



Clinical Study Synopsis for Public Disclosure

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Non-interventional Study Report

BI Study Number 1237-0065

c30537446-01

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1. ABSTRACT

Name of company: Boehringer Ingelheim Pharma GmbH & Co. KG			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium + Olodaterol			
Report date: 18 December 2019	Study number: 1237-0065	Version/Revision: Version 1.0	Version/Revision date: N/A
Title of study:	AERIAL®: Changes in health and functional status in patients with COPD during therapy with Spiolto® Respimat® Authors: Dr. [REDACTED] Dr. [REDACTED]		
Keywords:	Chronic obstructive pulmonary disease (COPD), bronchodilation, Spiolto® Respimat®, health status, functional status, patient satisfaction		
Rationale and background:	COPD patients often suffer from impaired health status including low physical activity or physical inactivity. At the time of preparation of this NIS, data regarding health status and physical activity/functional status in COPD patients when treated with Spiolto® Respimat® in routine clinical practice were only available from one non-interventional study. The aim of this NIS was to address this gap regarding limited real world data on health and functional status in COPD patients treated with Spiolto® Respimat®.		
Research question and objectives:	The primary objective of this NIS was to assess the proportion of patients achieving “therapeutic success” (= 0.4 point decrease in the CCQ score, assessing the health status, between baseline and approximately week 6). Secondary objectives were to evaluate changes in CCQ score and CCQ-4 score, assessing the functional state, from visit 1 (baseline visit at the start of the study) to visit 2 (final visit at the end of the study, approx. 6 weeks after visit 1), the patient’s general condition (physician’s evaluation) at visit 1 and at visit 2, as well as patient satisfaction with Spiolto® Respimat® at visit 2 and patients’ willingness to continue treatment with Spiolto® Respimat® after study end (proxy for adherence).		
Study design:	This was an open-label observational study according to §4, section 23 and §67, section 6 German Medicines Act. All included COPD patients have been receiving treatment with Spiolto® Respimat® for approximately 6 weeks, which is the average time between two medical consultations.		
Setting:	This study was performed by Boehringer Ingelheim		

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	<p>Pharma GmbH & Co. KG. The coordinating investigator was Prof. Dr. med. Adrian Gillissen (Ermstaklinik, Kreiskliniken Reutlingen, Bad Urach).</p> <p>The study was submitted to the ethics committee of the State Medical Council of Baden-Württemberg on February 16, 2017 and was accepted on March 07, 2017.</p> <p>It was planned to collect data from approximately 1300 patients from approximately 400 sites in Germany in the period between Q2 2017 and Q2 2018. 1322 patients were registered at 114 sites with the first patient registered on March 31, 2017 and the last on November 10, 2018. Site selection was performed to reflect routine COPD care in Germany and to secure representativeness of the COPD population. Almost all sites were non-hospital (general practitioner and pulmonologists), one site was a pulmonology clinic. Patients were enrolled consecutively and followed over an observational period of approximately 6 weeks.</p>		
Subjects and study size, including dropouts:	<p><u>Inclusion criteria (IC) were:</u></p> <ul style="list-style-type: none"> • Written informed consent prior to participation • Female and male patients ≥40 years of age • Patients diagnosed with COPD and requiring a combination of two long-acting bronchodilators (LAMA + LABA) according to approved Summary of Product Characteristics (SmPC) and Global Initiative For Chronic Obstructive Lung Disease (GOLD) COPD guideline recommendation 2017 (GOLD groups B to D) • Treatment with Spiolto® Respimat® according to SmPC at the discretion of the physician. <p><u>Exclusion criteria (EC) were:</u></p> <ul style="list-style-type: none"> • Patients with contraindications according to Spiolto® Respimat® SmPC • Patients already on a LABA/LAMA combination (free and fixed dose) in the last 6 weeks before study entry • Patients continuing LABA- inhaled corticosteroids (ICS) treatment should not be additionally treated with Spiolto® Respimat® in order to 		

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	<p>avoid a double dosing of long-acting beta-agonists</p> <ul style="list-style-type: none"> • Pregnancy and lactation • Current participation in any clinical trial or any other non-interventional study of a drug or device. <p>Between March 31, 2017 and November 11, 2018, screening was documented for 1351 patients across 114 sites in Germany. 1322 meet inclusion/exclusion criteria, attended visit 1 and received Spiolto® Respimat® treatment and thus were included in treated set (TS). Out of this number, 1140 patients attended visit 2 and had CCQ scores available at both study visits and were included in full analysis set (FAS).</p> <p>Median age of the patients from TS amounted to 65 years (range 40 to 104 years), whereby 49.5% of the patients were older than 65 years. 760 (57.5%) patients were male. Data on ethnicity and race were not collected.</p>		
Variables and data sources:	<p>All relevant data were documented in eCRF.</p> <p>Parameters collected and assessed at visit 1 and/or visit 2 included patient demographics, smoking status and pack-years, concomitant diseases / comorbidities, COPD-related and other concomitant medication, history of exacerbations, breathlessness based on the Modified Medical Research Council Questionnaire (mMRC), health and functional status based on CCQ scores, patient satisfaction with Spiolto® Respimat®, general condition of patient based on physician's global evaluation (PGE), safety and GOLD group.</p> <p>Primary and secondary endpoints were analyzed on the FAS. Safety endpoints and demographic/baseline data were analyzed on the TS. For categorical variables summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter are presented. For continuous variables number of values, mean, standard deviation, minimum, median, maximum and number of missing values are presented. Incidence rates and 95% CI are given when appropriate.</p>		
Results:	<p><u>Primary objective:</u></p> <p>The primary objective "therapeutic success" was achieved by 66.3% of patients while in 33.3% of patients the therapy with Spiolto® Respimat® did</p>		

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<p>not meet the threshold for therapeutic success (0.4 decrease in CCQ score).</p> <p><u>Secondary objectives:</u></p> <p>The median total CCQ score at visit 1 was 3.2 (range 0 to 6) and improved to 2.3 (range 0 to 6) at visit 2 approximately six weeks later. The median absolute change in CCQ score was 0.7 (range -2.5 to 4.9). The largest absolute changes were observed in categories “Symptoms” (median 0.75, range -3.5 to 5) and “Functional state (CCQ-4)” (median 0.75, range -3.75 to 4.75). The least improvement was observed for category “Mental state” (median 0.5, range -4.5 to 6).</p> <p>Patient’s general condition as assessed by physician (PGE) improved during the treatment period between visit 1 and visit 2. At visit 1, most of the patients had a PGE score of 4 (378 patients, 33.2%), followed by patients with PGE score 3 (281, 24.7%) and score 5 (195, 17.1%). At visit 2 approximately six weeks later, there was an improvement in patient’s general condition. The PGE score was 5 in 33.7% of the patients (n=350), 6 in 28.5% of the patients (n=325) and 4 in 19.6% of the patients (n=223). A single patient had no PGE score documented at visit 2.</p> <p>971 patients (85.2%) were “Very satisfied” and “Satisfied” with the overall treatment with Spiolto® Respimat®. Furthermore, 1008 (88.4%) and 979 (85.9%) patients were at least satisfied with inhaling and handling of the device, respectively.</p> <p>Of the 1254 patients attending visit 2 1194 patients (95.2%) declared a willingness to continue treatment with Spiolto® Respimat®. Among the remaining 60 patients (4.8%), the most frequent reasons for therapy discontinuation were “Patient’s wish” (38 patients, 3%) and “Adverse event” (13 patients, 1%).</p> <p><u>Safety analysis:</u></p> <p>The safety analysis was performed on all 1322 patients from the TS. Similar as in the former NIS SPIRIT, only 17 patients (1.3%) experienced at least one AE classified as drug-related by the investigator. Amongst the 23 documented drug-related AE, “vertigo” and “nausea”, “dry mouth”, “oedema peripheral”, “paraesthesia” and “hypertension” were the most</p>			

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	<p>often reported events whereat only “oedema peripheral” and “paraesthesia” are not mentioned in the SmPC.</p> <p>Most drug-related AEs had a NCI grade of 1 and the maximal documented NCI grade was 3.</p> <p>The dug-related AEs recovered/resolved in 13 patients and 4 patients had an ongoing drug-related AE at end of the observational study. There was only one serious AE (0.08% of all patients from TS) documented, namely “Pulmonary embolism”. This serious AE was not drug-related and is not mentioned in the Spiolto Respimat SmPC. This serious AE was life threatening, led to hospitalization and was ultimately fatal.</p>		
Discussion:	<p>Treatment with Spiolto® Respimat® under routine medical care conditions emerged as an effective and safe therapy, even in a COPD patient population suffering from a variety of concomitant diseases. However, most enrolled patients did not receive a prior treatment in accordance with the 2017 and just published 2020 GOLD guideline, indicating that investigators often do not follow GOLD recommendations for COPD therapy in real-world practice.</p> <p>Treatment with Spiolto® Respimat® improved health and functional status (as demonstrated by the CCQ score and CCQ-4 score) and the general condition of the patients evaluated by the investigator (as shown by PGE score). Of note, the largest benefit of Spiolto® Respimat® therapy in terms of improved health status was experienced by maintenance naïve patients. Symptoms and mental state were also improved by the treatment with Spiolto® Respimat® (as demonstrated by the scores for these CCQ domains). The great majority of patients was very satisfied and satisfied with the overall treatment with Spiolto® Respimat® as well as inhaling from and handling of the Respimat® device. Furthermore, nearly all patients declared their willingness to continue the treatment after study end.</p> <p>Safety analysis demonstrated that there were less drug-related AEs in this observational study than in prior clinical trials and in one non-interventional study in which all AE had to be collected. Thus in routine care, investigators seem not to enquire patients actively about AEs at visits.</p>		

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Marketing Authorisation Holder(s):	Boehringer Ingelheim International GmbH Binger Strasse 173 D-55216 Ingelheim am Rhein Germany		
Names and affiliations of principal investigators:	Investigators of each participating site are listed in a stand-alone document (see Annex 1 : List of stand-alone documents, which is available upon request).		