Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	c15737297-03
BI Study Number:	1237-0065
BI Investigational Product(s):	Spiolto® Respimat®
Title:	*AERIAL®: Changes in health and functional status in patients with COPD during therapy with Spiolto® Respimat®*
Brief lay title	*Not applicable*
Protocol version identifier:	*Version 2.0*
Date of last version of protocol:	*24 April 2017*
PASS:	*No*
EU PAS register number:	*Study not yet registered*
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 health status including functional status using CCQ scores in COPD patients receiving treatment with Spiolto® Respimat® after approximately 6 weeks in routine clinical practice.* ***Primary objective:*** *Assess proportion of patients achieving "therapeutic success" (= 0.4 point decrease in the CCQ score between baseline and approximately week 6)* ***Secondary objectives*** *are assessment of changes in CCQ and CCQ-4, 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® and willingness to continue treatment with Spiolto® Respimat® at visit 2 as proxy for adherence.*
Country(-ies) of study:	*Germany*
Author:	
Marketing authorisation holder(s):	*Boehringer Ingelheim International GmbH* *Binger Straße 173* *55216 Ingelheim am Rhein*
Date:	24 April 2017
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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
CCQ	Clinical COPD Questionnaire
CML	Local Clinical Monitor
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
eCRF	Electronic Case Report Form
EU	European Union
FDC	Fix Dose Combination
FEV1	Forced expiratory volume in one second
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICH	International Conference on Harmonisation
ICS	Inhalative Corticosteroides
IEC	Independent Ethics Committee
IPCRG	International Primary Care Respiratory Group
IRB	Institutional Review Board
ISF	Investigator Site File
LABA	Long-acting beta$_2$ adrenoceptor agonist
LAMA	Long-acting muscarinic antagonist
MACE	Major Adverse Cardiovascular Event
MAH	Marketing Authorisation Holder
MCID	Minimum Clinically Important Difference
MedDRA	Medical Dictionary for Drug Regulatory Activities
mMRC	Modified Medical Research Council
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
SADR	Suspected Adverse Drug Reaction
SAE	Serious Adverse Event
SAMA	Short-acting muscarinic antagonist
SGRC	St. George's Respiratory Questionnaire
SPC	Summary of Product Characteristics
TDI	Transitional dyspnoea index

VFA	Verband Forschender Arzneimittelhersteller
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

Table 3.1 Responsible parties

Function	Name / Location
Scientific Coordinator	
Therapeutic Area Respiratory Medicine (TA)	
Team Member Medical Affairs (TM MA)	
Team Member Epidemiology (TM Epi)	
Global Epidemiology (GEpi)	
Therapeutic Area Risk Management (TA RM), and Pharmacovigilance Working Group (PVWG)	
GPV CT Coordinator	
Trial Clinical Monitor	
Statistical Analysis	Boehringer Ingelheim Pharmaceuticals, Inc. Global Biom. And Clin. Appl./BDM
Data Management	Boehringer Ingelheim Pharmaceuticals, Inc. Global Biom. And Clin. Appl./BDM
Trial Programming	Boehringer Ingelheim Pharmaceuticals, Inc. Global Biom. And Clin. Appl./BDM
CRO	Project

4. ABSTRACT

Name of company: Boehringer Ingelheim Pharma GmbH & Co. KG			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide + Olodaterol			
Protocol date: 24 April 2017	**Study number:** 1237-0065	**Version/Revision:** 2.0	**Version/Revision date:** Not applicable
Title of study:	*AERIAL®: Changes in health and functional status in patients with COPD during therapy with Spiolto® Respimat®* *Author:*		
Rationale and background:	Clinical studies investigating treatment with Spiriva®, with Striverdi® Respimat® as well as with the LAMA-LABA combination Spiolto® Respimat® have shown significant improvement in exercise capacity in patients with COPD. However, real world exercise data with regards to the effects of a combination therapy with Spiolto® Respimat® in COPD patients who need two long-acting bronchodilators are still ongoing and thus not yet available. This NIS aims to investigate health and functional status of COPD patients treated with Spiolto® Respimat® by means of the CCQ questionnaire (CCQ and CCQ-4).		
Research question and objectives:	The primary objective of this NIS is to measure changes in health and functional status using the CCQ score, in COPD patients on treatment with Spiolto® Respimat® after approximately 6 weeks. A secondary objective is to evaluate changes in CCQ and CCQ-4 scores from visit 1 (baseline visit at the start of the study) to visit 2 (final visit at the end of the study, approx. 6 weeks after visit 1), the patient's general condition (physician's evaluation) at visit 1 and at visit 2, as well as patient satisfaction with Spiolto® Respimat® at visit 2 and patient's willingness to continue treatment with Spiolto® Respimat® after study end (proxy for adherence).		
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 combination therapy of two long-acting bronchodilators (LAMA + LABA) according to approved SmPC and GOLD guidelines, COPD GOLD groups B to D (Version 2017).		

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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 - CCQ and CCQ-4 scores - Patient satisfaction with Spiolto® Respimat® - Safety; ADR (serious and non-serious), fatal AEs, pregnancies - GOLD patient groups (B, C, D) - GOLD spirometric classification (1-4), if available		
Data sources:	To be completed by the physician: - Patient demographics - Patient medical files - Physician's Global Evaluation (PGE) at visit 1 and visit 2 - Patient satisfaction - Patient's willingness to continue treatment To be completed by the patient at visit 1: - mMRC breathlessness scale To be completed by the patient at visit 1 and at visit 2: - Health and functional status by CCQ questionnaire		
Study size:	1300 patients, 400 sites		

Name of company: Boehringer Ingelheim Pharma GmbH & Co. KG			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide + Olodaterol			
Protocol date: 24 April 2017	**Study number:** 1237-0065	**Version/Revision:** 2.0	**Version/Revision date:** Not applicable
Data analysis:	**Primary outcome:** "Therapeutic success" at visit 2 (0.4 - point decrease in the CCQ score from visit 1 to visit 2). **Secondary outcomes:** Change in the CCQ and CCQ-4 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 Patient's willingness to continue treatment Subgroup analysis for maintenance naïve patients and the ones already treated at baseline with long acting bronchodilators or LABA + ICS will be performed for the primary outcome. Subgroup analyses will be performed by GOLD spirometric classifications (2 vs. 3 vs. 4) and GOLD patient groups (B vs. C/D and B vs. C vs. D) for the primary outcome and changes in CCQ score for the secondary outcome		
Milestones:	Start of data collection Q2 2017 End of data collection Q2 2018 Final report of study results Q3 2018		

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
Start of data collection	Q2 2017
End of data collection	Q2 2018
Final report of study results:	Q3 2018

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 [I].

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases [I].

The inhalation of noxious substances such as smoke with harmful particles or gases (air pollution), but in the majority of cases tobacco smokingtriggers 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 [II].

According to the Helmholtz Centre in Munich [III], 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 or stages from 1 to 4 according to the reduction in forced expiratory volume in one second, FEV1 (%) from the age-related predicted value in the presence of a reduced (<70%) FEV1/ forced vital capacity ratio (standard for COPD diagnosis) [I].

GOLD reassessed their classification and separated the spirometric assessment from symptom evaluation. ABCD groups are now proposed to be derived exclusively from patient symptoms and their history of exacerbations [IV].
The most important treatment strategies include inhalative pharmacological treatment, beside 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) [I].

In accordance with the GOLD guidelines [IV], for mild COPD (group GOLD A) monotherapy with short-or long acting bronchodilators is the recommended first choice.

For group GOLD B, long-term inhaled treatment with long-acting bronchodilators (LABA, LAMA) is the primary recommendation. In case of persisting symptoms, therapy should be escalated to a LAMA/LABA combination.

For group GOLD C, an escalation from LAMA monotherapy to preferably LAMA plus LABA or, alternatively, to glucocorticosteroid plus LABA is recommended in case of further exacerbations.

For patients in group GOLD D a double or triple therapy consisting of LAMA plus LABA or inhaled corticosteroids plus LABA and/or LAMA, respectively, is recommended. In case LABA/LAMA/ICS is not sufficient, for some patients adding roflumilast or a macrolide may be an option, but also de-escalation from triple therapy with ICS to dual bronchodilation is considered as an option for some patients.

Pharmacological therapy for COPD is used to lessen symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. To date, COPD medications have not been conclusively shown to modify the long-term decline in lung function, 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 [IV].

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 [V]. Therefore, treatment with combination therapy is likely to be an effective option for the management of moderate-to severe COPD.

7.2 DRUG PROFILE

7.2.1 Tiotropium and Olodaterol

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® [VI, VII].
The Spiriva® Respimat® was developed from the Spiriva® pharmaceutical form. This device optimises the pulmonary deposition of the drug [VIII, VIX] and thus reduces the quantity of drug used [X].

The Respimat® 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 [XI]. Thus, deep pulmonary deposition is achieved 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 [XII, XIII, XIV] and also demonstrated a more rapid onset of effect [XV].
The drug has been authorised since 2013 in 43 countries worldwide and is available in Germany under the name Striverdi® Respimat® [XVI].

NIS AKTIV! (1222.56)
A prospective, open-label, non-interventional study was performed in Germany in 2014-2015 to evaluate the effectiveness of a free combination of Tiotropium plus Olodaterol on physical function in a broad range of COPD patients treated in primary care [XVII].
In this real-world clinical setting study enrolling 1858 patients in 800 sites, Tiotropium plus Olodaterol rapidly improved physical functioning in patients with moderate to very severe COPD within the first 4-6 weeks of treatment in general practice. Patients with less severe COPD (B and C) and no prior maintenance treatment demonstrated the greatest benefit. The majority of patients were
"satisfied" or "very satisfied" with the Respimat® inhaler.
Within a short time frame, the combination of Tiotropium plus Olodaterol improved physical functioning, translating into overall improved general condition in patients presenting with a broad COPD severity range.

The findings of significant better results in maintenance-naïve COPD patients and less severe COPD disease are in line with results of the post hoc subgroup analysis of two replicate randomised controlled studies (OTEMTO).

These results support the assumption of the benefit of using the combination of Tiotropium plus Olodaterol in early stages of COPD disease.

7.2.2 Spiolto® Respimat®

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) [V].

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) [V]. 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®.

Several studies investigated the impact of tiotropium/olodaterol on patient-related outcopmes as e.g. quality of life and exercice capacity.

The OTEMTO® studies [XVIII] are two replicate, randomised, double-blind, placebo-controlled Phase III studies investigating the effects of tiotropium/olodaterol on lung function and quality of life over 12 weeks in patients with moderate to severe chronic obstructive pulmonary disease (COPD). Post hoc analyses investigated the benefits of combination therapy over tiotropium monotherapy according to GOLD categories (GOLD 2-3 and GOLD A-D as well) or previous treatment.

Patients were randomised to receive one of four treatments delivered via Respimat® inhaler: Tiotropium/olodaterol 2.5/5 µg, Tiotropium/olodaterol 5/5 µg, Tiotropium 5 µg or placebo. Only results of the subgroup analyses for the licensed doses (tiotropium/olodaterol 5/5 µg, tiotropium 5 µg) and placebo were presented in this publication.

Results

Trial Population
Both studies (OTEMTO® 1 and 2) randomised a total of 1,623 patients, with 1,621 receiving treatment and 1,525 completing the study. Baseline characteristics were similar across the

subgroups except mean FEV1 values and baseline pulmonary medications, which differed between subgroups. Patients already on maintenance therapy tended to be ex-smokers and to have worse lung function compared to those who were treatment naïve.

Efficacy
Overall, tiotropium/olodaterol therapy produced better responses than monotherapy or placebo.

GOLD 2 and 3 subgroups showed similar improvements in trough FEV1 responses and FEV1 AUC0-3 with tiotropium/olodaterol and the same applied for TDI focal score. SGRQ total score improved with tiotropium/olodaterol 5/5 µg in the GOLD 2 subgroup (compared to tiotropium and placebo) and in the GOLD 3 subgroup (compared to placebo). Tiotropium/olodaterol showed significant treatment effects for all endpoints as compared to placebo. When compared to tiotropium monotherapy, significant treatment effects between treatments could also be noted for most endpoints, except FEV1 in both subgroups and SGRQ in GOLD 3 patients.

In GOLD A-D subgroups tiotropium/olodaterol showed better improvements in FEV1 AUC0-3 than monotherapy and placebo across all subgroups.

Trough FEV1 showed improved responses as compared to placebo in all subgroups. SGRQ total score as well as TDI focal score showed greater improvements with tiotropium/olodaterol as compared to placebo across all subgroups.

When compared to tiotropium monotherapy the combination treatment effects differed and showed best effects in the GOLD B subgroup with statistically significant difference vs tiotropium.
Subgroup analyses of the OTEMTO® studies demonstrated an improvement in lung function, and quality of life for tiotropium/olodaterol in patients with moderate (GOLD 2) as well as severe COPD (GOLD 3).

Following the GOLD classification A-D, tiotropium/olodaterol had a similar treatment effect on lung function in all patient groups whereas in regard to QoL, the improvement was most apparent in GOLD B patients.
The superior effect of tiotropium/olodaterol over monotherapy with each component has also been shown in post hoc analyses of the TONADO® studies.

Although the treatment effect of tiotropium/olodaterol on lung function was similar in all subgroups, the benefit of tiotropium/olodaterol for SGRQ was most pronounced in GOLD B patients.

Considering the finding that the fastest decline of lung function is seen in the early stages of the disease, initiation of an appropriate maintenance treatment could be of particular importance.
The authors conclude that the results of this post hoc analysis of the OTEMTO® studies clearly demonstrated that in all subgroups the improvement with tiotropium/olodaterol in

comparison to monotherapy and placebo was superior in lung function and patient related outcomes such as quality of life and dyspnoea.
Tiotropium/olodaterol can be considered for maintenance treatment of patients in a moderate and a more severe stage of the disease.

Tiotropium/olodaterol is a suitable option for initiating treatment already in patients with moderate COPD associated with the treatment goal of maintaining patients' functionality and slowing down disease progression.

The PHYSACTO trial [XIX] investigated the effect of 8 and 12 weeks' once-daily tiotropium/olodaterol, alone and combined with exercise training, on exercise endurance during walking in 303 patients with COPD. It could be shown that the treatment with tiotropium/olodaterol 5/5 µg, alone and combined with exercise training, improved walking exercise capacity compared to placebo in patients with moderate to severe chronic obstructive pulmonary disease who participated in a 12-week self-management behaviour- modification programme.

Further analysis of this data set [XX] has explored the impact of behaviour modification, combined with tiotropium/olodaterol treatment and exercise capacity, on physical activity and patient-reported outcomes in patients with moderate to severe chronic obstructive pulmonary disease. Self-management behaviour-modification was the most effective component in obtaining short-term increases in physical activity. Significant differences between treatment arms in amount of physical activity were not obtained with the given sample size. While physical activity did not increase with tiotropium/olodaterol 5/5 µg alone or in combination with exercise training compared to placebo, a reduction in symptom burden (perceived difficulty associated with physical activity) was observed.

Also the MORACTO™ [XXI] and the TORRACTO [XXII] studies give first hints on the improvement of exercise capacity and exercise endurance with tiotropium/olodaterol compared to placebo.

8. RESEARCH QUESTION AND OBJECTIVES

COPD Patients usually do not only show respiratory symptoms, but also physical incapacity and several comorbidities [XXIII]. These often result in impaired health status and reduced health-related quality of life and may lead to hospitalisations and increased mortality [XXIV]. Amongst others, low lung function [XXV], frequent exacerbations [XXVI] comorbidities [XXVII] and a low level of physical activity are negative factors for health status in COPD. Physical exercise [XXVIII] and pharmacological interventions may improving health status, as e.g. shown in the UPLIFT trial with tiotropium [XXIX].
The cross-sectional BOLD study assessed the impact of COPD on health status in a general population-based survey including almost 12000 subjects from 17 countries [XXX]. 2269 COPD patients (defined by a post-bronchodilator forced expiratory volume in 1 s/forced vital capacity <0.70) were found to show lower physical component scores (44±10 vs. 48±10 units, p<0.0001) and mental health component scores (51±10 vs. 52±10 units, p = 0.005) than subjects without COPD. The effect of reported heart disease, hypertension and diabetes on physical health component scores (-3 to -4 units) was considerably less than the effect of COPD GOLD grade 3 (-8 units) or 4 (-11 units).
Dyspnoea was the most important determinant of low physical and mental health component scores. In addition, lower forced expiratory volume in 1 s, chronic cough, chronic phlegm and the presence of comorbidities were all associated with a lower physical health component score.
The authors conclude COPD to be associated with poorer health status but the effect to be stronger on the physical than the mental aspects of health status. Severe COPD had a greater negative impact on health status than self-reported cardiovascular disease and diabetes.

The contribution of physical inactivity to disability in COPD can be difficult to distinguish from disease progression [XXXI]. However, it is clear that physical activity is significantly lower in patients with COPD than in healthy controls [XXXII, XXXIII].
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 [XXXIV, XXXV].
The loss of physical activity in COPD is also associated with increased mortality [XXXVI]. 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) [XXXVII].
Clinical studies [XXXVIII, XXXIX, XL] of both Spiriva® and Striverdi® Respimat® in COPD patients have demonstrated significant improvement in exercise capacity [XLI].

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.

In the AKTIV! observational study the combination of Tiotropium plus Olodaterol showed improved physical functioning, translating into overall improved general condition in patients presenting with a broad COPD severity range within a short time frame [XLII]. Thus, it is the first study to give a hint that the tiotropium + olodaterol combination may improve physical functioning and health condition.

Various questionnaires on quality of life and physical functioning are used to try assessing COPD patients' health status and physical state. The Clinical COPD questionnaire (CCQ) has been developed and validated in the Netherlands especially for COPD patients by Jan Kocks et al in 2006 [XLIII] to categorize patients' impairments generally and focus patients' treatment on their specific needs.

The CCQ is easy to apply. It takes less than 2 minutes to complete, is widely used to monitor COPD health status and control and consists of 10 questions, covering 3 domains: symptom domain (4 questions (#'s 1,2,5,6)); functional status domain (4 questions(#'s 7,8,9,10)) and mental status domain (2 questions (#'s 3,4)). The questionnaire is responsive to intervention and has been translated and validated in over 140 languages [XLIV]. The CCQ thus is a very well-known and widespread questionnaire, which is also included in the GOLD guidelines and is validated also in German language. It has been given maximum ranking in "COPD wellness tools" overview by the International Primary Care Respiratory Group (IPCRG) [XLV].

8.1 STUDY OBJECTIVES

The objective of this NIS is to measure changes in health and functional status by the CCQ, in COPD patients receiving treatment with Spiolto® Respimat® after approximately 6 weeks in routine clinical practice.
Each of the 10 CCQ questions is scored by the patient on a 7-point scale between 0 and 6 at baseline and end of the observation after approximately 6 weeks. The sum of the scores divided by 10 gives the CCQ score, which measures the health and functional status. A higher CCQ score is indicative of worse status.
The functional status (CCQ-4) is calculation as the sum of the 4 questions (#'s 7, 8, 9, 10) divided by 4. A change of 0.4 points is considered to be the MCID for both CCQ score and CCQ-4.

Primary objective: Assess the proportion of patients achieving "therapeutic success" (= 0.4 point decrease in the CCQ score between baseline and approximately week 6).

Secondary objectives are assessment of changes in CCQ and CCQ-4 from visit 1 (baseline visit at the start of the study) to visit 2 (final visit at the end of the study, approx. 6 weeks after visit 1), the patient's general condition (physician's evaluation) at visit 1 and at visit 2, as well as patient satisfaction with Spiolto® Respimat® and willingness to continue treatment with Spiolto® Respimat® at visit 2 as proxy for adherence.

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.

9.2 SETTING

9.2.1 Study sites

It is planned that data of approximately 1300 patients from approximately 400 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.

9.2.2 Study population

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 a combination of two long-acting bronchodilators (LAMA + LABA) according to approved SmPC and GOLD COPD guideline recommendation 2017 (GOLD COPD groups B to D)
- Treatment with Spiolto® Respimat® acc. to SmPC at the discretion of the physician.

Exclusion Criteria:

- Patients with contraindications according to Spiolto® Respimat® SmPC
- Patients already on a LABA/LAMA combination (free and fixed dose) in the last 6 weeks before study entry
- Patients continuing LABA-ICS treatment should not be additionally treated with Spiolto® Respimat® in order to avoid a double dosing of long-acting beta-agonists
- Pregnancy and lactation
- Current participation in any clinical trial or any other non-interventional study of a drug or device.

9.2.3 Study visits

Patients will be enrolled consecutively and will be followed over an observational period of approximately 6 weeks. Data as listed in Table 9.2.3.1 will be collected.

Two study visits will be performed. At Visit 1 (baseline) the patient will be included into the NIS. At visit 2, after approximately 6 weeks from baseline, the observation of the patient will end. The respective exams and data to be collected are listed in Table 9.2.3.1.

Table 9.2.3.1: 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 weeks before visit 1)	X	
Respimat® training (yes/no)	X	
COPD severity based on GOLD assessment[1]	X	
GOLD spirometric classification, if available[2]	X	
Smoking history	X	X
Concomitant diseases / Comorbidities	X	X
COPD related and other relevant concomitant medication	X	X
Health and functional status by CCQ 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®		X
Rationale 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 (B, C or D) will be automatically calculated within the eCRF based on available exacerbation history and mMRC.*
[2] *GOLD stage 1-4 spirometric classification of airflow limitation based on post-bronchodilator FEV_1 if available.*

9.2.4 Study discontinuation

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

9.3 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)
- Health and functional status based on CCQ 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 (B, C, D) based on GOLD guidelines 2017

9.3.1 Exposures

All patients will receive LAMA/LABA combination treatment with Spiolto® Respimat® according to the German SmPC.

Spiolto® Respimat® contains

- the long-acting anticholinergic tiotropium bromide.
  The dose dispensed is 2.5 micrograms of tiotropium per puff, equivalent to 3.124 micrograms tiotropium bromide 1 H_2O. The dose dispensed is the quantity available to patients after crossing the mouthpiece.
- the selective beta$_2$-adrenoceptor agonist olodaterol. The dose dispensed is 2.5 micrograms of olodaterol per puff (as olodaterol hydrochloride). The dose dispensed is the quantity available to patients after crossing the mouthpiece.

The recommended daily dose of Spiolto® Respimat® for adults is 5 micrograms of tiotropium ion (tiotropium) plus 5 micrograms of olodaterol, equivalent to inhaling 2 puffs from the Respimat® inhaler once daily at the same time of day.
The Summaries of Product Characteristics on Spiolto® Respimat® is contained in the NIS ISF in the "Summary of Product Characteristics" section.
Note: The recommended doses stated in the Summary of Product Characteristics should not be exceeded.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

"Therapeutic success" at visit 2 (0.4 -point decrease in the CCQ score from visit 1 to visit 2).

The primary outcome is not a safety outcome.

9.3.2.2 Secondary outcomes

- Changes in the CCQ and CCQ-4 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.
- Willingness to continue treatment with Spiolto® Respimat® at visit 2 as proxy for adherence

The secondary outcomes are not safety outcomes.

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 will be used to automatically calculate the GOLD patient group (B, C, or D) in the eCRF.

The CCQ questionnaire contains 10 questions about everyday physical activity and functioning. Each question can be scored by patients on a 7-point scale between 0 and 6. The sum of the scores divided by 10 gives the CCQ score, which measures the health and functional status. For the functional status calculation the sum of the 4 questions (# 7, 8, 9, 10) is divided by 4. A change of 0.4 points is considered to be the MCID. This questionnaire will be filled out by the patient and entered into the database. Patients will be asked to complete the CCQ in order to evaluate their health and functional status 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.

Willingness to continue treatment is assessed by a yes/no question.

9.5 STUDY SIZE

We assume that patients treated with Spiolto® Respimat® will have a CCQ therapeutic success rate similar to the SGRQ responder rate. In the TONADO studies[V] patients treated with Spiolto® Respimat® had a 57.5% SGRQ responder rates after 24 weeks.

The TONADO was a selected trial population, so a real world population would probably show somewhat lower numbers due to the wide diversity of potential patients that will be followed up. Therefore a 50% CCQ therapeutic success rate is a reasonable assumption.

Assuming a 50% therapeutic success rate for CCQ and a sample size of 1170 patients, the 95% confidence interval for the therapeutic success rate would be between 47.1% (lower limit) and 52.9% (upper limit).

Subgroups with long acting bronchodilators at baseline (i.e., LABA only, LAMA only, LABA and ICS) will be analyzed only if they include more than 20% of all patients. In the smallest subgroup (with at least 234 patients), assuming a 50% therapeutic success rate, the 95% confidence interval would be between 43.6% and 56.4%.
To account for a 10% drop-out rate, the sample size becomes 1300 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 and the safety requirements of the FDA (US Food & Drug Administration) concerning systems for the data acquisition of clinical studies in accordance with "Title 21 Code of Federal Regulations (21 CFR Part 11): Electronic Records; Electronic Signatures. Patient confidentiality will be strictly maintained.

9.6.1 Data Entry / EDC

Data entry into the eCRF follows the instructions in the EDC system user manual and is further supported by help and hint texts. Support documents will also be provided within the online system documents which give explanations to basic functions and field types in the eCRF.
With data entry into the EDC system, all changes and user information will be saved in an audit trail.
The data review and validation steps for a project are defined in the data validation plan (DVP).

The DVP includes all definitions of electronic checks and the defined manual checks, which will be performed directly in the EDC system or can be based on listings.
Electronic edit checks (eChecks) are performed automatically and directly when entering data into the eCRF. Missing data entries or implausibilities are indicated to the user immediately. Manual Checks are applied to verify the entered data validity and plausibility.

Queries can result from various sources:

- Manual Checks by data management
- Manual Checks by pharmacovigilance
- Source data verification during on-site monitoring

9.6.2 Source Documents

The source documents are contained in the patient's medical record. Data collected on the eCRFs must be traceable to these source documents in the patient's medical records as far as this is routine documentation. All original source documentation is expected to be stored at the site for the longest possible time required by local applicable regulations. The site will be instructed to notify the Sponsor before any destruction of medical records of study participants.

9.6.3 File Retention and Archiving

The study database and all study-specific documents received by will be transferred to BI regularly during and after the study period. Archiving will be performed by BI Pharma in accordance with BI SOPs.

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the investigator agrees to keep records, including the identity of participating patients, copies of all CRFs, SAE forms, source documents and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the study contract, whichever is longer.

Each site will receive a study site file at study initiation which contains all documents necessary for the conduct of the study and is updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least ten years after the completing participation in the study. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify the Sponsor.

9.7 DATA ANALYSIS

Planned analyses

More details will be described in the statistical analysis plan (SAP).

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

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. For example, if a patient is missing the CCQ score at Visit 1 and/ or Visit 2, that patient will be excluded from the analyses for the primary endpoint of therapeutic success and the secondary endpoint of change in CCQs from Visit 1 to Visit 2.
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 (main diagnosis and concurrent diagnosis according to MedDRA, version valid as at the time of database closure)
- COPD related and other concomitant medication (according to the WHO classification, version valid at the time of database closure)
- History of smoking
- Reported exacerbations
- Breathlessness based on mMRC score at visit 1
- Therapeutic success based on CCQ score; primary outcome
- Changes from Visit1 to Visit 2 in the CCQ and CCQ-4 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
- Willingness to continue; secondary outcome
- Adverse Drug Reactions (ADR & SADR), fatal AEs, pregnancies
- GOLD spirometric classifications (1, 2, 3, 4) and GOLD patient groups (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

9.7.1 Main analysis

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

9.7.3 Handling of missing data

For rules regarding the imputation of CCQ score, refer to www.ccq.nl (Section health care professionals, Scoring, missing data rules). 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.

Source data verification is planned to be performed in about 10% of the planned sites 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.

9.9 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.

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 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs)/ Independent Ethics Committee (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.

9.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, either on paper or via remote data capture.

9.10.2.1 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, depending on the study; also current medical records must be available.

For eCRFs all data must be derived from source documents.

9.10.2.2 Direct access to source data and documents

The investigator will permit study-related monitoring, audits 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. US Food and Drug Administration (FDA)). The Clinical Research Associate (CRA) / Clinical Monitor Local (CML) 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 9.10.2.1.

9.10.3 Completion of study

The EC/competent authority in each participating EU member state needs to be notified about the end of the study (last patient/patient out, unless specified differently in Section 9.2) or early termination of the study.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP), Guidelines for 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.

10.1 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.

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

Prior to patient participation in the study, written informed consent must 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 study 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.

10.2 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.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
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 adverse event 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 reaction
An adverse reaction 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 adverse event is at least a reasonable possibility. Adverse reactions 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

A serious adverse event 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 judgement 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 hospitalisation but might jeopardise 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 hospitalisation 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 Adverse Event of Special Interest (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 authorisation. 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 (e)CRF from signing the informed consent onwards until the end of the study:

- all adverse drug reaction (ADRs) (serious and non-serious),
- all AEs with fatal outcome

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 adverse event
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised 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 adverse event
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 subject has been enrolled into the study, after having taken Spiolto® Respimat®, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject 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.

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** associated with Spiolto® Respimat®	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to Spiolto® Respimat®	immediately within 24 hours
All **non-serious ADRs** associated with Spiolto® Respimat®	7 calendar days
All **pregnancy monitoring** forms associated with Spiolto® Respimat®	7 calendar days

All serious ADRs and all fatal AEs must be documented in the eCRF and reported to the Pharmacovigilance department of Boehringer Ingelheim **within 24 hours** after getting knowledge of the event. The Boehringer Ingelheim NIS AE form must be printed from the eCRF and sent per fax.

Non-serious ADRs and pregnancies must be documented in the eCRF and reported to the Pharmacovigilance department of Boehringer Ingelheim **within 7 calendar days** after getting knowledge of the event. The Boehringer Ingelheim NIS AE form must be printed from the eCRF and sent per fax.

If there is no eCRF access at the time of the report, the NIS AE form must alternatively be filled out by hand and sent to the following address by fax within 24 hours / 7 days after becoming known:

Boehringer Ingelheim Pharma GmbH & Co. KG
Pharmacovigilance Germany (PV Germany)
Binger Straße 173
55216 Ingelheim
Phone: +49 (6132) 72 - 2604
Fax: +49 (6132) 72 – 141522

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

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

Information required

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

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events 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.

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 finalisation of the Study Report.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	Appendix 1	20 January 2017	Physicians' Global Evaluation (PGE)
2	Appendix 2	20 January 2017	CCQ Questionnaire and mMRC
3	Appendix 3	20 January 2017	SAE Form

APPENDIX 1: PHYSICIANS' GLOBAL EVALUATION (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: CLINICAL COPD QUESTIONNAIRE (CCQ) AND MMRC

Clinical COPD Questionnaire

Patient number:_____
Date:_____

CLINICAL COPD QUESTIONNAIRE

Please **circle** the number of the response that best describes how you have been feeling during the **past week**. (Only **one** response for each question).

On average, **during the past week**, how often did you feel:	never	hardly ever	a few times	several times	many times	a great many times	almost all the time
1. Short of breath **at rest**?	0	1	2	3	4	5	6
2. Short of breath **doing physical activities**?	0	1	2	3	4	5	6
3. **Concerned** about getting a cold or your breathing getting worse?	0	1	2	3	4	5	6
4. **Depressed (down)** because of your breathing problems?	0	1	2	3	4	5	6
In general, **during the past week**, how much of the time:							
5. Did you **cough**?	0	1	2	3	4	5	6
6. Did you **produce phlegm**?	0	1	2	3	4	5	6
On average, **during the past week**, how limited were you in these activities **because of your breathing problems**:	not limited at all	very slightly limited	slightly limited	moderately limited	very limited	extremely limited	totally limited /or unable to do
7. **Strenuous physical activities** (such as climbing stairs, hurrying, doing sports)?	0	1	2	3	4	5	6
8. **Moderate physical activities** (such as walking, housework, carrying things)?	0	1	2	3	4	5	6
9. **Daily activities at home** (such as dressing, washing yourself)?	0	1	2	3	4	5	6
10. **Social activities** (such as talking, being with children, visiting friends/ relatives)?	0	1	2	3	4	5	6

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

Boehringer Ingelheim

Meldebogen für unerwünschte Ereignisse bei nicht-interventionellen Studien

BI Studien-Nr: 1237-0065	Land: GER
Zentrums-Nr:	Patienten-Nr.

Anzahl Seiten inkl. dieser Seite:

An: Boehringer Ingelheim	Von:
Boehringer Ingelheim GmbH&Co.KG Pharmacovigilance Germany Binger Straße 173 55216 Ingelheim Faxnummer 06131-72141522	[Praxis/Klinik-Stempel]

MIT IHRER UNTERSCHRIFT BESTÄTIGEN SIE, DASS DIE HIER GEGEBENEN INFORMATIONEN ZUTREFFEND SIND.

Bitte erfassen Sie alle Datumsfelder im ttmmmjjjj Format (z.B. 01Jan2016)

Art des Reports	Datum	Unterschrift des Beobachtenden Arztes	Bemerkungen
☐ Initial	___	_____	____
☐ Follow-up	___	_____	____
☐ Follow-up	___	_____	____
☐ Follow-up	___	_____	____
☐ Follow-up	___	_____	____
☐ Follow-up	___	_____	____
☐ Follow-up	___	_____	____

DEMOGRAPHISCHE ANGABEN ZUM PATIENTEN

Geburtsjahr: ____ Größe ___ (cm) Gewicht ___ (kg)

Falls unbekannt notieren Sie ‚unk'

Geschlecht: ☐ männlich ☐ weiblich Schwangerschaft: ☐ Nein ☐ Ja Gestationswoche

Falls eine Schwangerschaft vorliegt, schicken Sie bitte den Schwangerschaftsmeldebogen für Studien

Seite 1

001-MCS-09-118_RD-15 (1.0) / Saved on: 11 Nov 2016

Boehringer Ingelheim

Meldebogen für unerwünschte Ereignisse bei nicht-interventionellen Studien

BI Studien-Nr: 1237-0065	Land: GER
Zentrums-Nr:	Patienten-Nr.

INFORMATION ZUM EREIGNIS

Erfassen Sie bitte all Datumsfelder im Format ttmmmjjjj (z.B. 01Jan2016). Falls das Ereignis nicht beendet ist, notieren Sie 'CONT.' Erfassen Sie alle Zeitangaben im 24-Stunden Format (hh:mm). Ist die Zeit unbekannt, notieren Sie 'UNK.'

		Ereignis Nr. [ ]	Ereignis Nr. [ ]	Ereignis Nr. [ ]	Ereignis Nr. [ ]
Unerwünschtes Ereignis (Begriff) (falls bekannt, tragen Sie die Diagnose ein)					
Beginndatum					
Beginnzeitpunkt					
Enddatum					
Endzeitpunkt					
War das Ereignis schwerwiegend?		☐ Ja ☐ Nein	☐ Ja ☐ Nein	☐ Ja ☐ Nein	☐ Ja ☐ Nein
Falls es schwerwiegend war, geben Sie den Grund für die Einschätzung an	Tödlicher Ausgang	☐	☐	☐	☐
	Unmittelbar lebensbedrohlich	☐	☐	☐	☐
	Anhaltende oder signifikante Behinderung/Arbeitsunfähigkeit	☐	☐	☐	☐
	Erfordert/verlängert Hospitalisation	☐	☐	☐	☐
	Angeborene Anomalie / Geburtsdefekt	☐	☐	☐	☐
	Andere vergleichbare medizinische Kriterien (bitte unter ‚Beschreibung des Ereignisses' spezifizieren)	☐	☐	☐	☐
Wurde das Ereignis als Adverse Event of Special Interest (AESI) im Beobachtungsplan aufgeführt?		☐ Ja ☐ Nein	☐ Ja ☐ Nein	☐ Ja ☐ Nein	☐ Ja ☐ Nein
Gibt es einen vernünftigen Kausalzusammenhang zwischen dem unerwünschten Ereignis und Spiolto® Respimat®: (Bitte beschreiben Sie die Rationale und alternative Gründe auf Seite 3)					
Wurde das BI Medikament gemäß der Indikation in der NIS verabreicht		☐ Ja ☐ Nein	☐ Ja ☐ Nein	☐ Ja ☐ Nein	☐ Ja ☐ Nein
Begleitmedikation: Bitte gehen Sie zum Abschnitt Begleitmedikation um eine Kausalzusammenhang zu dokumentieren.					
Ausgang des Ereignisses (bitten nur einen ankreuzen)					
Wiederhergestellt (erfassen Sie das Enddatum oben)		☐	☐	☐	☐
Noch nicht wiederhergestellt		☐	☐	☐	☐
Wiederhergestellt mit Folgeschäden (erfassen Sie das Enddatum oben)		☐	☐	☐	☐
Unbekannt		☐	☐	☐	☐
Tödlich		☐	☐	☐	☐
Im Todesfall, war das Ereignis die primäre Todesursache?		☐ Ja ☐ Nein	☐ Ja ☐ Nein	☐ Ja ☐ Nein	☐ Ja ☐ Nein
Falls der Patient verstarb, geben Sie bitte das Datum an					
Wurde eine Autopsie durchgeführt?		☐ Ja ☐ Nein ☐ Unbekannt			
Wurde das Ereignis behandelt?		☐ Ja ☐ Nein	☐ Ja ☐ Nein	☐ Ja ☐ Nein	☐ Ja ☐ Nein
Falls ja, spezifizieren Sie die Therapie bitte unter „Beschreibung des Ereignisses".					
Wurde das verdächtige Medikament abgesetzt?		☐ Ja ☐ Nein ☐ NA	☐ Ja ☐ Nein ☐ NA	☐ Ja ☐ Nein ☐ NA	☐ Ja ☐ Nein ☐ NA
Falls ja, verschwand das Ereignis oder wurde nach Absetzen von Spiolto® Respimat® deutlich besser?		☐ Ja ☐ Nein	☐ Ja ☐ Nein	☐ Ja ☐ Nein	☐ Ja ☐ Nein
Wurde eine Re-Exposition versucht?		☐ Ja ☐ Nein ☐ NA	☐ Ja ☐ Nein ☐ NA	☐ Ja ☐ Nein ☐ NA	☐ Ja ☐ Nein ☐ NA
Falls ja, trat das Ereignis nach der Re-Exposition erneut auf?		☐ Ja ☐ Nein	☐ Ja ☐ Nein	☐ Ja ☐ Nein	☐ Ja ☐ Nein

Seite 2

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Boehringer Ingelheim

Meldebogen für unerwünschte Ereignisse bei nicht-interventionellen Studien

BI Studien-Nr: 1237-0065	Land: GER
Zentrums-Nr:	Patienten-Nr.

RATIONALE FÜR DIE KAUSALITÄTSBEURTEILUNG

Bitte dokumentieren Sie das/die Ereignis(se) und geben die Begründung für Ihre Kausalitätsbeurteilung zu Spiolto® Respimat® an. Geben Sie auch andere kausale Zusammenhänge an, wenn sie relevant sind.

Die Rationale für einen Kausalzusammenhang kann der zeitlichen Zusammenhang, andere Einflussfaktoren wie z.B. die Erkrankung oder Therapien, positive Reaktion nach Absetzen/Re-Exposition, Interaktionen mit anderen Medikamenten und/oder das Reaktionsmuster einschließen.

BESCHREIBUNG DES/DER EREIGNISSE(S)

Bitte geben Sie hier alle zusätzlichen Informationen an, die bisher noch nicht abgefragt wurden und die zur Beurteilung des Falles beitragen können, wie z.B. relevante Laborergebnisse oder andere diagnostische Informationen (inkl. Referenzwerte) und therapeutische Maßnahmen im Zusammenhang mit dem Ereignis.

Seite 3

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RELEVANTE BASELINE BEDINGUNGEN INKLUSIVE ANAMNESE

Erfassen Sie bitte all Datumsfelder im Format ttmmmjjjj (z.B. 01Jan2016). Falls das Ereignis nicht beendet ist, notieren Sie 'CONT.'

☐ Keine ☐ Ja (bitte unten angeben)	Falls begleitend, erfassen Sie bitte das Beginndatum	Zurückliegend - Bitte ankreuzen, wenn Ende vor Beginn des Ereignisses
1.		☐
2.		☐
3.		☐
4.		☐
5.		☐
6.		☐

BOEHRINGER-INGELHEIM PRODUKT

Indikation COPD

Name des BI Medikaments: Spiolto® Respimat®		
Formulierung		Inhalationslösung
Tägliche Gesamtdosis zu Beginn des Ereignisses (Dosis, Einheit)		____ Hub tgl. à 2,5 mg
Route		Inhalation
Startdatum		
Startzeit		
Datum der letzten Verabreichung vor Beginn des Ereignisses		
Enddatum		
Endzeit		
Wurde das Präparat korrekt angewendet?		☐ Ja ☐ Nein
Falls die Verabreichung nicht korrekt war, kreuzen Sie bitte alle zutreffenden Kästchen an: Überdosierung, Missbrauch, fehlerhafter Gebrauch, Medikationsfehler, sonstige (z.B. berufliche Exposition, fehlende Wirkung, unerwarteter Vorteil)		☐ Missbrauch / fehlerhafter Gebrauch ☐ Medikationsfehler ☐ Überdosierung ☐ andere:
Maßnahme mit Spiolto® Respimat® (*bitte eine ankreuzen*)	Dosis unverändert	☐
	Dosis reduziert	☐
	Dosis erhöht	☐
	Medikament abgesetzt	☐

Seite 4

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RELEVANTE VOR- UND BEGLEITMEDIKATION

Bitte verwenden Sie bevorzugt Handelsnamen. Dokumentieren Sie hier NICHT Medikation, die nur zur Behandlung unerwünschter Ereignisse eingesetzt wurden.

☐ Keine ☐ Ja (bitte unten angeben)	Indikation	Vor-medikation?	Start-/Enddatum tttmmmjjjj oder cont.	Tägliche Gesamtdosis zu Beginn des Ereignisses (Dosis, Einheit)	Route	Gibt es einen vernünftigen Kausal-zusammenhang zwischen dem Ereignis und der vergangenen oder jetzigen Begleit-medikation? Wenn ja, nennen Sie bitte die Ereignis-Nr. von S. 2
1.		☐	Start:			☐ Nein ☐ Ja
			Ende:			Ereignis Nr. ____
2.		☐	Start:			☐ Nein ☐ Ja
			Ende:			Ereignis Nr. ____
3.		☐	Start:			☐ Nein ☐ Ja
			Ende:			Ereignis Nr. ____
4.		☐	Start:			☐ Nein ☐ Ja
			Ende:			Ereignis Nr. ____
5.		☐	Start:			☐ Nein ☐ Ja
			Ende:			Ereignis Nr. ____
6.		☐	Start:			☐ Nein ☐ Ja
			Ende:			Ereignis Nr. ____
7.		☐	Start:			☐ Nein ☐ Ja
			Ende:			Ereignis Nr. ____
8.		☐	Start:			☐ Nein ☐ Ja
			Ende:			Ereignis Nr. ____

Seite 5

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ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

Will be completed after study approval by ethic's committee.

APPROVAL / SIGNATURE PAGE

Document Number: c15737297 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-nis-1237-0065

Title: AERIAL®: Changes in health and functional status in patients with COPD during therapy with Spiolto® Respimat®

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval–Clinical Monitor		25 Apr 2017 12:21 CEST
Approval- Therapeutic Area	Safety Evaluation	25 Apr 2017 12:26 CEST
Approval-	Medical Affairs	25 Apr 2017 12:35 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed