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**.

The synopsis is supplied for informational purposes only in the interests of scientific disclosure. It must not be used for any commercial purposes and must not be distributed, published, modified, reused, posted in any way, or used for any other purpose without the express written permission of Boehringer Ingelheim.

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

1. ABSTRACT

Name of company: Boehringer Ingelheim Pharma GmbH&Co.KG			
Name of finished medicinal product: Spiolto® Respimat® 2.5 microgram/2.5 microgram per puff inhalation solution			
Name of active ingredient: Pharmacotherapeutic group: drugs for obstructive airway diseases, adrenergics in combination with anticholinergics ACT code: R03AL06 active substances: tiotropium bromide + olodaterol			
Report date: 6 Nov 2017	**Study number:** 1237.42	**Version/Revision:** **Draft** 1.0	**Version/Revision date:** Not applicable
Title of study:	SPIRIT: 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. Author: Dr. [redacted] Germany Date: 6 November 2017		
Keywords:	Chronic obstructive pulmonary disease (COPD), bronchodilation, Spiolto® Respimat®, FDC, 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 exercise data on the effects of a fixed-dose combination therapy of tiotropium and olodaterol administered in a single device in COPD patients who need treatment with two long-acting bronchodilators are not yet available.		
Research question and objectives:	The primary objective of this NIS was to measure changes in physical functioning – as a surrogate for physical activity and exercise capacity – in COPD patients on treatment with Spiolto® Respimat® after approximately 6 weeks. Secondary objectives were to evaluate changes in the PF-10 score from visit 1 to visit 2 the patient's general condition (physician's evaluation) at visit 1 (baseline visit at the start of the study) and at visit 2 (final visit at the end of the study, approx. 6 weeks after visit 1), as well as patient		

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim Pharma GmbH&Co.KG			
Name of finished medicinal product: Spiolto® Respimat® 2.5 microgram/2.5 microgram per puff inhalation solution			
Name of active ingredient: Pharmacotherapeutic group: drugs for obstructive airway diseases, adrenergics in combination with anticholinergics ACT code: R03AL06 active substances: tiotropium bromide + olodaterol			
Report date: 6 Nov 2017	**Study number:** 1237.42	**Version/Revision:** **Draft** 1.0	**Version/Revision date:** Not applicable

	satisfaction with Spiolto® Respimat® at visit 2. The primary endpoint was "therapeutic success" at visit 2 (10-point increase in the PF-10 score between visit 1 and visit 2). 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 prospective observational study according to §4, section 23 and §67, section 6 German Medicines Act: all included COPD patients received treatment with Spiolto® Respimat® for approximately 6 weeks, which is the average time between two medical consultations.
Setting:	Between February 2016 and February 2017, 258 German investigational sites, mainly office-based pulmonologists and general practitioners, participated in NIS Spirit. The first patient was registered on 11 Feb 2016 and the last patient on 20 Feb 2017. Last patient last visit (LPLV) was on 06 Mar 2017.
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 SmPC and GOLD COPD guideline recommendation version 2015. Patients fulfilling 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

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim Pharma GmbH&Co.KG			
Name of finished medicinal product: Spiolto® Respimat® 2.5 microgram/2.5 microgram per puff inhalation solution			
Name of active ingredient: Pharmacotherapeutic group: drugs for obstructive airway diseases, adrenergics in combination with anticholinergics ACT code: R03AL06 active substances: tiotropium bromide + olodaterol			
Report date: 6 Nov 2017	**Study number:** 1237.42	**Version/Revision:** **Draft** 1.0	**Version/Revision date:** Not applicable

	or fixed dose) in the previous 6 months • 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 • Patient for whom further follow-up is not possible at enrolling site during 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. Overall, 1781 COPD patients had been screened. Of these, 1737 patients (97.5%) gave their written informed consent for study participation and received at least 1 application with Spiolto® Respimat® and could therefore be evaluated for baseline/demographic data and safety analysis. The full analysis set (FAS) for analysis of primary and secondary endpoints consisted of 1578 (88.6%) patients who received treatment with Spiolto® Respimat® and had visits 1 and 2 documented as well as filled in all questionnaires.
Variables and data sources:	The following parameters were collected and assessed at visit 1 and/or visit 2: - At baseline visit: • Patient demographics (year of birth, sex, height & weight) and smoking history • Medical history o Year of initial COPD diagnosis o GOLD spirometric classification (1, 2, 3, 4) and GOLD

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim Pharma GmbH&Co.KG			
Name of finished medicinal product: Spiolto® Respimat® 2.5 microgram/2.5 microgram per puff inhalation solution			
Name of active ingredient: Pharmacotherapeutic group: drugs for obstructive airway diseases, adrenergics in combination with anticholinergics ACT code: R03AL06 active substances: tiotropium bromide + olodaterol			
Report date: 6 Nov 2017	**Study number:** 1237.42	**Version/Revision:** **Draft** 1.0	**Version/Revision date:** Not applicable

	patient group (A, B, C, D) based on GOLD guidelines 2015 o Number of exacerbations and number of exacerbations leading to hospitalization within the last 12 months o Spiolto® Respimat® administration history o Treatment with other respiratory therapeutics within the last 6 months before start of Spiolto® Respimat® therapy • Severity of breathlessness based on the Modified Medical Research Council Questionnaire (mMRC) - At baseline visit and visit 2: • Medical history: o Treatment with other respiratory agents o Concomitant diseases and concomitant medication • General condition of the patient based on Physician's Global Evaluation (PGE) • Physical Functioning based on PF-10 scores - At Visit 2: • Spiolto® Respimat® administration • Patient satisfaction (with Spiolto® Respimat® therapy, with Respimat® inhaler and its handling) • Occurrence of adverse events since baseline visit Race and ethnicity was not collected as per study protocol.
Statistical methods:	All analyses are descriptive and were performed on the full analysis set.

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim Pharma GmbH&Co.KG			
Name of finished medicinal product: Spiolto® Respimat® 2.5 microgram/2.5 microgram per puff inhalation solution			
Name of active ingredient: Pharmacotherapeutic group: drugs for obstructive airway diseases, adrenergics in combination with anticholinergics ACT code: R03AL06 active substances: tiotropium bromide + olodaterol			
Report date: 6 Nov 2017	**Study number:** 1237.42	**Version/Revision:** **Draft** 1.0	**Version/Revision date:** Not applicable
	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:	Altogether 1737 patients were enrolled and started treatment with Spiolto® Respimat®; these patients were analysed for baseline/demographics and safety data (TS). 1578 patients (88.6 %) had both visits documented as well as filled in all questionnaires, thus being evaluable for analysis of primary and secondary endpoints (FAS). Efficacy was assessed using 2 different parameters: - patient reported outcome of physical activity in daily living using the PF-10 questionnaire - physician's evaluation (PGE score). At time of registration patients had a median age of 66.0 years (min: 40; max: 94). 57.0 % were male, 43.0 % female. The great majority (74.1 %) suffered from concomitant diseases mainly affecting the cardiac, metabolic/endocrine, vascular and / or gastrointestinal/hepatobiliary system. Most of the patients were smokers and ex-smokers, 40.0 % and 39.8 %, respectively. Median pack-years amounted to 30.0. The median time between initial diagnosis of COPD and baseline visit 1 was 3 years (min: 0; max: 63). 785 patients (45.2 %) were treatment-naïve, thus having not received any COPD-treatment, whereas 54.7 % of patients		

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim Pharma GmbH&Co.KG			
Name of finished medicinal product: Spiolto® Respimat® 2.5 microgram/2.5 microgram per puff inhalation solution			
Name of active ingredient: Pharmacotherapeutic group: drugs for obstructive airway diseases, adrenergics in combination with anticholinergics ACT code: R03AL06 active substances: tiotropium bromide + olodaterol			
Report date: 6 Nov 2017	**Study number:** 1237.42	**Version/Revision:** **Draft** 1.0	**Version/Revision date:** Not applicable

have been treated with respiratory therapeutics within the 6 months prior to start of study treatment.

Depending on GOLD version used, patients had different severities of COPD: 29.0 %, 17.5 %, 26.6 % and 26.9 % of patients were assigned to 2015 GOLD A, B, C and D, respectively, and 41.7 %, 34.3 %, 13.9 % and 10.1 % of patients to 2017 GOLD A, B, C and D, respectively. Since this observational study was performed in 2015-2016, GOLD 2017 classification cannot be applied to the patients. However, there were about 29% of patients assigned to group A who were not treated according to valid guideline.

The mean value of exacerbations during the last 12 months (0.95) and the mean value of exacerbation related hospitalizations during the last 12 months (0.15) were low. Most of the exacerbations were not accompanied by hospitalizations.

Primary endpoint:

Therapeutic success defined as a minimum 10-point increase of PF-10 score after approximately 6 weeks of Spiolto® Respimat® treatment (primary endpoint) has been observed for 51.5 % (CI 95%: 49.0-54.0) of FAS patients. Thus therapeutic success was seen for more than the 50 % as assumed in the observational plan for the analysed patient group and the primary endpoint was met. Stratification according to duration of Spiolto® Respimat® use (> 4 weeks compared to ≤ 4 weeks) resulted in greater percentage of patients in group '> 4 weeks' with therapeutic success, 53.3% (CI 95%: 50.59 - 56.03) and 42.1% (CI 95%: 35.9 – 48.42), respectively. At baseline visit 1, median PF-10 score was higher in group "≤ 4 weeks" than in patients treated for > 4 weeks, 55 and 45 points, respectively. However, at visit 2, median PF-10 score was 65 points in both

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim Pharma GmbH&Co.KG			
Name of finished medicinal product: Spiolto® Respimat® 2.5 microgram/2.5 microgram per puff inhalation solution			
Name of active ingredient: Pharmacotherapeutic group: drugs for obstructive airway diseases, adrenergics in combination with anticholinergics ACT code: R03AL06 active substances: tiotropium bromide + olodaterol			
Report date: 6 Nov 2017	**Study number:** 1237.42	**Version/Revision:** **Draft** 1.0	**Version/Revision date:** Not applicable

groups.

Secondary endpoints:

Change of PF-10 score from visit 1 to visit 2 amounted to a median of 10 points (min: -65; max: 95). Regarding satisfaction with Spiolto® Respimat® after approximately 6 weeks it could be seen that the great majority of patients was very satisfied or satisfied with the device and the treatment.

Most of the patients (52.7 %) had a PGE score of 3 and 4 at visit 1 corresponding to a mediocre general condition. This increased after approx. 6 weeks of treatment at visit 2 to a score of 5 and 6 in the majority of patients (53.3 %), corresponding to a good general condition.

General condition of patient (PGE score)		N 1578	% 100.00
Baseline (Visit 1)	1	19	1.20
	2	178	11.28
	3	358	22.69
	4	474	30.04
	5	297	18.82
	6	188	11.91
	7	57	3.61
	8	7	0.44
Week 6 (approximately) (Visit 2)	1	4	0.25
	2	58	3.68
	3	169	10.71
	4	286	18.12
	5	447	28.33
	6	394	24.97
	7	189	11.98
	8	27	1.71
	Missing	4	0.25

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim Pharma GmbH&Co.KG			
Name of finished medicinal product: Spiolto® Respimat® 2.5 microgram/2.5 microgram per puff inhalation solution			
Name of active ingredient: Pharmacotherapeutic group: drugs for obstructive airway diseases, adrenergics in combination with anticholinergics ACT code: R03AL06 active substances: tiotropium bromide + olodaterol			
Report date: 6 Nov 2017	**Study number:** 1237.42	**Version/Revision:** **Draft** 1.0	**Version/Revision date:** Not applicable

The highest value (=8) representing an excellent general condition was given to 7 patients at visit 1 and to 27 patients at visit 2.

Satisfaction with inhalation with the device was slightly higher than satisfaction with device handling and overall satisfaction with Spiolto® Respimat® treatment: 1381 patients (87.5 %) were very satisfied/satisfied with inhalation, followed by 1344 patients (85.2 %) and 1301 patients (82.5 %) satisfied with handling and overall satisfaction with Spiolto® Respimat® treatment, respectively.

Patient satisfaction		N 1578	% 100.00
Patient overall satisfaction with Spiolto® Respimat® treatment	Very satisfied	530	33.59
	Satisfied	771	48.86
	Rather satisfied	128	8.11
	Neither satisfied nor dissatisfied	63	3.99
	Rather dissatisfied	33	2.09
	Dissatisfied	42	2.66
	Very dissatisfied	10	0.63
	Not answered	1	0.06
Patient satisfaction with inhaling from the Respimat® device	Very satisfied	555	35.17
	Satisfied	826	52.34
	Rather satisfied	109	6.91
	Neither satisfied nor dissatisfied	55	3.49
	Rather dissatisfied	14	0.89
	Dissatisfied	12	0.76
	Very dissatisfied	5	0.32
	Not answered	2	0.13

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim Pharma GmbH&Co.KG			
Name of finished medicinal product: Spiolto® Respimat® 2.5 microgram/2.5 microgram per puff inhalation solution			
Name of active ingredient: Pharmacotherapeutic group: drugs for obstructive airway diseases, adrenergics in combination with anticholinergics ACT code: R03AL06 active substances: tiotropium bromide + olodaterol			
Report date: 6 Nov 2017	**Study number:** 1237.42	**Version/Revision:** **Draft** 1.0	**Version/Revision date:** Not applicable

Patient satisfaction with handling of the Respimat® inhalation device	Very satisfied	522	33.08
	Satisfied	822	52.09
	Rather satisfied	155	9.82
	Neither satisfied nor dissatisfied	47	2.98
	Rather dissatisfied	13	0.82
	Dissatisfied	13	0.82
	Very dissatisfied	5	0.32
	Not answered	1	0.06

Regarding safety, only 1 % of TS patients showed at least one investigator defined drug-related adverse event. 21 drug-related adverse events were documented in total, mostly “palpitations” and “cough” (14.3 % each of all events) and “dry mouth” (9. 5 % of all events). Almost all drug related AEs recovered / resolved. Maximum documented NCI grade of drug related AE per patient was grade 3. No drug-related AEs of grade 4 or 5 occurred. Only 3 patients had an ongoing drug-related AE after end of observational study. Three serious adverse events, in detail “cardiac arrest”, “cardiac failure” and “cough”, were documented in three different patients. Only one of these SAEs (“cough”) was a serious ADR; both other SAEs were not related to Spiolto® Respimat® use as adjudicated by the treating physicians. Two SAEs, “cardiac arrest” and “cardiac failure”, had a fatal outcome. Both patients who died had pre-existing cardiovascular diseases.

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.

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim Pharma GmbH&Co.KG			
Name of finished medicinal product: Spiolto® Respimat® 2.5 microgram/2.5 microgram per puff inhalation solution			
Name of active ingredient: Pharmacotherapeutic group: drugs for obstructive airway diseases, adrenergics in combination with anticholinergics ACT code: R03AL06 active substances: tiotropium bromide + olodaterol			
Report date: 6 Nov 2017	**Study number:** 1237.42	**Version/Revision:** **Draft** 1.0	**Version/Revision date:** Not applicable
	Patients of all degrees of COPD severity have been included, even about 29% of patients who were assigned to group A and thus were not treated according to valid guideline. This shows that investigators did not adhere to guidelines only, but were influenced by other factors. After approximately 6 weeks of treatment with tiotropium + olodaterol a therapeutic success was seen in more than 50 % of analyzed patients. This was accompanied by improvement in patients' general condition shown by the distribution of the PGE scores. Stratified analysis according to GOLD 2015 classification showed that patients in all GOLD groups have a benefit of Spiolto® Respimat®. Benefit was particularly high in GOLD group C and D patients who had a share of 54.1 % and 57.5 % with therapeutic success, respectively. The great majority of patients was very satisfied or satisfied with treatment, inhaling and handling of Spiolto® Respimat®. Regarding safety, there were less drug-related AEs documented than in prior clinical trials or non-interventional studies. Thus in routine care investigators did not seem to enquire patients about AEs at visits. Treatment with Spiolto® Respimat® under routine care conditions emerged as an effective and safe therapy even in a COPD patient population who suffered from several different concomitant diseases, mostly affecting the cardiac, metabolic/endocrine, vascular and / or gastrointestinal/hepatobiliary system. Most of the patients took concomitant medication in addition to COPD treatment. This NIS also revealed that patients were not always treated according to guidelines, thus other aspects beside severity of COPD seem to influence treatment decision of investigators.		
Marketing	Boehringer Ingelheim International GmbH		

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim Pharma GmbH&Co.KG			
Name of finished medicinal product: Spiolto® Respimat® 2.5 microgram/2.5 microgram per puff inhalation solution			
Name of active ingredient: Pharmacotherapeutic group: drugs for obstructive airway diseases, adrenergics in combination with anticholinergics ACT code: R03AL06 active substances: tiotropium bromide + olodaterol			
Report date: 6 Nov 2017	**Study number:** 1237.42	**Version/Revision:** **Draft** 1.0	**Version/Revision date:** Not applicable
Authorisation Holder(s):			
Names and affiliations of principal investigators:	The co-ordinating investigator was Dr. [redacted] 258 participating sites		