Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	**c20825865-01**
BI Study Number:	1237-0072
BI Investigational Product(s):	Spiolto® Respimat®
Title:	*Changes in clinical control of COPD patients measured by the Clinical COPD Questionnaire during therapy with Spiolto® Respimat® in routine clinical practice*
Brief lay title	*A study on the control of chronic obstructive pulmonary disease (COPD) in patients taking the combination of tiotropium and olodaterol using the Respimat® inhaler*
Protocol version identifier:	*Version 1.0*
Date of last version of protocol:	*26 March 2018*
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:	*NL/H/3157/001/DC*
Procedure number:	*n.a.*
Marketing authorisation holder(s):	*MAH:* *<u>This study is initiated, managed and sponsored by:</u>*
Joint PASS:	*No*

Research question and objectives:	*The objective of this NIS is to measure changes in clinical control using Clinical COPD Questionnaire (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 after approximately 6 weeks of treatment)* ***Secondary objectives*** *are assessment of changes in the different CCQ domains, the Symptom domain (questions 1,2, 5, 6 of the CCQ) Mental state (questions 3,4 of the CCQ) and Funcional state domain known in literature also as CCQ-4 (questions 7, 8, 9 and 10 of the CCQ), 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:	*It is planned that data of approximately 4500 patients in 11 countries will be collected (Bulgaria, Czech Republic, Hungary, Israel, Lithuania, Poland, Romania, Russia, Slovenia, Switzerland and Ukraine).*
Author:	
Date:	*26 March 2018*

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of special interest
AUC	Area under the Curve
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
CTCAE	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
SmPC	Summary of product characteristics
TDI	Transitional dyspnoea index
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

Function	Name
Scientific Coordinator	
Therapeutic Area Respiratory Medicine (TA)	
Team Member Medical Affairs (TM MA)	
Scientific Advisor Medical Affairs	
Team Member Epidemiology (TM Epi)	
Deputy Global Epidemiology (GEpi)	
Therapeutic Area Risk Management (TA RM), and Pharmacovigilance Working Group (PVWG) chairperson	
GPV CT Coordinator	
Trial Clinical Monitor	
Statistical Analysis	
Data Management	
Trial Programming	

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide + Olodaterol			
Protocol date: 26 March 2018	**Study number:** 1237-0072	**Version/Revision:** 1.0	**Version/Revision date:** Not applicable
Title of study:	*Changes in clinical control of COPD patients measured by the Clinical COPD Questionnaire during therapy with Spiolto® Respimat® in routine clinical practice*		
Rationale and background:	Clinical studies investigating treatment with Spiriva® (tiotropium bromide), with Striverdi® (Olodaterol) Respimat® as well as with the LAMA-LABA combination Spiolto® Respimat® have shown significant improvement in symptoms, health related quality of life and exercise capacity in patients with COPD. However, real world data with regards to the effects of a combination therapy with Spiolto® Respimat® in COPD patients who need two long-acting bronchodilators are not yet available. This NIS aims to investigate the potential changes in clinical control of COPD patients using the Clinical COPD Questionnaire (CCQ) and its three domains during treatment with Spiolto® Respimat®.		
Research question and objectives:	The primary objective of this NIS is to assess therapeutic success, measured by the a predefined decrease of the CCQ score in COPD patients on treatment with Spiolto® Respimat® after approximately 6 weeks. A secondary objective is to evaluate changes in full CCQ score and its symptom, mental state and functional state domains 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, and patient's willingness to continue treatment with Spiolto® Respimat® after study end (proxy for adherence).		
Study design:	Open-label observational: 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 2018).		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide + Olodaterol			
Protocol date: 26 March 2018	**Study number:** 1237-0072	**Version/Revision:** 1.0	**Version/Revision date:** Not applicable
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 - Exacerbation history - Breathlessness based on mMRC score - CCQ and the CCQ symptom, mental state and functional state domain 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 - Document patient's willingness to continue treatment To be completed by the patient: - mMRC breathlessness scale at visit 1 - Health and functional status by CCQ questionnaire at visit 1 and 2 - Patient satisfaction survey at Visit 2		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide + Olodaterol			
Protocol date: 26 March 2018	**Study number:** 1237-0072	**Version/Revision:** 1.0	**Version/Revision date:** Not applicable
Study size	It is planned that data of approximately 4500 patients in 11 countries will be collected (Bulgaria, Czech Republic, Hungary, Israel, Lithuania, Poland, Romania, Russia, Slovenia, Switzerland and Ukraine).		
Data analysis:	**Primary outcome:** For the primary outcome, the percentage of patients with therapeutic success will be presented together with the 95% confidence interval, whereupon "Therapeutic success" is defined as 0.4 - point decrease in the Clinical COPD Questionnaire (CCQ) score from visit 1 to visit 2. **Secondary outcomes:** For secondary outcomes, the Physician's Global Evaluation (PGE) at visit 1 and visit 2, patient satisfaction and willingness to continue treatment at visit 2 with Spiolto® Respimat® at visit 2 as proxy for Adherence are categorical variables so they will be analysed as tabulations of frequencies. Change from Visit 1 to Visit 2 in the CCQ and CCQ symptom, mental state and functional state score is a continuous outcome, so it will be analysed with N / mean / SD / min / median / max.		

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
Start of data collection	Q2 2018
End of data collection	Q1 2019
Final report of study results:	Q4 2019

7. RATIONALE AND BACKGROUND

7.1 MEDICAL BACKGROUND

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].

COPD is currently the fourth leading cause of death in the world and projected to be the third by 2020. It represents therefore an important public health challenge. Globally the COPD burden is projected to increase in the coming decades because of continued exposure to COPD risk factors and aging of the population [I].

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

Inactivity is believed to be crucial to the development of the extra-pulmonary effects of the disease like skeletal muscle weakness, osteoporosis and cardiovascular disease. Recent data suggest that patients suffering from COPD with low levels of physical activity have increased risk for hospital admission and have significantly enhanced mortality. Epidemiological data suggest that this may directly or indirectly lead to more rapid decline in lung function [III].

Physical activity is reduced early in the disease progression, as of GOLD Stage 2 [III]. More recent evidence from large placebo controlled clinical trials indicates that COPD patients are experiencing a steeper absolute decline in lung function with GOLD 2 airflow limitation than with GOLD 3 and 4 [IV]. All these observations suggest the importance of early optimal treatment of the disease.

Long-acting bronchodilators, such as long-acting muscarinic antagonists (LAMAs), are the cornerstone of maintenance therapy for patients with moderate to very severe chronic obstructive pulmonary disease (COPD) whose symptoms are not adequately controlled by short-acting bronchodilators alone [V, VI].

An option recommended by GOLD guideline for patients not adequately controlled on a single long-acting bronchodilator is to combine a LAMA with a long-acting β2-agonist (LABA) [VI]. For patients with severe breathlessness initial therapy with two bronchodilators might be considered [I]. The rationale for combining bronchodilators with different mechanisms is based on the notion of additive relaxation of airway smooth muscle by direct

inhibition of cholinergic activity and functional antagonism of bronchoconstriction through β2-adrenergic pathways, with the expectation of an increase in the degree of bronchodilation for equivalent or lesser side effects. Several recent studies have provided evidence in support of this increased bronchodilatory effect when LABAs are added to LAMAs.

Fixed-dose combinations of a short-acting β2–agonist and a short-acting anticholinergic have been developed and have been shown to be safe, efficacious and convenient for the patient (e.g., Berodual®: Fenoterolhydrobromid + Ipratropiumbromid, Combivent®: salbutamol + ipratropium bromide [VII]. Olodaterol is a highly selective and nearly full β2 agonist [VIII, IX] that provides 24-h bronchodilation in patients with COPD [X, XI, XII, XIII]. Olodaterol is also associated with symptomatic benefit [XIV] and enhanced exercise capacity [XV].

The complementary modes of action of tiotropium and olodaterol have previously been demonstrated in animal models, phase II clinical trials and during the Phase IIIa programs [XVI, XVII, XVIII, XIX].

In the Phase III program the additional benefits of the tiotropium + olodaterol fixed-dose combination (FDC) over its mono-components has been assessed on lung function, quality of life (St. George's Respiratory Questionnaire -SGRQ), dyspnea (Transition Dyspnea Index-TDI) and exercise endurance time. Another clinically important potential benefit of the tiotropium + olodaterol FDC over the mono components, the impact on exacerbations of COPD, is currently evaluated in a Phase IIIb trial.

7.2 DRUG PROFILE

7.2.1 Fixed Dose Combination of Tiotropium and Olodaterol

Tiotropium + olodaterol FDC, Spiolto®, is an aqueous solution of tiotropium and olodaterol contained in a cartridge. It is administered by using the Respimat® inhaler. One cartridge is used per inhaler, which is inserted into the device prior to first use.

The Respimat® inhaler uses mechanical energy to create a soft mist which is released over a period of approximately 1.5 seconds. It produces a slowly dispersing, long-lasting mist with very fine-particle distribution that is readily able to circulate into the lower respiratory tract in the lungs [XX]. Thus, deep pulmonary deposition is achieved and the product is efficiently administered to the target site.

Tiotropium + olodaterol FDC was shown to be safe and well tolerated over 1 year in a moderate to very severe COPD population. The overall incidences of adverse events (AEs), serious adverse event (SAEs), fatal AEs, frequencies for cardiac events and major adverse cardiovascular event in the tiotropium + 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 [XXI].

The clinical trials conducted to date have shown tiotropium + 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 [XXI, XXII]. 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 patients centered outcomes. For further information please refer to the SmPC of Spiolto® Respimat®.

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 improve 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 [XV].

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

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 [XLI] 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. CCQ is used to monitor the clinical control of COPD. It 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 [XLII]. The CCQ thus is a well-known and widespread questionnaire, which is included in the GOLD guidelines and is validated in several languages.
In a head to head comparison of CAT and CCQ the patients preferred the latter as it reflected their status better than CAT by giving more details on breathing problems which was more important for them than sleep or energy [XLIII]. CCQ has been given maximum ranking in "COPD wellness tools" overview by the International Primary Care Respiratory Group (IPCRG) [XLVI].

8.1 STUDY OBJECTIVES

The objective of this NIS is to measure changes in clinical control 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 at the 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 state score is a calculation of the sum of the 4 questions (#'s 7, 8, 9, 10) divided by 4, the symptom score is calculation of the sum of the 4 questions (#'s 1, 2, 5, 6) divided by 4 and the mental state score is a calculation of the sum of the 2 questions (#'s 3, 4) divided by 2. More details will be described in the statistical analysis plan.

A change of 0.4 points is considered to be the MCID for the total CCQ score [XLIV].

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

Secondary objectives are assessment of changes in CCQ and in the CCQ symptom, mental state and functional state domains 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) 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 4500 patients from approximately 11 countries will be collected. Site selection will be performed to reflect routine COPD care 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 based upon the investigator's decision requiring a new prescription of Spiolto® Respimat® (combination of two long-acting bronchodilators) according to Spiolto® Respimat® SmPC, GOLD COPD Strategy Document 2018 (GOLD COPD groups B to D) and local COPD guidelines

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 status/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
	X	X
General condition of patient evaluated by Physician's Global Evaluation (PGE), completed by the physician	X	X
Safety: Adverse Drug Reactions (serious and non-serious), fatal AE, pregnancy	X	X
Patient satisfaction with Spiolto® Respimat®, completed by the patient		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) at baseline
- Clinical control based on CCQ and CCQ symptom, mental state and functional state domain scores
- 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-2018

9.3.1 Exposures

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

Spiolto® Respimat® contains

- the long-acting anticholinergic tiotropium bromide.
  The dose dispensed is 2.5 micrograms of tiotropium per puff
- the selective beta$_2$-adrenoceptor agonist olodaterol. The dose dispensed is 2.5 micrograms of olodaterol per puff (as olodaterol hydrochloride).

The recommended daily dose of Spiolto® Respimat® for adults is 5 micrograms of 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 outcome

"Therapeutic success" approximately 6 weeks at visit 2 (0.4 point decrease in the Clinical COPD Questionnaire - CCQ score from visit 1 to visit 2).

9.3.2.2 Secondary outcomes

- Changes in the Clinical COPD Questionnaire (CCQ) and the CCQ symptom, mental state and functional state domain scores from visit 1 (baseline) to visit 2 (approximately 6 weeks)
- General condition of the patient, evaluated by the physician (PGE score) at visit 1(baseline) and visit 2 (approximately 6 weeks).
- Patient satisfaction with Spiolto® Respimat® at visit 2 (approximately 6 weeks).
- Willingness to continue treatment with Spiolto® Respimat® at visit 2 (approximately 6 weeks) as proxy for adherence

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, concomitant medication, previous exacerbation history.

All patients will be enrolled consecutively. The study physician has the ultimate responsibility for the collection and reporting of all clinical and patient data through the eCRFs as well as ensuring that they are accurate and complete.

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. 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 total CCQ score. For the functional status calculation the sum of the 4 questions (# 7, 8, 9, 10) is divided by 4, for the symptom domain the sum of the 4 questions (# 1, 2, 5, 6) is divided by 4 and for the mental state domain the sum of the 2 questions (# 3, 4) is divided by 2. 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 clinical control before and approximately 6 weeks after treatment with Spiolto® Respimat®.

The patients will be asked by the physician to estimate the daily average rescue medication (eg. SABA, like Salbutamol) use in the week before Visit 1 and in the week before Visit 2

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 considering the following:

1) CCQ has the great advantage of simplicity for the patient, having a very good correlation (rho = 0.67 to rho = 0.72) with the St George respiratory questionnaire (SGRQ) [XLV].

2) In TONADO studies [XXI] patients treated with Spiolto® Respimat® had a 57.5% SGRQ responder rates after 24 weeks.

The TONADO had 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 responder rate is a reasonable assumption.

Assuming a 50% therapeutic success rate for CCQ and a sample size of 4050 patients, the 95% confidence interval for the therapeutic success rate would be between 48.5% (lower limit) and 51.5% (upper limit).

To account for a 10% drop-out rate, the sample size becomes approximately 4500patients.

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.

9.7 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. Proportion 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 symptom, mental state and functional state scores; secondary outcome
- Patient reported daily average number of puffs of COPD rescue medication (eg. SABA, like Salbutamol) at the week before Visit 1 and the week before Visit 2
- 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.

9.7.2 Secondary analyses

For secondary analyses, the Physician's Global Evaluation (PGE) at visit 1 and visit 2, patient satisfaction and willingness to continue treatment at visit 2 are categorical variables so they will be analysed as tabulations of frequencies. Change from Visit 1 to Visit 2 in the CCQ and CCQ symptom, mental state and functional state score is a continuous outcome, so it will be analysed with N / mean / SD / min / median / max.

The safety data will be reported according to local requirements.

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.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The intention of this NIS is to collect data on the changes in health and functional status in patients with COPD during therapy with Spiolto® Respimat® in a real world setting.

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 centres 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.

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.

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

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 Competent Authorities (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 eCRF from signing the informed consent onwards until the end of the study:

- all (serious and non-serious) adverse drug reaction(ADRs), related to Spiolto® Respimat®,
- 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. The separate NIS (S)AE form must in addition be used and forwarded to the local Pharmacovigilance as indicated in the form.*

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. pre-existing 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 the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

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 (S)AE form is to be completed and forwarded to the local Pharmacovigilance point of contact for each country within 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:

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

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/email the NIS (S)AE form.

Information required
For each reportable adverse event, the investigator should provide the information requested on the appropriate eCRF pages and the (S)AE NIS form.

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

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

- Informed Consent Form
- CCQ Questionnaire
- Physician's Global Evaluation (PGE)*
- Breathlessness Scale (mMRC)
- Statistical Analysis Plan (SAP)
- Data Management Plan (DMP)
- Serious Adverse Event Report in Non-Interventional Studies - (S)AE NIS Form
- Pregnancy Monitoring Form

All of the above documents will be archived in the Trial Master File in its original English master version.

* *to be completed directly within the eCRF*

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

1. Physician's Global Evaluation (PGE)*

* *to be completed directly within the eCRF*

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

2. Patient Satisfaction Questionnaire

Please choose the number which best describes your satisfaction with Spiolto® Respimat®.

What is your <u>overall satisfaction</u> with the Spiolto® Respimat® treatment?

1	2	3	4	5	6	7
very dissatisfied	dissatisfied	rather dissatisfied	neither satisfied nor dissatisfied	rather satisfied	satisfied	very satisfied
☐	☐	☐	☐	☐	☐	☐

How satisfied are you with <u>inhaling</u> from the Respimat® device?

1	2	3	4	5	6	7
very dissatisfied	dissatisfied	rather dissatisfied	neither satisfied nor dissatisfied	rather satisfied	satisfied	very satisfied
☐	☐	☐	☐	☐	☐	☐

How satisfied are you with the <u>handling</u> of the Respimat® inhalation device?

1	2	3	4	5	6	7
very dissatisfied	dissatisfied	rather dissatisfied	neither satisfied nor dissatisfied	rather satisfied	satisfied	very satisfied
☐	☐	☐	☐	☐	☐	☐

3. 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

4. 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

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		26 Mar 2018 15:20 CEST
Author-Other		26 Mar 2018 17:47 CEST
Author-Trial Statistician		26 Mar 2018 19:02 CEST
Approval- Safety Evaluation Therapeutic Area		27 Mar 2018 09:02 CEST
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Approval-Team Member Medical Affairs		02 Apr 2018 10:29 CEST
Author-Trial Clinical Monitor		03 Apr 2018 10:10 CEST
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Approval- Safety Evaluation Therapeutic Area		03 Apr 2018 10:34 CEST
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Approval- of Global Epidemiology		03 Apr 2018 14:38 CEST
Author-Other		04 Apr 2018 12:14 CEST
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