Non-interventional Study Protocol

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BI Investigational Product(s):	Spiolto® Respimat®
Title:	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
Protocol version identifier:	1.0
Date of last version of protocol:	3 December 2015
PASS:	No
EU PAS register number:	Not yet available (study will be registered in EU PAS Register (ENCePP) and clinicaltrials.gov)
Active substance:	R03AL06 Tiotropium bromide + Olodaterol
Medicinal product:	Spiolto® Respimat® 2.5 microgram/2.5 microgram per puff inhalation solution
Product reference:	Spiolto® Respimat® 2,5 Mikrogramm/2,5 Mikrogramm pro Hub Lösung zur Inhalation
Procedure number:	DCP: NL/H/3157/001 / DC Zul.-Nr.: 92213.00.00
Marketing authorisation holder(s):	MAH: Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein Study initiator: Boehringer Ingelheim Pharma GmbH&Co.KG Binger Straße 173 55216 Ingelheim am Rhein
Joint PASS:	No

Research question and objectives:	The objective of this NIS is 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. A secondary objective is to evaluate 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 satisfaction with Spiolto® Respimat® at visit 2.
Country(-ies) of study:	Germany
Author:	[redacted]
Marketing authorisation holder(s):	Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein
Date:	3 December 2015

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of special interest
AMG	Arzneimittelgesetz (German Drug Act)
AUC	Area under the Curve
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (German CA)
CI	Confidence Interval
CML	Local Clinical Monitor
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
eCRF	Electronic Case Report Form
EU	European Union
FDC	Fix Dose Combination
FEV1	Forced expiratory volume in one second
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICH	International Conference on Harmonisation
ICS	Inhalative Corticosteroides
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
LABA	Long-acting $beta_2$ adrenoceptor agonist
LAMA	Long-acting muscarinic antagonist
MedDRA	Medical Dictionary for Drug Regulatory Activities
NCI - CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIS	Non-Interventional Study
PF-10	Patient questionnaire
PGE	Physician's Global Evaluation
SABA	Short-acting $beta_2$ adrenoceptor agonist
SAE	Serious Adverse Event
SAMA	Short-acting muscarinic antagonist
SPC	Summary of Product Characteristics
VFA	Verband Forschender Arzneimittelhersteller
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

Table 3: 1 Responsible parties

Function	Name / Location
Scientific coordinator	[redacted]
Therapeutic Area [redacted] Respiratory Medicine (TA[redacted])	[redacted]
Team Member Medical Affairs (TM MA)	[redacted]
Team Member Epidemiology (TM Epi)	[redacted]
[redacted] Global Epidemiology ([redacted] GEpi)	[redacted]
Therapeutic Area [redacted] Risk Management (TA[redacted] RM), and Pharmacovigilance Working Group (PVWG) [redacted]	[redacted]
GPV Study Coordination	[redacted]
Trial clinical monitor	[redacted]
Statistical analysis	[redacted] Boehringer Ingelheim Pharmaceuticals, Inc. Global Biom. And Clin. Appl./BDM
Data management	[redacted] Boehringer Ingelheim Pharmaceuticals, Inc. Global Biom. And Clin. Appl./BDM
Trial Programming	[redacted] Boehringer Ingelheim Pharmaceuticals, Inc. Global Biom. And Clin. Appl./BDM
CRO	Alcedis GmbH Winchesterstr. 3 35394 Gießen (Europaviertel) Germany Project [redacted]: [redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide + Olodaterol			
Protocol date: 3 December 2015	**Study number:** 1237.42	**Version/Revision:** 1.0	**Version/Revision date:**
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. Author [redacted], [redacted]		
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 is 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. A secondary objective is to evaluate 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 satisfaction with Spiolto® Respimat® at visit 2.		
Study design:	Open-label observational study according to §4, section 23 and §67, section 6 German Medicines Act: all included COPD patients are receiving treatment with Spiolto® Respimat® for approximately 6 weeks, which is the average time between two medical consultations.		
Population:	COPD patients requiring a fixed combination therapy of two long-acting bronchodilators (LAMA + LABA) according to approved SmPC and GOLD guidelines.		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide + Olodaterol			
Protocol date: 3 December 2015	**Study number:** 1237.42	**Version/Revision:** 1.0	**Version/Revision date:**
Variables:	- Patient demographics (age, gender, height & weight) - Concomitant diseases / Comorbidities - Concomitant medication - General condition of patient based on Physician's Global Evaluation PGE) - Smoking history - Exacerbations - Breathlessness based on mMRC score - Physical Functioning based on PF-10 scores - Patient satisfaction with Spiolto® Respimat® - Safety; ADR (serious and non-serious), fatal AEs, pregnancies - GOLD spirometric classifications (1, 2, 3, 4) - GOLD patient groups (A, B, C, D)		
Data sources:	To be completed by the physician: - Patient demographics - Patient medical files - Physician's Global Evaluation (PGE) at visit 1 and visit 2 To be completed by the patient at visit 1 and at visit 2: - Physical Functioning Questionnaire (PF-10) To be completed by the patient at visit 2 only: Patient satisfaction survey.		
Study size:	2000 patients, 650 sites		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide + Olodaterol			
Protocol date: 3 December 2015	**Study number:** 1237.42	**Version/Revision:** 1.0	**Version/Revision date:**
Data analysis:	**Primary outcome:** "therapeutic success" at visit 2. (10-point increase in the PF-10 score between visit 1 and visit 2). **Secondary outcomes:** Change 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 Patient satisfaction with Spiolto® Respimat® at visit 2 [redacted]		
Milestones:	Start of data collection	January 2016	
	End of data collection	December 2016	
	Final report of study results	April 2017	

5. AMENDMENTS AND UPDATES

none

6. MILESTONES

Milestone	**Planned Date**
Start of data collection	January 2016
End of data collection	December 2016
Final report of study results:	April 2017

7. RATIONALE AND BACKGROUND

7.1 MEDICAL BACKGROUND

Chronic obstructive pulmonary disease (COPD) is the term used to describe the occurrence of chronic bronchitis with or without pulmonary emphysema. It is a common lung disease, characterised by gradual airway constriction. This leads to a gradual limitation of the flow of air to and from the lungs, causing ventilation disorders, which in the majority of cases manifest as shortness of breath (dyspnoea). COPD is often preceded by a long-standing history of initially acute and then chronic bronchitis and pulmonary infections [1]

In clinical practice, COPD is defined by its characteristically low airflow in lung function tests. In contrast to asthma, this limitation of airflow is poorly reversible and gets progressively worse over time. The consequence is respiratory failure, resulting in an inadequate supply of oxygen to the internal organs and peripheral tissues[1].

COPD is caused by the inhalation of noxious substances such as smoke with harmful particles or gases (air pollution), but in the majority of cases by tobacco smoking. The noxious substance triggers an abnormal inflammatory response in the lung. This inflammatory response leads to increased mucus production, tissue remodelling and, connected with this, to a narrowing of the air passages in the lower respiratory tract. As a result, the pulmonary parenchyma is destroyed and pulmonary emphysema is caused. Over time, there are further systemic consequences, such as myopathy, osteoporosis, cor pulmonale and hypertension with severe restriction of physical functioning. Recurrent acute exacerbations (e.g. due to pulmonary infections) bring about a further deterioration in the condition of the lungs[1].

The guidelines of the Deutsche Atemwegsliga (German Respiratory Association), for example, contain a detailed description of COPD and its causes, diagnosis and treatment[2]. According to the Helmholtz Centre in Munich[3], COPD is one of the most common diseases in the world. In its recent estimates from 2007, the World Health Organization assumes that there are 210 million sufferers, with the trend on the increase. The disease currently ranks fourth in the list of the most common causes of death. According to WHO forecasts, it will have moved up to third place in these statistics by 2020. The Organization has named indoor air pollution in developing countries, such as that caused by cooking on an open fire, and the fact that more and more women in industrialised nations smoke, as the reasons for the global increase in cases of COPD. Thus, disease rates are set to rise in the future, particularly in the female population.

COPD is diagnosed from the clinical presentation and also from mechanical lung function tests, such as spirometry, body plethysmography, measurement of diffusion and blood gas analysis.
It is classified into degrees of severity 1 to 4 according to the reduction in forced expiratory volume in one second, FEV_1 (%) from the age-related predicted value in the presence of a reduced (<70%) FEV_1/forced vital capacity ratio [1].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) include also symptoms and risk of exacerbations in their staging system, ranging from A to D [4].

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The most important treatment strategies are cessation of tobacco abuse and/or exposure to the noxious trigger, vaccinations against, pneumococci and, rehabilitation activities such as respiratory muscle stretch gymnastics and lung training (according to exercise capacity) and pharmacological treatment [1].

In accordance with the GOLD guidelines [4], for mild COPD (stage GOLD A) monotherapy with short-acting bronchodilators (ß-2 sympathomimetics, SABA and/or anticholinergics, SAMA) is the recommended first choice.
At stage GOLD B, long-term inhaled treatment with long-acting bronchodilators (LABA, LAMA) is firstly recommended. A combination of LAMA and LABA is another option.
At stage GOLD C, glucocorticosteroid + LAMA or LABA is recommended as first choice. Alternatives are LAMA + LABA, LAMA + phosphodiesterase-4 inhibitors or LABA + phosphodiesterase-4 inhibitors.
Patients at stage GOLD D should be treated with a double or triple therapy consisting of inhaled corticosteroids + LABA and/or LAMA.

Pharmacological therapy for COPD is used to lessen symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance [4]. To date, COPD medications have not been conclusively shown to modify the long-term decline in lung function [4], so patients should be treated with the agents most likely to result in effective bronchodilation and prevention of exacerbations.

The GOLD strategy states that bronchodilators are the mainstay of COPD management, long-acting inhaled bronchodilators are convenient and more effective at producing maintained symptom relief than short-acting bronchodilators, and combining bronchodilators of different classes (e.g. LAMAs and LABAs) may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single agent [4].

Recently, the fixed combination of tiotropium and olodaterol has been shown to increase lung function significantly in moderate to very severe COPD, and to a greater extent than with either agent alone [5]. Therefore, treatment with combination therapy is likely to be an effective option for the management of moderate-to severe COPD.

7.2 DRUG PROFILE

Tiotropium bromide is a long-acting (24-hour) inhaled anticholinergic bronchodilator (known as a LAMA), used in the treatment of COPD. The drug is authorised in many countries around the world, including in Germany since 2002 under the name Spiriva® [6], [7].

The Spiriva® Respimat® was developed from the Spiriva® pharmaceutical form, which optimises pulmonary deposition of the drug [8], [9], and means that the Respimat® is able to reduce the quantity of drug used [10].
It produces a slowly dispersing, long-lasting mist with very fine particle distribution that is readily able to circulate into the lower respiratory tract and the lungs [11]. Thus, even when coordination of breathing is poor, pulmonary deposition is optimal and the product is efficiently administered to the target site. The Respimat® does not contain any propellant gas.

Olodaterol is a highly selective, long-acting beta$_2$-adrenoceptor agonist (known as a LABA) for long-term once-daily bronchodilator treatment in COPD patients with impaired airflow including chronic bronchitis and/or emphysema.

The efficacy and safety of olodaterol in the treatment of moderate to severe COPD (GOLD 2-4) was studied in a Phase III programme in over 3000 patients and showed that the additional administration of olodaterol via Respimat® brought about an effective and long-lasting improvement in lung function (FEV1) over 24h compared to conventional standard treatment (e.g. long- and short-acting anticholinergics, short-acting beta-agonists, inhaled corticosteroids and xanthines [12], [13], [14] and also demonstrated a more rapid onset of effect [15].

The drug has been authorised since 2013 in [redacted] countries worldwide and is available in Germany under the name Striverdi® Respimat® [16].

First treatment experiences with the free combination of tiotropium and olodaterol in COPD patients were reported from two replicate, double-blind, randomized, 12-week studies (ANHELTO 1 and ANHELTO 2) evaluating the efficacy and safety regarding the combination of olodaterol 5 µg once daily (via Respimat®) plus tiotropium 18 µg once daily (via HandiHaler®) versus tiotropium 18 µg once daily (via HandiHaler®) plus placebo (via Respimat®) in patients with moderate to severe COPD[17].

Primary efficacy endpoints were area under the curve from 0 to 3 hours of forced expiratory volume in 1 second (FEV1 AUC 0–3) and trough FEV1 after 12 weeks (for each trial). A key secondary end point was health status assessed by St George's Respiratory Questionnaire (SGRQ) total score.

The free combination of olodaterol plus tiotropium resulted in significant improvement compared to tiotropium + placebo in FEV1 AUC 0 to 3 (treatment differences: 0.117 L [p = 0.001], ANHELTO 1; 0.106 L [p = 0.001], ANHELTO 2) and trough FEV1 (treatment differences: 0.062 L [p = 0.001], ANHELTO 1; 0.040 L [p = 0.0029], ANHELTO 2). These positive results were supported by secondary endpoints.

The effects described above translated into improvement of SGRQ total scores (treatment difference –1.85; p = 0.0001). The safety profile of olodaterol plus tiotropium, however, was similar to tiotropium monotherapy.

Both studies demonstrate that the free combination of olodaterol (Respimat®) plus tiotropium (HandiHaler®) provide significantly higher bronchodilatory efficacy than tiotropium alone in COPD patients.

The new medicinal product Spiolto® Respimat® delivers the two ingredients described above as fixed combination in one device and is indicated as bronchodilating long-term treatment in adult COPD patients for symptom relieve.

EU registration was given July, 1st, 2015, based on 2 pivotal, replicate, multinational 1-year, randomised double-blind, active-controlled, parallel-group Phase III studies, TOnado 1 and 2 (Study 1237.5 and Study 1237.6), assessed the efficacy and safety of once-daily treatment with a fixed-dose combination (FDC) of olodaterol (a LABA), and tiotropium (a LAMA), delivered via the Respimat® Soft Mist™ inhaler and compared to the individual mono-components in patients with moderate to very severe COPD (GOLD 2–4)[5].

Patients were randomised to one of five treatment groups and received tiotropium plus olodaterol FDC 2.5 / 5 µg or 5 / 5 µg, or tiotropium 2.5 µg or 5 µg, or olodaterol 5 µg delivered once daily via Respimat® inhaler for 52 weeks.

Inclusion and exclusion criteria:
Patients with moderate to very severe COPD (GOLD 2-4) were included if:

- Post-bronchodilator FEV1 <80% of predicted normal
- Post-bronchodilator FEV1/FVC <70%
- Age ≥40 years with a smoking history (current or former) of >10 pack-years

Patients with moderate to very severe COPD (GOLD 2-4) were excluded if:

- Significant disease other than COPD

The key results on efficacy are summarized below:

- Across 25 countries, study 1237.5 (TOnado 1, n=2624) and study 1237.6 (TOnado 2, n=2539) randomised a total of 5163 patients, of whom 5162 patients were treated and 84.6% completed the studies.
- At 24 weeks, both studies demonstrated significant improvements in lung function (FEV1 AUC 0–3 response [p <0.0001] and trough FEV1 response [p<0.05]) compared with either tiotropium or olodaterol monotherapy.
- At 24 weeks, only the higher-dose combination of olodaterol and tiotropium (5 µg / 5 µg) provided statistically significant improvement in SGRQ total scores compared with either monotherapy (FDC 5/5 µg versus olodaterol 5 µg: 95% CI - 1.693 (-2.778, -0.608), p<0.01; versus tiotropium 5 µg 95% CI - 1.233 (-2.313, - 0.153), p<0.05).
  The responder rates were also significantly greater for the higher-dose FDC compared with either olodaterol or tiotropium alone (nominal p<0.05).
- Generally, patients who had more severe disease at baseline also had a lower response to treatment, although inhaled corticosteroid use did not affect the response to the combination treatment.

The key results on safety are summarized below:

Overall, 74.4% of patients reported at least one adverse event (AE). The rate of serious AEs (16.4%) was broadly similar across all treatment groups.
In the two studies, the overall fatality rate was 1.5%. Of the 75 deaths, 14 occurred in the olodaterol 5 µg group, 12 in the tiotropium 2.5 µg group, 17 in the tiotropium 5 µg group, 14 in the FDC tiotropium / olodaterol 2.5 / 5 µg group, and 18 in the FDC tiotropium / olodaterol 5 / 5 µg group.
Most treatment-emergent AEs were respiratory events (incidence >3%) and predominantly included COPD exacerbations, which were reported most often in the monotherapy groups, and infections, which occurred most frequently in the FDC tiotropium plus olodaterol 2.5 / 5µg group.
There were no safety concerns with regard to laboratory parameters and vital signs.

The incidence of major adverse cardiac events and cardiac disorders were similar across treatment groups.

The authors concluded that these two 1-year studies, TOnado 1 and TOnado 2, demonstrated that once-daily treatment with a FDC of olodaterol and tiotropium may present an effective and well-tolerated maintenance treatment for patients with moderate to very severe COPD

(GOLD 2–4). In particular, the higher-dose FDC (5 µg / 5 µg) appeared to offer the optimum combination.

In conclusion, the phase III clinical trials conducted to date have shown tiotropium plus olodaterol FDC to be a safe, well tolerated and efficacious combination therapy according to treatment guidelines in a moderate to very severe COPD patient population. The overall incidences of adverse events (AEs), serious adverse event (SAEs), fatal AEs, frequencies for cardiac events and Major adverse cardiovascular event (MACE) in the tiotropium plus olodaterol FDC treatment group were similar to the mono-components. The nature and frequency of AEs in general was consistent with the disease under study. There were no results in the clinical development program suggesting the need for absolute contraindications for the combination product.
The observed incremental bronchodilator response for the combination compared to the individual components translated into benefits that were meaningful to the patient, with improvements in several patient centred outcomes. For further information please refer to the SmPC of Spiolto® Respimat®.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 RATIONALE FOR PERFORMING THE STUDY

The contribution of physical inactivity to disability in COPD can be difficult to distinguish from disease progression [18]. However, it is clear that physical activity is significantly lower in patients with COPD than in healthy controls [19],[20].

COPD prevents patients from carrying out daily activities due to exercise intolerance, which is often attributed to limited pulmonary ventilation.
However, a number of observations have suggested that, for many COPD patients, other factors are involved, including deconditioning due to physical inactivity. This may be related to avoidance of exertion as a result of fear of dyspnoea. Furthermore, physical inactivity has been associated with skeletal muscle weakness and exercise intolerance [18],[21], [22].

The loss of physical activity in COPD is also associated with increased mortality [23]. Data from a study of 2386 patients with COPD demonstrated that, following adjustment for all relevant confounders, subjects who reported low, moderate or high physical activity had a significantly lower risk of all-cause mortality than those with very low physical activity ($p = 0.001$) [24].

Clinical studies of both Spiriva® [25], [26], [27] and Striverdi® Respimat® in COPD patients have demonstrated significant improvement in exercise capacity [28].

The benefits of tiotropium + olodaterol FDC have been studied in controlled Phase III programs on exercise endurance, however, data regarding physical activity when treated with Spiolto® Respimat® is not available from a real world setting.

8.2 STUDY OBJECTIVES

The objective of this NIS is to measure changes in physical functioning – serving as a surrogate for physical activity and exercise capacity – in COPD patients on treatment with Spiolto® Respimat® after approximately 6 weeks in routine clinical practice.

The secondary objectives are to evaluate 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 satisfaction with Spiolto® Respimat® at visit 2.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a self-controlled, non-interventional study (NIS), as referred to in §4.23 and §67.6 AMG, enrolling consented COPD patients who will be treated with Spiolto® Respimat® according to the approved SmPC.

Patients will be enrolled consecutively and will be followed over an observational period of approx. 6 weeks. Data as listed in table 9.1:1 will be collected.

Table 9.1: 1 Visit flow chart and data collection parameters

Parameter	**Visit 1; baseline visit**	**Visit 2; approx. 6 weeks after baseline visit**
Informed Consent	X	
Inclusion / Exclusion Criteria	X	
Patient demographics (age, gender, height, and weight)	X	
Start of COPD	X	
Number of exacerbations in the last 12 months	X	
Number of exacerbations leading to hospitalization in the last 12 months	X	
mMRC breathlessness scale, completed by the patient	X	
Past COPD therapies (6 months before visit 1)	X	
Respimat® training (yes/no)	X	
COPD severity based on GOLD assessment[1]	X	
Smoking history	X	X
Concomitant diseases / Comorbidities	X	X
COPD related and other relevant concomitant medication	X	X
Physical functioning (PF-10) questionnaire, completed by patient	X	X
General condition of patient evaluated by Physician's Global Evaluation (PGE)	X	X
Safety: Adverse Drug Reactions (serious and non-serious), fatal AE, pregnancy	X	X
Patient satisfaction with Spiolto® Respimat®, survey completed by the patient		X
Rational for Spiolto® Respimat® treatment discontinuation (if applicable)		X
Continuation or discontinuation of treatment with Spiolto® Respimat® after the study (yes/no)		X

[1] GOLD patient group (A, B, C or D) will be automatically calculated within the eCRF based on available exacerbation history, mMRC, and GOLD spirometric classification of airflow limitation based on post-bronchodilator FEV_1 if available.

Baseline characteristics of patients being eligible and who gave Informed Consent, but were not treated in the study will also be collected.

9.1.1 Outcomes

Primary outcomes:

"Therapeutic success" at visit 2 (10-point increase in the PF-10 score between visit 1 and visit 2).

Secondary outcomes:

- 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.
- Patient satisfaction with Spiolto® Respimat® at visit 2.

9.2 SETTING

It is planned that data of approximately 2000 patients from approximately 650 sites in Germany will be collected. Site selection will be performed to reflect routine COPD care in Germany in order to secure representativeness of the COPD population.

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated or not.

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any efficacy/safety information that could significantly affect continuation of the study, or any other administrative reasons, i.e. lack of recruitment.
3. Violation of the observational plan or the contract by a study site or investigator, disturbing the appropriate conduct of the study

9.2.1 Inclusion criteria

Patients can be included if all of the following criteria are met:

- 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

9.2.2 Exclusion criteria

- 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 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.

9.3 VARIABLES

The following parameters will be collected and assessed at visit 1 and/or visit 2:

- Patient demographics (age, gender, height & weight),
- Smoking status (current smokers, former smokers, and never smokers) and pack-years,
- Concomitant diseases / Comorbidities such as cardiovascular disease, diabetes mellitus, musculoskeletal impairment, renal diseases, liver diseases, osteoporosis, gastroesophageal reflux (GERD), or lung cancer,
- COPD-related and other concomitant medication such as beta-blockers, beta-agonists, corticosteroids, or proton pump inhibitors,
- Reported exacerbations based on medical history in the last 12 months and exacerbations leading to hospitalization in the last 12 months,
- Assessment of the severity of breathlessness based on the Modified Medical Research Council Questionnaire (mMRC),
- Physical Functioning based on PF-10 scores*,
- Patient satisfaction with Spiolto® Respimat® to assess the overall satisfaction with Spiolto® Respimat® as well as specific inhalation from the device and device handling,
- General condition of patient based on Physician's Global Evaluation (PGE) to assess the general condition of the patient at the beginning and at the end of the study,
- Safety Reporting; Adverse Drug Reactions (serious and non-serious), fatal AEs, and pregnancies at the beginning and at the end of the study,
- GOLD spirometric classifications (1, 2, 3, 4) and GOLD patient groups (A, B, C, D) based on GOLD guidelines

*The PF-10 is a sub-domain of the SF-36 and consists of 10 questions evaluating the extent of experienced restrictions while conducting usual activities. Each question of the PF-10 can be answered with "yes, limited a lot", "yes, limited a little", or "No, not limited at all", with a

score of 1, 2, or 3. The scores over the 10 questions will be summed, resulting in a value between 10 (a patient answering all questions with "yes, limited a lot") and 30 (a patient answering all questions with "No, not limited at all"). The final sum of the individual scores will be standardized to a range of 0 to 100 using the following formula: 100*(sum-10)/20.

9.4 DATA SOURCES

Medical records collected through routine clinical care will be used to assess the inclusion/exclusion criteria of patients. Such medical records will be used for patient demographics, smoking history, collection of previous COPD medication, concomitant diseases, and concomitant medication.

All patients will be enrolled consecutively.

The treating physician will use the Physician's Global Evaluation (PGE) to evaluate the general condition of the patient on an 8-point ordinal scale from 1 (very poor) to 8 (excellent). PGE will be completed before and approx. 6 weeks after treatment initiation.

The modified Medical Research Council (mMRC) scale will be used to assess the breathlessness state of the patient before the treatment. The mMRC stage (0 to 4) collected from the patient, as well as the exacerbation history and the post-bronchodilator FEV1, will be used to automatically calculate the GOLD patient group (A, B, C, or D) in the eCRF.

The physical functioning (PF-10) questionnaire is a subscale of the validated 36-Item Short Form Health Survey and contains 10 questions about everyday physical activity and functioning. Patients will be asked to complete the PF-10, in order to evaluate their physical functioning before and after treatment with Spiolto® Respimat®.

A patient satisfaction survey will also be completed at visit 2, using a 7-point ordinal scale with divisions from very dissatisfied to very satisfied.

9.5 STUDY SIZE

In a previous study (205.426) with over 1000 patients treated with Sprivia® Respimat® therapeutic success (= 10-point increase in the PF-10 score between baseline and week 6) was achieved in 61% of patients.

In this study a therapeutic lower success rate is expected as patients may be already on maintenance treatment at baseline.

Assuming a 50% therapeutic success rate and 1860 patients, the 95% confidence interval for the therapeutic success rate would be between 47.7% (lower limit) and 52.3% (upper limit).

To account for a 7% drop-out rate, the sample size becomes 2000 patients.

9.6 DATA MANAGEMENT

A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning and validation. The electronic Case Report Forms (eCRFs) will include programmable edits to obtain immediate feedback if data are missing (also negative answers, unknown), out of range, illogical or potentially erroneous. These rules may encompass simple checks such as range validation or presence/absence of data. Concurrent manual data review may be performed based on parameters dictated by the DMP. Ad hoc queries to the sites may be generated and followed up for resolution. A source data quality audit may be initiated to ensure that the data in the database is accurate. Source data verification (SDV) will be performed at sites identified by a risk-based approach as needed.

The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system will meet the standards of the International Committee on Harmonization guideline E6R1 regarding electronic study data handling. Patient confidentiality will be strictly maintained.

9.7 DATA ANALYSIS

9.7.1 Statistical design – Model

Details will be described in the statistical epidemiological analysis plan (SEAP).

9.7.2 Null and alternative hypotheses

No formal hypothesis testing will be performed since this is a self-controlled study.

9.7.3 Planned analyses

All patients who have received at least one dose of Spiolto® Respimat® will be included in the analysis; this is the treated set. All analyses will be performed on the treated set (as-treated analysis). If patients have missing values for an outcome, those patients will be excluded for that outcome's analysis.

The assessment will be carried out using SAS® software. The statistical characteristics presented in the end-of-text tables will be N / mean / SD / min / median / max. for continuous variables. Tabulations of relative and absolute frequencies will be presented for categorical variables. Incidence rates and 95% CI will be given when appropriate.

The analyses will relate to the following data:

- Patient demographics (gender, age, height, weight)
- Comorbidities

- COPD related and other concomitant medication
- History of smoking
- Reported exacerbations
- Breathlessness based on mMRC score at visit 1
- Physical Functioning based on PF-10 scores (therapeutic success at visit 2); primary outcome
- Changes from visit1 to visit 2 in the PF-10 score (secondary outcome)
- Patient satisfaction with Spiolto® Respimat® at visit 2 only; secondary outcome
- General condition of the patient: evaluated by the physician (Physician´s Global Evaluation (PGE)), (secondary outcome)
- Adverse Drug Reactions (ADR & SADR), fatal AEs, pregnancies
- GOLD spirometric classification (1,2, 3, 4)
- GOLD patient groups (A, B, C, D)
- Details of treatment with inhaled respiratory agents before the study
- Details of treatment with respiratory agents during the study
- Reasons for ending treatment during the observation period
- Details of treatment continuation / discontinuation

Main analysis

For the primary outcome, the proportion of patients with therapeutic success will be presented together with the 95% confidence interval.

Further analyses

The patient's general condition (PGE) at visit 1 and visit 2, mMRC at visit 1 and patient satisfaction at visit 2 are categorical variables so they will be analyzed as tabulations of frequencies. Change from visit 1 to visit 2 in the PF-10 score is a continuous outcome, so it will be analyzed with N / mean / SD / min / median / max.

Further exploratory analyses may be done to examine the distribution of baseline and follow-up covariates and their potential impact on the primary outcome; details will be specified in the analysis plan.

[redacted]

The safety data will be reported according to local requirements.

As similar studies will also be performed in other European countries, data pooling might be considered at the end.

9.7.4 Handling of missing data

If less than half of the PF-10 questions are missing for a patient, the missing values will be replaced with the mean of the other values and the PF-10 score will be calculated. If half or more than half of the PF-10 questions are missing, no score will be calculated and the PF-10 score will be marked as missing. No other missing data will be imputed. Every effort will be made to collect complete data at the specified time points. Any removal from the analysis will be documented, stating the site and patient number as well as the reason for removal.

9.8 QUALITY CONTROL

To improve and secure data quality, automatic data checks upon data entry will be done within the eCRF. In the eCRF, plausible ranges of values for numeric data entries as well as logical data entries and listings will be provided for each entry field. Based on this, checks on completeness and plausibility will be performed upon data entry in the eCRF.

Validity of data entry thus is ensured by integrated validation checks performed by the system, indicating missing or implausible entries to the document list or investigator. All corrections will be visible from the systems audit trail.

No regular source data verification is planned in this study. However, in case of decreasing compliance (i.e. of missing data, data discrepancies, protocol violations, etc.) a for-cause audit or risk-based monitoring visit will be performed.

9.8.1 Administrative requirements

This NIS will be performed in compliance with §4.23 and §67.6 of the Medicines Act of the Federal Republic of Germany (AMG) and the recommendation of the Federal Institute for Drugs and Medical Devices and the Paul Ehrlich Institute for the planning, performance and analysis of observational studies as well as applicable BI standard operating procedures (SOPs).

In compliance with §67.6 AMG, this NIS will be notified by Boehringer Ingelheim Pharma GmbH & Co. KG to the National Association of Statutory Health Insurance Physicians, the Central Federal Association of Health Insurance Funds, the Association of Private Health Insurance Funds as well as the competent federal higher authority Federal Institute for Drugs and Medical Devices (BfArM), or to the appropriately authorised institute.
In addition, the National Association of Statutory Health Insurance Physicians, the Central Federal Association of Health Insurance Funds and the Association of Private Health Insurance Funds will be given the names of the participating physicians and will be told the nature and level of payments made to them and will be provided with a copy of the contracts entered into with them.

Copies of the notifications, unless made purely electronically, will be kept in the relevant section of the investigator site file.

Additionally, an entry in the publicly accessible database at clinicaltrials.gov is planned, in accordance with the announcement of the Association of Research-Based Pharmaceutical Companies (VFA).

The NIS will be submitted to the competent Ethics Committee before it starts, as will any amendments to the observational plan. A copy of the opinion can be found in the appropriate section of the clinical trial master file.

In addition, every participating physician is to be advised by his/her ethics committee in accordance with the rules of professional conduct.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The intention of this NIS is to collect new data on the physical functioning and exercise capacity of COPD patients on treatment with Spiolto® Respimat® in a real world setting.

An NIS appears the most suitable instrument for obtaining information about the use of medicines in everyday therapeutic practice and thus for investigating prospectively questions in everyday therapeutic practice.

Consecutive enrolment will be employed to minimize selection bias. The entry criteria are non-restrictive which will permit the enrolment of a broad patient population. The choice of treatment is at the discretion of the investigator.

Selection bias could occur at the site level and the patient level. To minimize the site level selection bias, the goal is to have participating centers that have access to all available treatment options which are approved for use in that country for the targeted COPD patients. To minimize selection bias at the patient level, consecutive enrolment is performed. Information bias will be minimized by the use of standard eCRF, questionnaire and physicians' training on the study protocol.

An additional limitation is that the physical functioning questionnaire (PF-10) is only assessing 10 items of the full 36-Item Short Form Health Survey (SF-36).

The 7-item satisfaction scale, which is to be completed by the patient in order to measure satisfaction with Spiolto® Respimat® use, is a self-designed Boehringer-Ingelheim scale, without a public source or validation status.

9.10 OTHER ASPECTS

9.10.1 Informed consent, data protection, study records

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, and as close as possible to the standards of the International Conference of Harmonisation (ICH) Tripartite Guideline for Good Clinical Practice (GCP), Guidelines for Good Epidemiological Practice (GEP), Good Pharmacoepidemiology Practice (GPP) and relevant BI Standard Operating Procedures (SOPs).Standard medical care

(prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

Insurance cover is not necessary for a NIS in Germany.

9.10.1.1 Study approval, patient information, and informed consent

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

This NIS will be performed in compliance with §4.23 and §67.6 of the Medicines Act of the Federal Republic of Germany (AMG) and the recommendation of the Federal Institute for Drugs and Medical Devices and the Paul Ehrlich Institute for the planning, performance and analysis of observational studies as well as applicable BI standard operating procedures (SOPs).

The NIS will be reviewed by the submitted to the competent Ethics Committee before it starts, as will any amendments to the observational plan. A copy of the opinion can be found in the appropriate section of the clinical trial master file.

In addition, every participating physician is to be advised by his/her ethics committee in accordance with the rules of professional conduct.

The physician will explain the nature of the study to the patient and obtain written informed consent prior to patient participation in the study be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

The written informed consent has to be obtained before the patient is enrolled in the NIS and the observations are entered in the eCRF.

It must be documented in the eCRF that the informed consent of the patient was obtained before the start of the observation.

9.10.1.2 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

To provide further quality assurance of the documented patient observations, a random source data validation will take place at approx. 10% of sites and involve an on-site review of the documented data for completeness and consistency. An additional check/review of the quality assurance of this NIS can be performed.

9.10.1.3 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, also current medical records must be available.

For eCRFs all data must be derived from source documents:

- Patient demographics (age, gender, height, and weight);
- History of smoking
- Reported exacerbations
- Past COPD therapies (6 months before visit 1)
- Respimat® training (Yes/No)
- GOLD spirometric classification (1,2, 3, 4)
- GOLD patient groups (A, B, C, D)
- Concomitant diseases / Comorbidities
- Concomitant COPD and other relevant medication
- Breathlessness based on mMRC score
- Physical Functioning (PF-10) Questionnaire
- Patient Satisfaction Questionnaire
- Adverse Drug Reactions (ADR & SADR), fatal AEs, pregnancies
- Rational for Spiolto® Respimat® treatment discontinuation (if applicable)
- Details of treatment continuation / discontinuation .

9.10.1.3.1 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and

medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.1.4

9.10.1.4 Statement of confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities, i.e. the CA.

9.10.1.5 Completion of study

The EC/competent authority in Germany will be notified about the end of the trial (last patient out) or early termination of the trial.

9.10.1.6 Protocol violations

There are no protocol waivers. All protocol violations must be reported to the sponsor immediately.

10. PROTECTION OF HUMAN SUBJECTS

Please refer to section 9.10.1.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse drug reaction (ADR)

An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. ADRs may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event (SAE)

A serious adverse event (SAE) is defined as any AE which

- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs

The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the eCRF from signing the informed consent onwards until the end of the study:

- all ADRs (serious and non-serious),

  all AEs with fatal outcome (serious adverse events),
  Note*: For all patients on these data must be recorded on the AE pages in the eCRF. They will automatically be reported to the Pharmacovigilance department of Boehringer Ingelheim within 24 hours after data entry in the form of a PDF file via a secure email connection. The Boehringer Ingelheim SAE/AE form will be generated from the eCRF

All ADRs, including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of AEs

The definition of an adverse drug reaction (ADR) implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event (AE). An ADR, in contrast to an AE, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).

- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).

  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of AEs

The intensity of AEs should be classified and recorded according to the NCI-CTCAE criteria in the eCRF.

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a female subject has been enrolled into the study, after having taken , the investigator must report any drug exposure during pregnancy to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Expedited Reporting of AEs and Drug Exposure During Pregnancy

The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study (V2):

Type of Report	Timeline
All **serious ADRs** related to	immediately within 24 hours
All **AEs with fatal outcome**	immediately within 24 hours
All **non-serious ADRs** related to	7 calendar days
All **pregnancy monitoring** forms	7 calendar days

All ADRs (serious and non-serious) and all fatal AEs will automatically be reported to the Pharmacovigilance department of Boehringer Ingelheim within 24 hours after data entry in the form of a PDF file via a secure email connection. The Boehringer Ingelheim SAE/AE form will be generated from the eCRF.

Therefore, data entry for all ADRs and all fatal AEs within the timelines given above is mandatory.

If there is no Internet access at the time of the report, the SAE form must alternatively be sent to the following address by fax or e-mail within 24 hours after becoming known:

Boehringer Ingelheim Pharma GmbH & Co. KG
Pharmacovigilance Germany (PV Germany)
Binger Straße 173
55216 Ingelheim
Fax: +49 (6132) 72 – 141522
PV_local_Germany@boehringer-ingelheim.com

In this case, these data must be entered into the eCRF later as soon as possible.

The same timelines apply if follow-up information becomes available for the respective events. All additional information has to be entered into the eCRF and will be transmitted automatically within 24 hours.

In specific occasions the Investigator could inform the Sponsor upfront via telephone.

Information required

For each reportable AE, the investigator should provide the information requested on the appropriate eCRF pages.

Reporting of related AEs associated with any other BI drug

The investigator is encouraged to report all AEs related to any BI drug other than the Spiolto® Respimat® according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE

occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results of this non-interventional study will be disclosed on encepp.eu and clinicaltrials.gov. and a study specific publication plan will be developed to describe planned publications

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13.1 PUBLISHED REFERENCES

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13.2 UNPUBLISHED REFERENCES

Not applicable

14. APPENDICES

Appendix 1: Physicians' Global Evaluation (PGE)
Appendix 2: PF-10 Questionnaire
Appendix 3: SAE Form

APPENDIX 1: PGE

General condition of the patient at the initial examination (Visit 1)
Please mark with a cross as applicable

Poor		Satisfactory		Good		Excellent	
1	2	3	4	5	6	7	8

General condition of the patient after 4 to 6 weeks of treatment (Visit 2)
Please mark with a cross as applicable

Poor		Satisfactory		Good		Excellent	
1	2	3	4	5	6	7	8

APPENDIX 2: PF-10 QUESTIONNAIRE AND MMRC

Patient No.: Gender: Year of birth:

PF-10 Questionnaire

The following questions are about activities you might do during a typical day. Does your present state of health limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all	Not answered
a) Vigorous activities, e.g. running, lifting heavy objects, participating in strenuous sports*				
b) Moderate activities, e.g. moving a table, vacuuming, bowling, playing golf*				
c) Lifting or carrying shopping bags*				
d) Climbing several flights of stairs*				
e) Climbing one flight of stairs*				
f) Bending, kneeling, stooping				
g) Walking more than a kilometre*				
h) Walking several hundred metres*				
i) Walking one hundred metres*				
j) Bathing or dressing yourself*				

Modified Medical Research Council (mMRC) Questionnaire for Assessing the Severity of Breathlessness

Please circle the number which best describes your grade of breathlessness.

I only get breathless with strenuous exercise.	0
I get short of breath when hurrying on the level or walking up a slight hill.	1
I walk slower than people of the same age on the level because of breathlessness, or have to stop for breath when walking at my own pace on the level.	2
I stop for breath after walking about 100 meters or after a few minutes on level.	3
I am too breathless to leave the house or I am breathless when dressing or undressing.	4

APPENDIX 3: (S)AE FORM

Please send immediately to Boehringer Ingelheim Pharma GmbH & Co. KG at fax No. 06132-72-141522 or PV Germany.de@boehringer-ingelheim.com. Do not complete shaded areas.

Boehringer Ingelheim	Report of Serious/Non-Serious Adverse Events In Non-Interventional Study (NIS) NIS Title: 1237.42 Spiolto® Respimat®	OPI Case ID Number:	Reporter's Name / Telephone and Fax Number
Site Number: |__|__|__|__|		Pat. initials |__|__|__| Pat. No. |__|__|	BI CTMS Number: 1237.42

Gender	Year of birth	Age	Height (cm)	Weight (kg)	Race	Pregnant
1 ☐ male 2 ☐ female	|__|__|__|__|	|__|__|	|__|__|__|	|__|__|__| . |__|	1 ☐ white 2 ☐ black 3 ☐ Asian	0 ☐ no 1 ☐ yes Week: |__|__|

☐ Initial report ☐ Follow-up report:	Date of Event (Enter date for **each** event)				Intensity of event (CTCAE grade)	Event treated 0 = no 1 = yes if yes, please explain under Description.	Because of the event, administration of Spiolto® Respimat® was: 1= continued 2= reduced 3= discontinued 4= increased 5= finished as per the observational plan 6= discontinued and resumed 7= not applicable	Outcome of event 1= recovered 2= not yet recovered 3= permanent damage 4= fatal 5= unknown	Was the event serious? 0 = no 1 = yes If yes, state relevant code number 1= fatal** 2= immediately life-threatening 3= persistent or significant disability / incapacity 4= requires hospitalisation 5= requires prolongation of hospitalisation 6= congenital anomaly 7= other/further comparable med. criteria (drug dependence, abuse, cancer, etc.) **If fatal, please attach a copy of the death certificate	Causal Relationship. Is there a justified suspicion of a causal relationship between the event and the use of Spiolto® Respimat®	
Event Describe all observed events and symptoms as well as all non-serious events related to the serious event	If continuing please enter "Cont" in the "End date" column									Repor-ter 0= no 1= yes	PV Ger 0= no 1= yes
	Onset date Day/Mth/ Year	Time in hh:mm (24)	End date Day/Mth/ Year	Time in hh:mm (24)							
1.											
2.											
3.											
4.											

Description of the above-mentioned events (if necessary, please give number as per the above table, Event column):

Please send immediately to Boehringer Ingelheim Pharma GmbH & Co. KG at fax No. 06132-72-141522 or PV Germany.de@boehringer-ingelheim.com. Do not complete shaded areas.

Boehringer Ingelheim Site Number: |__|__|__|__|	Report of Serious/Non-Serious Adverse Events In Non-Interventional Study (NIS) NIS Title: 1237.42 Spiolto® Respimat®	OPU Case ID Number: Pat. initials |__|__|__| Pat. No. |__|__|	BI CTMS Number: 1237.42

Medication / Treatment If a drug, give brand name and generic name	Pharm. form	Total daily dose at start (dose, unit)	Method of administration	Start (date Day / Month / Year	End (date) Day / Month / Year	Given for which indication?	Other suspected drug: Is there a causal relationship between the event and concomitant therapy?	
Boehringer Ingelheim drug Spiolto® Respimat®							Reporter: 0= no If yes, Enter event number	PV Ger: 0= no If yes, Enter event number
Concomitant treatment (relevant) 1.								
2.								
3.								
4.								

Concurrent diagnoses (relevant):

1. _____

2. _____

_____

Comments (attendant circumstances, alternative explanation for event, any re-exposure, etc.)	Name of reporter
_____ _____	_____ _____ Signature Date Day/Month/Year

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

The stand-alone documents for this non-interventional study are:

- Informed Consent Form
- Statistical and Epidemiological Analysis Plan (SEAP)

The above documents will be archived in the Trial Master File in their original English master version.

ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

Not applicable

APPROVAL / SIGNATURE PAGE

Document Number: c03809777 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-1-1237-42-observational-plan

Title: 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

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Trial Clinical Monitor	[redacted]	03 Dec 2015 10:46 CET
Approval-Therapeutic Area [redacted]	[redacted]	03 Dec 2015 11:25 CET
Author-Trial Statistician	[redacted]	03 Dec 2015 15:27 CET
Approval-[redacted] Safety Evaluation Therapeutic Area	[redacted]	03 Dec 2015 16:29 CET
Approval-Other	[redacted]	04 Dec 2015 11:39 CET
Approval-Team Member Medicine	[redacted]	07 Dec 2015 10:09 CET
Approval-On behalf of [redacted] or [redacted] or [redacted]	[redacted]	07 Dec 2015 13:58 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed