmia was considered to be related to Spiriva Respimat but not serious, and the palpitation was considered to be not related to Spiriva Respimat.

For AEs 'anticholinergic-related AEs', cystitis (1 patient, 3 events), diabetes mellitus (1 patient, 2 events), constipation, dizziness, dry throat, dysuria, gastritis, stomatitis, urinary tract infection and vertigo positional (1 patient, 1 event, each) were reported. Of these AEs, constipation, dry throat and dysuria were considered to be related to Spiriva Respimat but not serious.

For AEs as 'asthma related death/hospitalization/intubation', asthma (14 patients, 16 events), hyperventilation and wheezing (1 patient, 1 event, each) were reported. One patient who experienced asthma died due to the event. The event was considered to be not related to Spiriva Respima. Of the 16 events, 3 were reported as serious, which required hospitalization. All the 3 events were considered to be not related to Spiriva Respimat. Any changes in the precaution were not considered necessary from the results of the surveillance because of the small number of the patients, while the AEs defined in the priority survey items included AEs considered to be related to Spiriva Respimat and were thus classified as expected ADRs.

Effectiveness

The effectiveness was evaluated based on the change of asthma control status from baseline at Week 52, which is the secondary endpoint in the surveillance. The asthma control status was rated on a 3-point scale of well controlled, insufficiently controlled and poorly controlled based on asthma symptoms (in the daytime or at night), use of reliever and limitation of activities including exercise (refer to "Asthma prevention and management guideline" [Ohta K, Ichinose M, Japanese Guideline for Adult Asthma 2014, Allergology Int, 2014,63:293-333]). A total of 45 patients had worsened asthma control status, 24.3% [45/185 evaluable patients in the

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	asthma control status at baseline and Week 52].		
Discussion:	Adverse Drug Reactions Of 340 patients included in the safety set, 21 ADRs were reported in 19 patients. The incidence of ADR was 5.59% (19/340 patients). At the primary system organ class level, the most frequently reported ADRs were 'respiratory, thoracic and mediastinal disorders' (10 events in 9 patients, 2.65% [9/340 patients]), and 'general disorders and administration site conditions' (4 events in 4 patients, 1.18% [4/340 patients]). At the preferred term level, the most frequently reported ADRs were thirst, cough, dysphonia (3 events in 3 patients, 0.88% [3/340 patients], each), and dyspnoea (2 events in 2 patients, 0.59% [2/340 patients]). These ADRs were described in the precaution of the Japanese package insert (expected ADRs). Effectiveness (the change of asthma control status from baseline at Week 52) Of 308 patients in the efficacy analysis set, 248 patients had asthma control status at baseline. For those with good control at baseline, 66.67% (8/12 patients) maintained at week 52. For those with insufficient control at baseline, 58.12% (68/117 patients) improved, 17.95% (21/117 patients) maintained, 4.27% (5/117 patients) worsened. A total of 45 patients worsened asthma control status, that were 24.3% (45/185 patients) in the 185 evaluable patients in the asthma control status at baseline and Week 52. As described above, there were no notable issues in safety and effectiveness analysis of the surveillance, and any changes in the precaution were not to be considered necessary from the results of the surveillance.		
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investigators:			