Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

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: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide(Ba679)+ Olodaterol(BI 1744)			
Report date: 02 Aug 2019	**Study number:** 1237.58	**Version/Revision:** NA	**Version/Revision date:** NA

Title of study:	Assessment of physical functioning and handling of Spiolto® Respimat® in patients with chronic obstructive pulmonary disease (COPD) requiring long-acting dual bronchodilation in routine clinical practice.
Keywords:	COPD; Spiolto® Respimat®; long-acting dual bronchodilation, fixe-dose combination; physical activity; NIS
Rationale and background:	Reduced physical activity resulting in deconditioning and restricted physical functioning is a common constraint of patients with moderate to very severe COPD. Clinical studies investigating treatment with Spiolto® Respimat® and its single components have shown significant improvements in exercise capacity in patients with COPD. Real-world data from Spain on the effects of a fixed-dose combination (LABA+LAMA) therapy with tiotropium and olodaterol administered in a single device, in COPD patients who need treatment with two long acting bronchodilators, is not available yet.
Research question and objectives:	The primary objective of the study was to measure changes in physical functioning - serving as a surrogate for physical activity and exercise capacity - in COPD patients being treated with Spiolto® Respimat® after approximately 6 weeks. The secondary objectives were to assess the changes in PF-10 score from visit 1 (baseline visit at start of the study) to visit 2 (final visit, approximately 6 weeks after visit 1), the patient's general condition (physician's assessment – PGE score) at visit 1 and at visit 2, as well as patient satisfaction with Spiolto® Respimat® at visit 2.
Study design:	Open-label observational study, including COPD patients in Spain receiving treatment with Spiolto® Respimat® for approximately 6 weeks, which is the average time between two medical consultations.
Setting:	Patients 'data from 57 Spanish sites was collected (primary care centres). Sites were selected to reflect routine clinical practice for COPD in order to ensure the representativeness of the population with COPD.
Subjects and study	Patients who met all the selection criteria indicated below were considered

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide(Ba679)+ Olodaterol(BI 1744)			
Report date: 02 Aug 2019	**Study number:** 1237.58	**Version/Revision:** NA	**Version/Revision date:** NA

size, including dropouts:

eligible to take part in the study:

Inclusion criteria

1. Written informed consent prior to participation
2. Female and male patients ≥ 40 years of age
3. Patients diagnosed with COPD and requiring long-acting dual bronchodilation (LAMA + LABA) treatment according to approved Spiolto® Respimat® SmPC and COPD GOLD guideline recommendation

Exclusion criteria

1. Patients with contraindications according to Spiolto® Respimat® SmPC
2. Patients who had been treated with a LABA/LAMA combination (free and fixed dose) in the previous 6 months
3. Patients continuing LABA-ICS treatment should not be additionally treated with Spiolto® Respimat® in order to avoid a double dosing of long-acting beta-agonists
4. Patients for whom further follow-up was not possible at the enrolling site during the planned study period of approximately 6 weeks
5. Pregnancy and lactation
6. Patients currently listed for lung transplantation
7. Current participation in any clinical trial or any other non-interventional study of a drug or device

It was planned to collect data from approximately 1000 patients of 200 primary care centres from 10 autonomous communities in Spain (Castilla León, Cataluña, La Rioja, Murcia, País Vasco, Galicia, Aragón, Baleares, Navarra and Extremadura). The recruitment period was planned to be completed in 6 months. Finally, as only 82 of these 200 sites could be initiated in the 5 authorized autonomous communities, and the recruitment rate was very low, it was extended up to 16 months. In spite of this, only 58 investigators from 57 sites included 257 patients: 85 patients were enrolled in Castilla y León, 13 patients in Cataluña, 14 patients in La Rioja, 78 patients in Murcia and 67 patients in País Vasco. The included patients in Cataluña were lower than expected because the Ethics Committee that integrated the majority of the primary care centers in that region rejected the study. Hence, the final number of patients included was not

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide(Ba679)+ Olodaterol(BI 1744)			
Report date: 02 Aug 2019	**Study number:** 1237.58	**Version/Revision:** NA	**Version/Revision date:** NA
	representative of the population of that region. Other participating regions enrolled a number of patients that was proportional to the region's population, although the recruitment was lower than expected in all of them. All enrolled patients (257) were eligible and considered for the analysis population set of the Screening patients (patients with signed informed consent and date of registration). 253 patients were considered for the Treated Set (subjects who received at least one dose of Spiolto® Respimat®), and 234 patients for the Full Analysis Set (subjects who received treatment with Spiolto® Respimat® and had available PF-10 scores at visit 1 and visit 2).		
Variables and data sources:	**For the primary objective:** Percentage of patients with "Therapeutic success" at Week 6 approximately (10-point increase in the PF-10 score between visit 1 and visit 2). **For the secondary objectives:** - Changes in PF-10 score from visit 1 to visit 2 - Patient's general condition assessed by the physician (PGE score) at visit 1 and visit 2. - Patient satisfaction with Spiolto® Respimat® at visit 2. In addition, at visit 1 and/or visit 2 the following parameters were analyzed: • Patients demographic data (age, sex, height and weight) • Smoking status • Reported exacerbations • Dyspnoea based on the mMRC score at visit 1 • GOLD spirometric classification (1, 2, 3, 4) • GOLD group of patients (A, B, C, D) • Comorbidities • Medication related to COPD and other concomitant medication • Details of treatment with inhaled drugs for the airways prior to the study • Details of treatment with inhaled drugs for the airways during the study • Reasons for ending treatment during the observation period • Details of treatment continuation/discontinuation		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide(Ba679)+ Olodaterol(BI 1744)			
Report date: 02 Aug 2019	**Study number:** 1237.58	**Version/Revision:** NA	**Version/Revision date:** NA
	• Adverse drug reaction (ADR and SADR), fatal AEs, pregnancies		
Statistical methods:	In this observational study, cross-sectional data was collected at the start of the study and longitudinal follow-up data was collected in the 6-week period for patients with COPD disease requiring dual bronchodilator therapy in routine clinical practice. Main analysis: The main analysis population consisted of the Full Analysis Set. The primary endpoint was the percentage of patients with therapeutic success at visit 2, at approximately 6 weeks, (defined as a 10-point increase in the PF-10 score between visit 1 and visit 2). It was analyzed using absolute and relative frequencies, together with the 95% confidence interval. For the secondary endpoints: - The change from visit 1 to visit 2 in the PF-10 score was a continuous assessment criterion, so it was analyzed by: n (total number of valid values), mean, standard deviation (SD), 95% confidence interval of the mean (95% CI), median, 25th and 75th percentiles (P25 and P75, respectively), minimum and maximum (min and max, respectively). - The patient's general condition (PGE score) at visit 1 and visit 2, the mMRC at visit 1 and patient satisfaction at visit 2 were categorical endpoints, so they were analyzed in frequency tables. Further endpoint: The following subgroup analysis were performed: - Subgroup analysis for maintenance naïve patients and the ones already treated at baseline with long acting bronchodilators were performed for the primary outcome. - Subgroup analyses were performed by GOLD spirometric classifications (2 vs. 3/4) and GOLD patient groups –version 2014 and 2017- (B vs.C/D and B vs. C vs. D) for the primary endpoint and changes in PF-10 for the secondary outcome. In addition, as planned in the protocol, a descriptive subgroup analysis was developed for the primary endpoint of the following subgroups based on baseline endpoints (visit 1) and follow-up endpoint (visit 2). These analyses were described in the Statistical Analysis Plan:		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide(Ba679)+ Olodaterol(BI 1744)			
Report date: 02 Aug 2019	**Study number:** 1237.58	**Version/Revision:** NA	**Version/Revision date:** NA
	- Baseline treatment with ICS (Yes vs No), only in the case of subgroups representing more than 20% - Age (< 65 years vs ≥ 65 years) - Exacerbations in the last 12 months (≤ 1 vs ≥ 2) - Exacerbations related to hospitalisations (0 vs ≥ 1) - Continuation of treatment with Spiolto® Respimat® after 6 weeks of study (visit 2) - Patient satisfaction with Spiolto® Respimat® after 6 weeks of treatment (visit 2) Baseline data were described using a cross-sectional approach. Longitudinal follow-up data were summarised descriptively. Due to the observational nature of this study, it was not planned to carry out (confirmatory) hypothesis testing in a strict statistical sense. Analyses were descriptive in nature and confidence intervals and p-values from statistical models were used for exploratory purposes. No adjustments for multiple testing were carried out in the statistical significance evaluation. No interim analysis was conducted for this study.		
Results:	257 patients were enrolled in this study, of which 253 took at least one documented administration of Spiolto® Respimat®. Patients population consisted of 73.1% of males (n=185) and 26.9% of females (n=68). 64.4% of patients were older than 65 years old (n=163), with a mean (SD) age of 68.41 (10.83) years old. 51.8% of the total number of patients were ex-smokers (n=131), 36.8% were current smokers (n=93) and only 11.5% of patients were non-smokers (n=29). The mean time from the COPD diagnosis to the baseline visit date was 6.59 (SD 6.56) years, with 48.2% of patients experiencing a moderate COPD exacerbation episode in the last 12 months (n=122). The mean (SD) baseline FVC was 2401.64 (1186.65) ml, FVC (%) 71.02 (25.56), FEV_1 1513.62 (735.69) ml, FEV_1 (%) 56.86 (18.36) and FEV_1/FVC 0.60 (0.10). According to the GOLD classification of severity, 66.4% of patients had moderate COPD (n=89) and 20.9% severe COPD (n=28). 71.1% of patients reported to have concomitant disease (n=180), with		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide(Ba679)+ Olodaterol(BI 1744)			
Report date: 02 Aug 2019	**Study number:** 1237.58	**Version/Revision:** NA	**Version/Revision date:** NA

	cardiovascular diseases, musculoskeletal disorders and diabetes mellitus being the most frequent of them. 68.9% of patients received concomitant medication (n=173), with 75.1% receiving medication for the cardiovascular system (n=130). 58.2% of patients (n=147) had already received treatment for COPD in the previous 6 months, with LAMA being the most frequent medication given (32.5%). On the other hand, 7.9% of patients (n=20) received during the study other inhaled medications for the COPD, in addition to the study treatment. After approximately 6 weeks of treatment (visit 2), 155 patients (66.2%) showed "Therapeutic success", which means that 2 out of 3 patients experienced an improvement in the development of their ability to carry out routine activities after being treated with Spiolto® Respimat®. Mean PF-10 score was 55.90 (SD 22.65) at visit 1, and 71.94 (SD 20.03) at visit 2, with a mean difference of 16.04 (SD 18.18) ($p<0.0001$). In patients with therapeutic success, the average increase in the PF-10 score was 24.43 (SD 15.49) points, which was more than double the definition given for "therapeutic success", established in 10 points. A statistically significant improvement in the general condition of the patients (PGE score) between visit 1 and visit 2 was also observed: 33.3% of patients (n=78) obtained a good or excellent pooled PGE score at visit 1. This percentage increased to 73.5% (n=172) at visit 2 ($p<0.0001$). Moreover, 77.2% patients (n=170) showed satisfaction with the treatment, with 8 out of 10 patients satisfied or very satisfied with the inhalation and with the handling of the Respimat® inhalation device. Only 4 patients suffered an adverse event, 3 of them adverse drug reactions (2 coughs and 1 oropharyngeal pain) and 1 serious adverse event (ischaemic stroke) with outcome of exitus, not assessed as being causally related with the study treatment. There was no pregnancy reported during the study.
Discussion:	In clinical trials improvement of lung function and clinical symptoms of COPD patients were accompanied by enhanced quality of life as measured by patient's questionnaires. This observational study was intended to measure changes in physical functioning in COPD patients on once daily treatment with tiotropium/olodaterol fixed combination after approximately

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide(Ba679)+ Olodaterol(BI 1744)			
Report date: 02 Aug 2019	**Study number:** 1237.58	**Version/Revision:** NA	**Version/Revision date:** NA

6 weeks in routine clinical practice.

Patients of all degrees of COPD severity have been included.

After approximately 6 weeks of treatment with tiotropium + olodaterol a therapeutic success for improvement in physical functioning was seen in 66.2% of the analyzed patients. This was accompanied by an improvement in patients' general condition shown by the shift to higher PGE scores at Visit 2 compared to Visit 1. In addition, More than 77% of the patients included in FAS were generally satisfied or very satisfied with Spiolto® Respimat® treatment (77.2%), with inhaling from the Respimat® device (79.9%) as well as with the handling of the device (79.0%).

Regarding safety, no unexpected drug-related AEs occurred. The number of drug-related AEs documented was considered to be low, and the events documented were in line with the SmPC.

Thus, Spiolto® Respimat® treatment during approximately 6 weeks showed an improvement in the parameters defined by the primary endpoint of this NIS even in a patient population who suffered from several different concomitant diseases, mainly affecting the cardiovascular, musculoskeletal metabolic/endocrine systems. Most patients took concomitant medications for the treatment of concomitant diseases in addition to COPD treatment.

The intention of this NIS was to collect new data on the physical functioning and exercise capacity of COPD patients on treatment with Spiolto® Respimat® in a real world setting. A sample of approximately 1000 patients would have offered the opportunity to document and assess the physical functioning and exercise capacity of COPD patients on treatment with Spiolto® Respimat® in a representative patient population. However, only 257 evaluable patients were enrolled in the study due to recruitment failure in Spain. Therefore, the number of included patients in this study may be too low for the results to be representative for COPD patient population in Spain.

Other study limitations or potential impacts on generalizability were the 7-item satisfaction scale, which was a self-designed Boehringer-Ingelheim scale without a public source or validation status.
The number of patients included, as compared to the initial planned number, also limited the statistical power to see differences in the subgroup analyses.

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide(Ba679)+ Olodaterol(BI 1744)			
Report date: 02 Aug 2019	**Study number:** 1237.58	**Version/Revision:** NA	**Version/Revision date:** NA
Marketing Authorisation Holder(s):	MAH: Boehringer Ingelheim International GmbH Binger Straße173 55216 Ingelheim am Rhein This study was initiated, managed and sponsored by: Boehringer Ingelheim España, S.A C/ Prat de la Riba, 50 08174 Sant Cugat del Vallés (Barcelona)		
Names and affiliations of principal investigators:	The coordinating investigator was the following: Dr. [redacted] [redacted] Spain		