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Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide + Olodaterol			
Report date: 07 December 2018	**Study number:** 1237.45	**Version/Revision:** 1.0 Final	**Version/Revision date:** N.A.

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:	Chronic obstructive pulmonary disease (COPD), bronchodilation, Spiolto® Respimat®, physical functioning, NISND
Rationale and background:	Reduced physical activity resulting in deconditioning and restricted physical functioning is a common problem of patients with moderate to 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 on physical functioning and 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.
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 (Visit 2) compared to baseline (Visit 1). The secondary objective was to evaluate the changes in PF-10 score from Visit 1 to Visit 2, the patient's general condition (Physician's Global Evaluation – PGE score) at Visit 1 (=baseline visit at the start of the study) and at Visit 2 (= final visit approx. 6 weeks after Visit 1), as well as patient satisfaction with Spiolto® Respimat® at Visit 2. The primary endpoint of this NIS was to determine the percentage of patients with therapeutic success at Visit 2 [approximately 6 weeks after Visit 1 (=baseline)] as reported by patients using the PF-10 questionnaire. Secondary endpoints were changes in the PF-10 score from Visit 1 to Visit 2, general condition of the patient evaluated by the physician (PGE score) at Visit 1 and Visit 2, and patient satisfaction with Spiolto® Respimat® at Visit 2.
Study design:	Open-label observational study conducted in 6 countries, including COPD patients receiving treatment with Spiolto® Respimat® for approximately 6

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	weeks, which is the average time between two medical consultations.
Setting:	Between August 2016 and November 2017, 68 investigation sites in 6 countries (Belgium, Denmark, Luxembourg, the Netherlands, Portugal, Sweden), mainly office based pulmonologists and general practitioners, participated in this NIS. The first patient was screened on 08 November 2016 and the last patient was screened on 28 September 2017. Last patient out (LPO) was on 14 December 2017. In total, 132 patients of the planned 1200 patients were screened in 30 investigational sites. Patient enrolment was discontinued prematurely due to recruitment failure.
Subjects and study size, including dropouts:	The following inclusion criteria were defined: • Written informed consent prior to participation • Female and male patients ≥ 40 years of age • Patients diagnosed with COPD and requiring long-acting dual bronchodilation (LAMA + LABA) treatment according to approved Spiolto® Respimat® SmPC and COPD GOLD Strategy Document recommendation Patients fulfilling any of the following exclusion criteria were excluded from study participation: • Patients with contraindications according to Spiolto® Respimat® SmPC • Patients who have been treated with a LABA/LAMA combination (free and fixed dose) in the previous 6 weeks • 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 • Patients for whom further follow-up is not possible at the enrolling site during the planned study period of approx. 6 weeks • Pregnancy and lactation • Patients currently listed for lung transplantation • Current participation in any clinical trial or any other non-interventional study of a drug or device

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	A total of 132 patients were screened. Patient enrolment was terminated prematurely due to recruitment failure. Of these, 3 patients were excluded because they already had started Spiolto® Respimat® treatment before informed consent. Another 2 patients were excluded because they had no Visit 1. 127 patients (96.2%) were enrolled, registered and received at least one dose Spiolto® Respimat® and therefore were included in the Treated Set. The Full Analysis Set (FAS) for analysis of primary and secondary end points consisted of 107 patients (81.1%) who received treatment with Spiolto® Respimat® and had Visits 1 and 2 documented as well as completed all questionnaires.

Variables and data sources:	The following parameters were collected and assessed at Visit 1 and/or Visit 2:
	At Visit 1 (baseline visit):
	• Patients demographics (year of birth, gender, height & weight)
	• Medical history:
	  o Year of initial COPD diagnosis
	  o Number of exacerbations and number of exacerbations leading to hospitalization within the last 12 months
	  o Spirometric COPD severity, according to GOLD classification (1, 2, 3,4) and according to GOLD classification ABCD
	• Spiolto® Respimat® administration (date of first administration, training of Respimat® handling provided)
	• Severity of breathlessness based on the Modified Medical Research Council Questionnaire (mMRC) score
	
	At Visit 1 and Visit 2
	• Patients smoking history at Visit 1 and changes in smoking habits at Visit 2
	• Medical history:
	  o Concomitant diseases
	  o COPD related and other relevant concomitant medication
	  o Treatment with other respiratory therapeutics (Visit 1: within

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	the last 6 months; Visit 2: changes in treatment since Visit 1) • General condition of the patient based on Physician's Global evaluation (PGE) • Physical functioning based on PF-10 scores At Visit 2 • Patient satisfaction with Spiolto® Respimat® therapy (with the overall Spiolto® Respimat® treatment, inhaling from the Respimat® inhaler and its handling) • Patient compliance with the inhaler therapy • Decision whether treatment with Spiolto® Respimat® will be continued or not • Occurrence of any serious/non-serious ADR, fatal AE or pregnancy
Statistical Methods:	All analyses for primary and secondary endpoints are descriptive and were performed on the full analysis set. For the primary endpoint, the percentage of patients with therapeutic success was presented together with the 95% confidence interval. For the secondary endpoints, i.e. for general condition of patients and patient's satisfaction with Spiolto® Respimat®, the number and percentage of patients within each category was displayed. For absolute changes in PF-10 score, summary statistics (mean, standard deviation, minimum, median, maximum) were provided. No formal interim analysis was performed.
Results:	A total of 132 patients were screened, but 3 patients were excluded because they already had started Spiolto® Respimat® treatment before informed consent. Another 2 patients were excluded because they had no Visit 1, however the reason for not performing Visit 1 was missing. 127 patients (96.2%) could be included in the Treated Set (TS). Due to different reasons (e.g. patient's wish, loss of contact) Visit 2 was documented only for 114 patients (86.4%). 107 of these patients (81.1%) with evaluable Visit 2 and with all questionnaires available were evaluable for analysis of primary and secondary end points, defined as Full Analysis set (FAS).

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Demographics (TS)

More women (78 patients; 61.4%) than men (49 patients; 38.6%) were enrolled. The median age at registration was 70 years (range 40-89 years).

79 patients (59.8%) suffered from concomitant diseases, mostly affecting the cardiac, vascular, metabolic/endocrine and muscular-skeletal/dermatological system. About half of the patients received concomitant medication other than respiratory therapeutic agents (52.8%).

30.7% of the patients were smokers and 64.6% were ex-smokers. Median pack-year history of 35 for both smokers and ex-smokers. 4.7% had never smoked.

Study Disease (TS)

Most patients had documented COPD degree of spirometric severity of 2 (48.8 %) or 3 (36.3 %). The main outcome of the mMRC questionnaire evaluation was grade 2 (38.6%), followed by grade 1 (36.2%). Most patients (76.4 %) had shown no or only one exacerbation in the last 12 months (46.5 % and 29.9 %, respectively).

Based on GOLD version 2014 classification, 39.4% of patients had GOLD D, followed by GOLD B (22.8%), GOLD A (20.5%) and GOLD C (17.3%). When applying GOLD version 2017 classification, based on “exacerbations and symptoms only”, the share of patients with GOLD D decreased to 14.2%, 48.0% of patients had GOLD B, 28.4% GOLD A and 9.5% GOLD C.

Primary Endpoint (FAS)

Percentage of patients with therapeutic success, defined as a minimum 10-point increase in the PF-10 score after approximately 6 weeks of treatment with Spiolto® Respimat®, was observed for slightly less than half of the patients in FAS (44.9% [Cl-95% 35.2-54.8%].

Secondary Endpoints (FAS)

Change of PF-10 score from Visit 1 to Visit 2 amounted to a mean of 7.6 points (SD: 17.6). Median change was 5 points.

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	PF-10 score		
	Baseline (Visit 1)	Mean (SD)	49.53 (22.41)
		Median (min, max)	50.00 (0.00, 100.00)
		CI 95%	45.23 – 53.82
	Week 6 (approximately) (Visit 2)	Mean (SD)	57.17 (23.04)
		Median (min, max)	55.00 (0.00, 100.00)
		CI 95%	52.75 – 61.58
	Change of PF-10 score between baseline and approx. 6 weeks		
		Mean (SD)	7.64 (17.60)
		Median (min, max)	5.00 (-55.00, 60.00)
		CI 95%	4.27-11.01
	Most of the patients had a PGE score of 4 (26.2%) or 6 (17.8%) at Visit 1. At Visit 2 an improvement of general condition was observed. Greatest share of patients had a PGE score of 6 (30.8%) or 7 (18.7%) corresponding to a good general condition. The PGE score shifted from a median score of 5 at Visit 1 to a median score of 6 at Visit 2.		

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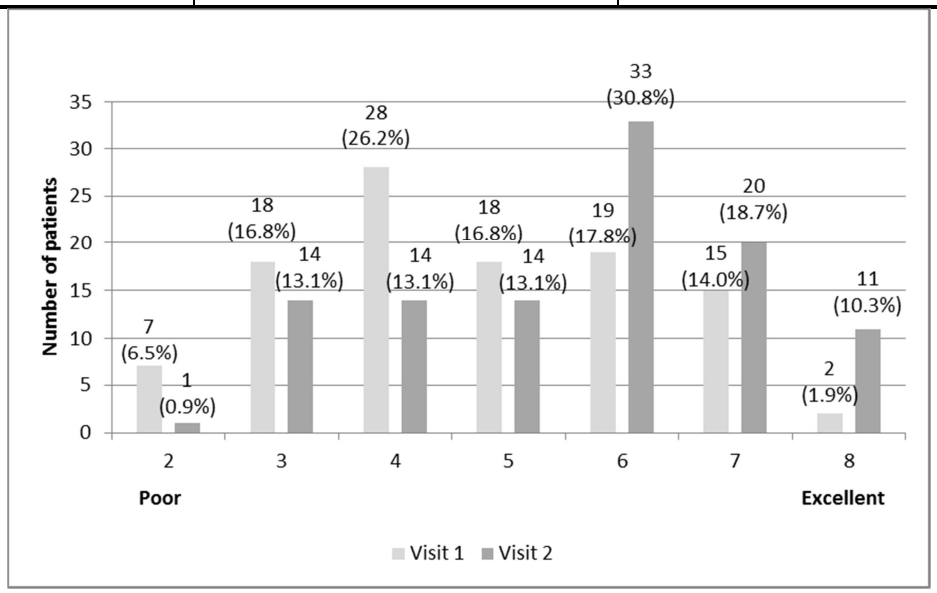

More than 70% of the patients included in FAS were at least satisfied or rather satisfied with Spiolto® Respimat® treatment (79.4%), with inhaling from the Respimat® device (84.1%) as well as with the handling of the device (86.0%).

Patient satisfaction		N	%
Patient overall satisfaction with Spiolto® Respimat® treatment	Very satisfied	20	18.69
	Satisfied	43	40.19
	Rather satisfied	22	20.56
	Neither satisfied nor dissatisfied	14	13.08
	Rather dissatisfied	4	3.74
	Dissatisfied	3	2.80
	Very dissatisfied	1	0.93
	Number of patients	107	100.00
Patient satisfaction with inhaling from the Respimat® device	Very satisfied	25	23.36
	Satisfied	45	42.06

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	Rather satisfied	20	18.69
	Neither satisfied nor dissatisfied	10	9.35
	Rather dissatisfied	5	4.67
	Dissatisfied	2	1.87
	Number of patients	107	100.00
Patient satisfaction with handling of the Respimat® inhalation device	Very satisfied	33	30.84
	Satisfied	45	42.06
	Rather satisfied	14	13.08
	Neither satisfied nor dissatisfied	9	8.41
	Rather dissatisfied	5	4.67
	Dissatisfied	1	0.93
	Number of patients	107	100.00

Safety (TS)

No patients in the treated set died during the observation. 3 patients (2.4%) showed at least one investigator defined non-serious drug related adverse event and one patient had had an investigator defined non-serious drug related adverse event leading to discontinuation of trial drug.

A total of 3 non-serious drug-related adverse events were documented, these were “cough”, “dry mouth” and “Dyspnoea”. One of the 3 patients recovered from his event. A therapy was not required. None of the patients with events were pregnant. For one patient treatment was discontinued due to “Dyspnoea”. Serious Treatment Emerging Adverse Events did not occur.

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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 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 44.9% of analyzed patients. This was accompanied by improvement in patients' general condition shown by the shift to higher PGE scores at Visit 2 compared to Visit 1. More than 70% of patients were at least satisfied or rather satisfied with Spiolto® Respimat® treatment, and over 80% were at least satisfied or rather satisfied with inhaling from and handling of the Respimat® device. Regarding safety, no unexpected drug-related AEs occurred. All documented drug-related AEs were in line with the SmPC. 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 1200 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 107 evaluable patients were enrolled in the study due to recruitment feasibility in MIDI. The number of patients is too low for the results to be representative for COPD patients in the 6 participating countries.		
Marketing Authorisation Holder(s):	Boehringer Ingelheim International GmbH Binger Strasse 173 D-55216 Ingelheim am Rhein Germany <u>This study was initiated, managed and sponsored by:</u> Boehringer Ingelheim nv Division Medicine/Medical Affairs		

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