Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	c26538106-02
BI Study Number:	1237-0087
BI Investigational Product(s):	Spiolto® Respimat®
Title:	*EVELUT®:* Assessment of dyspnea and other symptoms as patient reported outcomes (PRO) in patients with chronic obstructive pulmonary disease (COPD), symptomatic on LABA/ICS maintenance therapy (now) treated with Spiolto® Respimat® (tiotropium/olodaterol) in comparison to open or fixed triple combination treatment in routine clinical practice.
Brief lay title	Spiolto® Respimat® (tiotropium/olodaterol) versus triple combination therapy in everyday clinical treatment practice for chronic obstructive pulmonary disease (EVELUT®)
Protocol version identifier:	*Version 2.0*
Date of last version of protocol:	*27 May 2019*
PASS:	*No*
EU PAS register number:	*EUPAS29784*
Active substance:	*R03AL06 tiotropium bromide and 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: [redacted]

	Study Initiator: [redacted]
Joint PASS:	No
Research question and objectives:	The primary objective of this prospective NIS is to investigate the comparative effectiveness of Spiolto® Respimat® in the new reusable inhaler vs any free or fixed-dosed triple therapy (LAMA + LABA + ICS) in reducing dyspnea (as measured via mMRC questionnaire) and symptom burden (as measured via CAT™) in COPD patients who are dyspneic despite LABA/ICS maintenance treatment when switched to either Spiolto® Respimat® or to any triple therapy, both in a real-word setting. This study aims to analyze the comparative effectiveness of Spiolto® Respimat® in the new reusable inhaler vs any triple therapy in reducing dyspnea and symptom burden from each individual patient's score difference between baseline and after approximately 12 weeks of treatment. Two descriptive primary endpoints will be assessed: (1) Difference in mMRC (modified Medical Research Council) score at baseline and after end of observation (ca. 12 weeks of treatment, Visit 2) (2) Difference in CAT™ (COPD assessment test) score at baseline and after end of observation (ca. 12 weeks of treatment, Visit 2) Secondary endpoints to be determined and compared in an exploratory manner include: • Patients' general condition according to the Physician's Global Evaluation (PGE) score at baseline and end of the observation period, • Patient satisfaction with inhaler and therapy at end of observation period according to a seven-point ordinal scale (ranging from very dissatisfied to very satisfied as documented in non-interventional BI studies (BI 1237-0042, 1237-0043, 1237-0044, 1237-0045, 1237-0065, 1237-0072), • proportion of responders with $\Delta_{mMRC} \geq 1$ and proportion of responders with $\Delta_{CAT} \geq 2$. Descriptive analyses of handling of the new reusable Respimat® inhaler and user experiences will be performed.

	Additional groupwise descriptive statistics will be calculated with respect to • exacerbations (overall and stratified by levels of eosinophils (where available)), • hospitalizations due to COPD exacerbations, • adherence, • levels of eosinophils (where available in patient documentation), • improvement in dyspnea and responder rates (overall and according to levels of eosinophils (where available)), and • improvement in lung function (overall and stratified by levels of eosinophils; where available in patient documentation)
Country(-ies) of study:	Germany
Author:	[redacted]
Marketing authorisation holder(s):	[redacted]
Date:	7 June 2019
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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)
BI	Boehringer Ingelheim
CAT™	COPD Assessment Test
CI	Confidence Interval
CML	Clinical Monitor Local
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
DVP	Data Validation Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FDC	Fixed Dose Combination
FEV_1	Forced expiratory volume in one second
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GP	General Practitioner
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	National Cancer Institute
NIS	Non-Interventional Study

PGE	Physician's Global Evaluation
PRO	Patient-reported outcome
SABA	Short-acting $beta_2$ adrenoceptor agonist
SADR	Suspected Adverse Drug Reaction
SAE	Serious Adverse Event
SAMA	Short-acting muscarinic antagonist
SGRQ	St. George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
TDI	Transitional dyspnea index
VFA	Verband Forschender Arzneimittelhersteller
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Table 3.1 Responsible parties

Function	Name / Location
Scientific Coordinator	[redacted]
Therapeutic Area [redacted] Respiratory Medicine (TA[redacted])	
Team Member Medical Affairs (TM MA)	
Team Member Epidemiology (TM Epi)	
[redacted] Global Epidemiology ([redacted] GEpi)	
G0(",K(/52>J"(, [redacted] Risk Management (TA[redacted] RM), and Pharmacovigilance Working Group (PVWG) [redacted]	
9!R Q5/)E O##")2-,5#"	
NIS [redacted]	
Statistical Analysis	
Data Management	
Trial Programming	
CRO	

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 and Olodaterol			
Protocol date: 27 May 2019	**Study number:** 1237-0087	**Version/Revision:** 2.0	**Version/Revision date:** 7 June 2019
Title of study:	*EVELUT®:* Assessment of dyspnea and other symptom burden as patient reported outcomes (PRO) in patients with chronic obstructive pulmonary disease (COPD), symptomatic on LABA/ICS maintenance therapy (now) treated with Spiolto® Respimat® (tiotropium/olodaterol) in comparison to open or fixed triple combination treatment (LAMA + LABA + ICS) in routine clinical practice *Author:* [redacted]		
Rationale and background:	Dyspnea is the most relevant symptom burden that leads to diagnosis, initiation or change of maintenance COPD therapy. Clinical studies have demonstrated that the LAMA-LABA combination Spiolto® Respimat® significantly improves dyspnea in COPD patients1. However, real world data with regard to the effects of dual bronchodilation with Spiolto® Respimat® vs triple therapy (LAMA + LABA + ICS) in COPD patients that are dyspneic and symptomatic despite being on a LABA/ICS maintenance therapy are not yet available. This non-interventional study (NIS) aims to investigate alleviation of dyspnea and other symptom burden in COPD patients who are symptomatic (dyspneic) despite LABA/ICS maintenance therapy and who are switched to Spiolto® Respimat® in the new reusable inhaler or triple therapy at the discretion of their attending physician. If a patient has symptoms other than dyspnea that led to a change from LABA/ICS, these patients will also be included into the study; except for those classified as acute exacerbations by the treating physician. Dyspnea will be assessed with the mMRC questionnaire; symptom burden will be evaluated by the CAT™ questionnaire.		

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The mMRC and CAT™ are widely used simple measures of breathlessness and symptoms and are easy to complete; they relate well to other measures of health status and can therefore be used to monitor dyspnea and symptoms in COPD patients[2]. Furthermore, the questionnaires are responsive to intervention, predict future mortality risk, and, finally, have been translated and validated in Germany[3, 4, 5, 6].

Treatment guidelines recommend effective bronchodilation as the basis of COPD therapy in most patients. In contrast, ICS is seen as an obligatory part of pharmacological treatments only in patients with concomitant asthma or as a therapeutic option for patients that further exacerbate despite dual bronchodilation therapy or that have a high risk for exacerbation and high levels of eosinophils[7, 8, 9].

However, LABA/ICS-fixed dose combinations (FDC) remain the most widely prescribed therapy in COPD. Dyspnea is one of the most relevant patient-reported symptoms in COPD. In order to achieve better symptom control, therapy can be adjusted by the attending physician from LABA/ICS to either dual bronchodilation or any triple therapy (free or fixed-dose: dual bronchodilation plus inhaled corticosteroid, ICS).

BI developed a novel reusable Respimat® inhaler to simplify assembly and daily use, optimize the dose indicator and make it reusable with up to 6 cartridges. The updated design is intended to improve the usability and environmental impact of the Respimat® inhaler, while preserving the pharmaceutical features and basic functions of the disposable Respimat® inhaler.

According to GOLD 2019, it is a clinical core question whether inhalative COPD therapy of patients, who suffer from dyspnea and other symptoms despite LABA/ICS treatment, should be switched to either LAMA/LABA or triple therapy (LAMA + LABA + ICS; free or fixed-dose).

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	The recent GOLD update supports the design of this study. GOLD 2019 suggests that patients who do not suffer from frequent exacerbations and who present with persistent breathlessness or exercise limitation on LABA/ICS treatment, should either be escalated to triple therapy or switched to LAMA/LABA. A switch from LABA/ICS to LAMA/LABA is suggested in case the initial indication of ICS was inappropriate or if there has been a lack of response to ICS treatment, or if ICS side effects warrant discontinuation. Currently, no prospective clinical evidence is available that supports a direct switch from LABA/ICS to LAMA/LABA instead of moving to triple therapy if an initial indication for ICS use is lacking. Therefore, this study aims to investigate if patients who are symptomatic under LABA/ICS treatment and are switched to LAMA/LABA do not suffer more from dyspnea and symptoms compared to triple therapy.		
Research question and objectives:	The primary objective of this NIS is to investigate the changes in dyspnea (as measured via mMRC (Modified Medical Research Council) questionnaire) and symptom burden (as measured via CAT™ (COPD Assessment Test)) in COPD patients who are dyspneic despite LABA/ICS maintenance treatment when switched to either Spiolto® Respimat® in the new reusable inhaler or to any triple therapy (free or fixed-dosed). More precisely, this study aims to assess analyze the comparative effectiveness of Spiolto® Respimat® in the new reusable inhaler vs any triple therapy in changes in dyspnea and symptom burden from each individual patient's difference between baseline and after approximately 12 weeks of treatment. Two primary endpoints will be assessed: • Difference in mMRC (modified Medical Research Council) score at baseline and after end of observation (approx. 12 weeks of treatment, Visit 2) • Difference in CAT™ (COPD assessment test) score at baseline and after end of observation (approx.. 12 weeks of treatment, Visit 2)		

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	MMRC and CAT™ are both of interest as primary endpoints. The comparative effectiveness on the primary endpoints will be determined based on model coefficients (along with 95% confidence intervals) and statistical testing of these coefficients. Since the study is exploratory in nature, no multiplicity adjustment is planned. Secondary endpoints to be determined and compared in an exploratory manner include • patients' general condition according to the Physician's Global Evaluation (PGE) score at baseline and end of the observation period of approximately 12 weeks, • patient satisfaction with inhaler and therapy at end of observation period according to a seven-point ordinal scale (ranging from very dissatisfied to very satisfied as documented in non-interventional trial (BI 1237-0042, 1237-0043, 1237-0044, 1237-0045, 1237-0065, 1237-0072), • proportion of responders with $\Delta_{mMRC} \geq 1$ and proportion of responders with $\Delta_{CAT} \geq 2$		
Study design:	Open-label comparative multicentric cohort study according to §4, section 23 and §67, section 6 German Medicines Act. All included COPD patients receive a LABA/ICS maintenance treatment until visit 1 and are switched at visit 1 at the discretion of the attending physician to either tiotropium/olodaterol in the new reusable Respimat® inhaler or any triple therapy (LAMA + LABA + ICS) according to clinical routine. Observational period will be approximately 12 weeks after switch, which is the average time between two medical consultations. NIS based on newly collected data.		
Population:	COPD patients on LABA/ICS maintenance therapy with dyspnea (mMRC ≥ 1) and other symptoms (CAT™ ≥ 10), who are switched to either Spiolto® Respimat® in the new reusable inhaler or any triple therapy (LAMA + LABA + ICS) as an open or fixed combination according to approved SmPCs at baseline at the discretion of their attending physician.		

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Inclusion Criteria:

- Diagnosis of COPD
- Symptomatic (with regard to dyspnea (mMRC Dyspnea score ≥1) AND with regard to symptoms (CAT™ Score ≥10) at the same time)
- Patients on LABA/ICS maintenance therapy who are switched to Spiolto® Respimat® in the new reusable inhaler or a free/fixed triple combination of LAMA + LABA + ICS at Visit 1 at the discretion of the treating physician.
- Adults who are contractually capable and mentally able to understand and follow the instructions of the study personnel
- Male or female
- Patients aged ≥40 years of age
- Written informed consent prior to study participation
- The patient is willing and able to follow the procedures outlined in the protocol

Exclusion Criteria:

- Patients with contraindications acc. to SmPC
- Patients not on LABA/ICS maintenance treatment at visit 1, eg, mono or dual bronchodilation only, ICS only, or a triple combination of LAMA + LABA + ICS (either as a fixed combination product or as separate components)
- Lack of informed consent
- Pregnant and/or lactating females
- Acute exacerbation of COPD (within 4 weeks prior to Visit 1)

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	• Frequently exacerbating patients, i. e. patients with ≥2 moderate exacerbations within the last 12 months or ≥1 exacerbation leading to hospitalization within the last 12 months • Acute respiratory failure (pH <7,35 and / or respiratory rate >30/min within 3 months prior to Visit 1) • History or current diagnosis of asthma • History or current diagnosis of asthma-COPD overlap • History or current diagnosis of allergic rhinitis within the last 5 years • History or current diagnosis of lung cancer within the last 5 years • Participation in a parallel interventional clinical trial		
Variables:	The following parameters will be collected and assessed at visit 1 and/ or visit 2: • Specialization of attending physician (GP, pulmonologist, internal specialist) • Patient demographics (age, gender, height, weight) • History of COPD • Rationale for changing COPD maintenance therapy • Reported number and severity of exacerbations in the last 12 months • Number of exacerbations leading to hospitalization in the last 12 months according to medical files • Device training yes/no, reason for no training • GOLD patient groups (A, B, C, D, calculated[i]) based on GOLD guidelines 2019		

[i] *GOLD patient group (A, B, C or D) will be automatically calculated within the eCRF based on available exacerbation history, mMRC and CAT*

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	• GOLD spirometric classifications (1, 2, 3, 4 and date of exam, where available[ii]) • Eosinophils in peripheral blood and date of exam, where available • Smoking history, current 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) • Current (within the last 6 months) COPD related and other relevant concomitant medication such as beta-blockers, beta-agonists, corticosteroids, or proton pump inhibitors at date of Visit 1 • Assessment of the severity of dyspnea based on the Modified Medical Research Council Questionnaire (mMRC), completed by the patient • Health and functional status by CAT™ questionnaire, completed by the patient • General condition of patient based on Physician's Global Evaluation (PGE) at the beginning and at the end of the study • Patient satisfaction with inhaler, inhalation, treatment and handling, according to a seven-point ordinal scale (ranging from very dissatisfied to very satisfied) • Safety: ADRs (serious and non-serious), fatal AEs, pregnancies during the study • Patient's willingness to continue or discontinue treatment with either triple therapy or Spiolto® Respimat® after the study (yes/no) • Rationale for treatment discontinuation (if applicable)		

[ii] *GOLD stage 1-4 spirometric classification of airflow limitation based on post-bronchodilator FEV1*

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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 with inhaler, inhalation, treatment and handling • Patient's willingness to continue or discontinue treatment To be completed by the patient at visit 1 and at visit 2: • Health and functional status by CAT™ questionnaire • mMRC breathlessness scale		
Study size:	Ca. 900 patients, approx. 150 recruiting sites		
Data analysis:	Main analysis: The estimation of the relative treatment effect concerning the primary outcomes is subject to potential confounding; therefore adjusted analyses are required and will be performed. Multiple analytical approaches will be applied to allow an assessment of the sensitivity of the results to these approaches: • Propensity score matching (primary analysis; requires data to be discarded from the analysis) • Propensity score weighting (uses the complete data set) • Multivariable regression modeling (uses the complete data set) The relative treatment effect will be determined based on model coefficients (along with 95% confidence intervals) and statistical testing of these coefficients. Since the study is exploratory, no multiplicity adjustment is planned.		

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	[redacted]		
	Handling of missing data: Multiple imputation will be applied to estimate the propensity score model and the multivariable regression models. In descriptive analyses, the fraction of missing observations will be reported.		
Safety:	Adverse drug reactions (ADRs; serious and non-serious), fatal adverse events (AEs), pregnancies during the study		
Milestones:	Start of data collection Q2 2019 End of data collection Q2 2020 Final report of study results Q4 2020		

5. AMENDMENTS AND UPDATES

V 1.0 dated 9 April 2019
V 2.0 dated 13 May 2019

- Changes as recommended by the ethics committee in chapter 9.2.3.: Enhanced clearance on the order of subject information – informed consent (including time for consideration, if necessary) – start of study medication
- Clarifications and corrections in verbal expressions and spelling errors

6. MILESTONES

Milestone	Planned Date
Start of data collection	Q2 2019
End of data collection	Q2 2020
Final report of study results:	Q4 2020

7. RATIONALE AND BACKGROUND

7.1 MEDICAL BACKGROUND

7.1.1 COPD

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases[9].

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 may emerge. 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) result in further deterioration of lung function and health status of COPD patients[10].

According to the Helmholtz Centre in Munich[11], 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 COPD patients, with an increasing trend. The disease currently ranks fourth in the list of the most common causes of death. According to WHO forecasts, COPD will be the third leading cause of death worldwide 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.

7.1.2 Assessment and Classification of COPD

COPD is characterized by persistent airflow limitation. The degree of airflow limitation is associated with many disease outcomes, but was poorly predictive of dyspnea or symptomatic burden.

COPD is classified into severity stages from I to IV according to the reduction in forced expiratory volume in one second, FEV_1 (%) from the age-related predicted value in the presence of a reduced (<70%) FEV_1/ forced vital capacity (FVC) ratio[9] .

However, lung function alone does not explain the heterogeneous features of COPD. Therefore, GOLD proposed a new classification system for COPD, combining symptom assessment and exacerbation risk including spirometry to identify disease severity.
For assessing symptoms, GOLD 2011 primarily recommends the use of the Modified British Medical Research Council (mMRC) questionnaire[4] or the COPD Assessment Test (CAT™)[12]. The mMRC scale is a 5-point (0–4) scale based on the severity of dyspnea.

The CAT™ comprises eight items relating to the severity of cough, sputum, dyspnea, chest tightness, capacity for exercise and activities, confidence, sleep quality and energy levels while mMRC scale is a quantitative assessment tool only for breathlessness. These questionnaires are used to distinguish patients with less severe symptoms from patients with more severe symptoms.

Together with the exacerbation risk, the symptomatic burden allows to differentiate COPD patients into four groups.

In addition to the spirometric evaluation, the ABCD assessment tool was proposed by GOLD to highlight the importance of patient symptoms and exacerbation risk. Thus, ABCD groups and their associated implications for pharmacotherapy recommendations are derived exclusively from patient symptoms and their history of exacerbations.

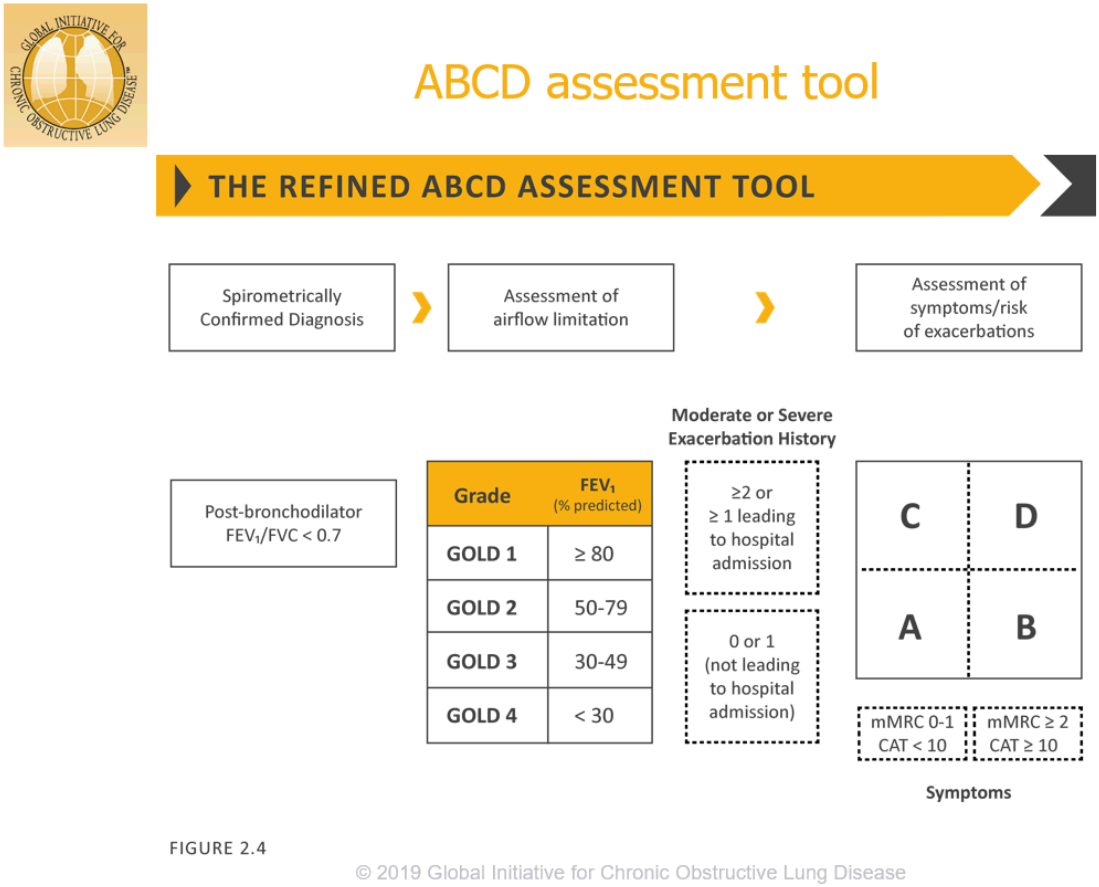

Figure 1 ABCD assessment tool

7.1.3 Pharmacotherapy of COPD

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[9].
Pharmacotherapy for COPD aims at reducing symptoms, reducing the frequency and severity of exacerbations, and improving health status and exercise tolerance. To date, COPD treatments are not able to modify the long-term decline in lung function, so patients should be treated with effective bronchodilation in order to improve quality of life and to reduce the risk of exacerbations[9, 13].

In accordance with GOLD 2019[9], bronchodilators are considered as initial treatment of choice for most of the patients (GOLD A: monotherapy with short or long acting bronchodilator; GOLD B: long-acting bronchodilator (LABA or LAMA); GOLD C: LAMA). In GOLD D-patients, therapy should be initiated with a LAMA, except for patients with severe symptoms (LAMA + LABA) or patients with high levels of eosinophils (LABA + ICS).

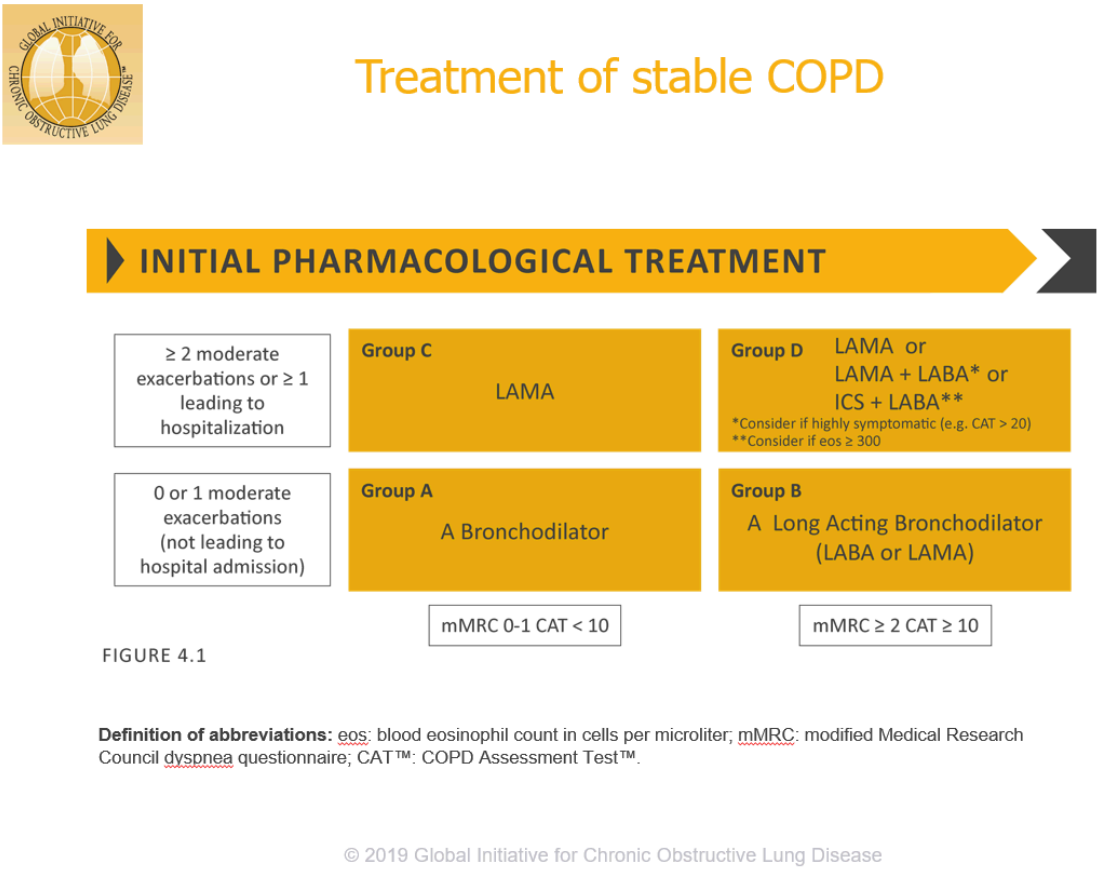

Figure 2 Treatment of stable COPD

After initiation of therapy, patients should be reassessed to evaluate the success of treatment and to identify any potential barriers for successful treatment. Following review of the patient response to treatment initiation, adjustments in pharmacological treatment may be necessary.

According to GOLD 2019, the reassessment focuses on two distinct patient groups

i) Patients that mainly suffer from dyspnea
ii) Patients that mainly experience exacerbations

Bronchodilators are the mainstay of COPD management. Long-acting inhaled bronchodilators are convenient and more effective at achieving symptom relief than short-acting bronchodilators, and combining bronchodilators of different classes (e.g. LAMAs and LABAs) may improve efficacy compared to increasing the dose of a single agent[9].

LABA/ICS-fixed dose combinations (FDC) remain the most widely prescribed therapy in COPD. Dyspnea is one of the most relevant patient-reported symptoms in COPD. In order to achieve better symptom control, therapy can be changed by the attending physician from LABA/ICS to either dual bronchodilation or any triple therapy (free or fixed-dose: dual bronchodilation plus inhaled corticosteroid, ICS). Both symptomatic patients and patients at high risk of exacerbations, who are symptomatic on LABA/ICS therapy, should receive either LAMA/LABA or triple therapy. Therefore, it is considered highly relevant to generate real world data on patient-reported outcomes, esp. on dyspnea, for patients, who are symptomatic on LABA/ICS therapy and are switched to either LAMA/LABA or triple therapy.

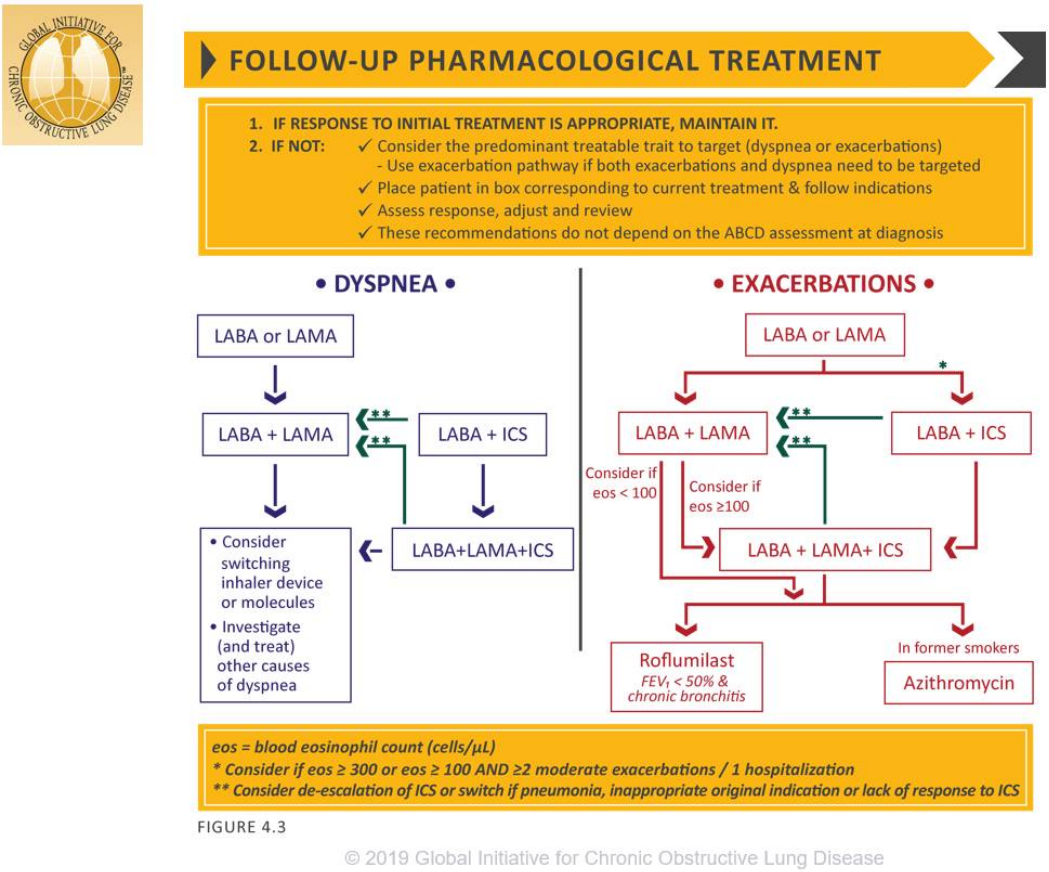

Figure 3 Follow-up pharmacological treatment

7.1.4 Tiotropium/Olodaterol in COPD treatment

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[13]. Therefore, treatment with combination therapy is likely to be an effective option for the management of moderate-to very severe COPD[1].

The TOviTO program has investigated the benefits of treatment with a combination of tiotropium and olodaterol administered via a single inhaler in > 16.000 COPD patients in all disease stages and severities. Tiotropium/olodaterol 5/5 µg significantly improved forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 3 hours, trough FEV_1 health status and breathlessness versus the mono-components and placebo. Tiotropium/olodaterol 5/5 µg also increased endurance time and reduced dynamic hyperinflation during constant work rate cycle ergometry.

Tiotropium/olodaterol is inhaled by the patient via a soft-mist inhaler, Respimat®. BI developed a novel reusable Respimat® inhaler to simplify assembly and daily use, optimize the dose indicator and make it reusable with up to six cartridges. The updated design is intended to improve the usability and environmental impact of the Respimat® inhaler, while preserving the pharmaceutical performance and basic functions of the disposable Respimat® inhaler.

7.1.5 Dyspnea

Dyspnea is the most relevant symptom that leads to diagnosis, initiation or change of maintenance COPD therapy. Clinical studies have demonstrated that the LAMA-LABA combination Spiolto® Respimat® significantly improves dyspnea in COPD patients[2]. However, real world data with regard to the effects of dual bronchodilation with Spiolto® Respimat® vs triple therapy in COPD patients that are dyspneic and symptomatic despite being on a LABA/ICS maintenance therapy are not yet available.

The mMRC and CAT™ questionnaires are widely used simple measures of breathlessness and symptoms and are easy to complete. They relate well to other measures of health status and can be used to monitor dyspnea and symptoms in COPD patients. Furthermore, the questionnaires are responsive to intervention, predict future mortality risk, and, finally, have been translated and validated in Germany[3, 4, 5, 6].

7.1.6 Intention of the study

This non-interventional study (NIS) aims to investigate alleviation of dyspnea and symptom burden in COPD patients who are symptomatic (dyspneic) despite LABA/ICS maintenance therapy and who are switched to Spiolto® Respimat® in the new reusable inhaler or to triple therapy at the discretion of their attending physician. If a patient has symptoms other than dyspnea that led to a change from LABA/ICS, these patients will also be included into the study - except for those classified as acute exacerbations by the treating physician. Dyspnea will be assessed with the mMRC questionnaire; symptom burden will be evaluated with the CAT™ questionnaire.

The recent GOLD update supports the design of this study by suggesting that patients with persistent breathlessness or exercise limitation on LABA/ICS treatment and not suffering frequently from exacerbations receive

- either addition of a LAMA to escalate to triple therapy or
- a switch from LABA/ICS to LAMA/LABA

  if the original indication of ICS was
- inappropriate, or
- if there has been a lack of response to ICS treatment, or
- if ICS side effects warrant discontinuation.

The current study aims at strengthening the database on this key therapeutic decision in everyday practice. Currently, no prospective clinical evidence is available supporting a direct switch from LABA/ICS to LAMA/LABA instead of moving to triple therapy if there is no indication for an ICS. Therefore this proposal aims at investigating if patients that are symptomatic under LABA/ICS treatment can be switched to LAMA/LABA and do not do worse compared to a triple therapy.

7.2 DRUG PROFILE

7.2.1 Tiotropium and Olodaterol

Tiotropium is a long-acting (24-hour) inhaled anticholinergic bronchodilator (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®[14, 15].

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[16]. The drug has been authorized since 2013 in 43 countries worldwide and is available in Germany under the name Striverdi® Respimat®[17].

The Respimat® is a hand-held propellant-free soft mist inhaler[18, 19, 20]. It produces a slowly dispersing, long-lasting mist with very fine-particle distribution that is readily able to circulate into the lower respiratory tract and the lungs[21]. Thus, deep pulmonary deposition is achieved and the product is efficiently administered to the target site. The Respimat® does not contain any propellant gas.

Recently, the Respimat® was development further to generate an improved second-generation Respimat® inhaler (new reusable Respimat® inhaler) Human factor studies assessing the usability of the new inhaler and *in vitro* assessment of aerosol performance demonstrated the functionality of the updated inhaler[22].

7.2.2 Spiolto® Respimat®

The 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[23].
EU registration was given 1 July2015. This was based on 2 pivotal replicate, multinational 1-year, randomized double blind, active-controlled, parallel-group Phase III studies, TOnado 1 and 2 (Study 1237.5 and Study 1237.6). These 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)[12].

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 FEV_1 <80% of predicted normal
- Post-bronchodilator FEV_1/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 (FEV_1 AUC 0–3 response [p <0.0001] and trough FEV_1 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)[12]. In particular, the higher-dose FDC (5 µg / 5 µg) appeared to offer the optimum combination.

In conclusion, the phase III clinical trials conducted within the TOviTO trial program in more than 16.000 patients in all stages and severities of COPD have shown tiotropium plus olodaterol (5 / 5 µg) FDC to be a safe, well tolerated and efficacious combination therapy according to treatment guidelines in a moderate to very severe COPD patient population. Tiotropium/olodaterol significantly improved forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 3 hours, trough FEV_1, health status, and breathlessness versus the mono-components and placebo. Tiotropium/olodaterol also increased endurance time and reduced dynamic hyperinflation during constant work rate cycle ergometry. 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[1]. For further information, please refer to the SmPC of Spiolto® Respimat®[23].

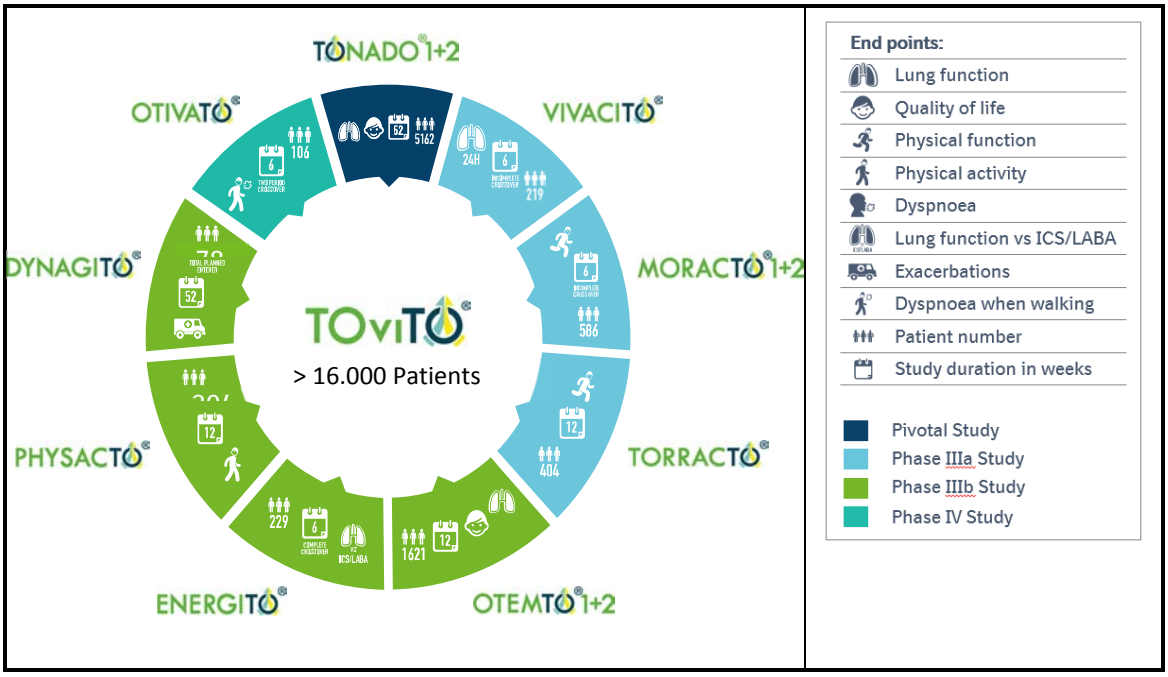

Figure 4 Overview TOviTO trial program

8. RESEARCH QUESTION AND OBJECTIVES

Clinical studies[24, 25, 26] have demonstrated that Spiolto® Respimat® provides significant improvement in dyspnea as compared to the single active substances and placebo in COPD patients. Tiotropium/olodaterol improved transitional dyspnea index (TDI) and St. George's Respiratory Questionnaire (SGRQ) compared with mono-components, with patients more likely to achieve clinically important improvements in TDI (risk ratio [RR]: 1.17, 95% confidence interval [CI]: [1.07, 1.28] versus tiotropium and RR: 1.14, 95%CI: [1.01, 1.28] versus OLO) and in SGRQ (RR: 1.21, 95%CI: [1.12, 1.30] versus tiotropium and RR: 1.28, 95%CI: [1.18, 1.40] versus olodaterol)[27, 28, 3, 29, 30].

The benefits of tiotropium/olodaterol FDC on dyspnea have been studied in a controlled Phase III program, however, data regarding dyspnea for COPD patients symptomatic despite a long-term treatment with LABA/ICS and being switched to either Spiolto® Respimat® in the new reusable inhaler or a triple combination of LABA, LAMA and ICS is not available from a real world setting.
For the identification and quantification of dyspnea in COPD patients, the Modified British Medical Council (mMRC) questionnaire has been developed[31]. It relates very well to other measures of health status and predicts future mortality risk[32, 9].
Though dyspnea seems to be the most challenging symptom for many patients and often leads to therapy initiation or change, it is now recognized that COPD affects patients beyond dyspnea. Therefore, in today's GOLD guidelines a comprehensive assessment of symptoms is required. The COPD Assessment Test, CAT™, is a suitable, concise, 8-item measure of health-impairment in COPD patients. It correlates closely with the SGRQ and has been extensively studied and documented[33, 34, 9].

8.1 STUDY OBJECTIVES

The primary objective of this prospective NIS is to investigate the comparative effectiveness of Spiolto® Respimat® in the new reusable inhaler vs any free or fixed-dosed triple therapy in reducing dyspnea (as measured via mMRC) questionnaire) and symptom burden (as measured via CAT™) in COPD patients who are dyspneic despite LABA/ICS maintenance treatment when switched to either Spiolto® Respimat® inhaler or to any triple therapy (LAMA + LABA + ICS) by their attending physician in an real-world setting.

Primary objective:
This study aims to analyze the comparative effectiveness of Spiolto® Respimat® in the new reusable inhaler vs any triple therapy in reducing dyspnea and symptom burden from each individual patient's score difference between baseline and after 12 weeks of treatment.
Two primary endpoints will be assessed:

- Difference between mMRC (modified Medical Research Council) score at baseline and after end of observation (ca. 12 weeks of treatment, Visit 2)
- Difference between CAT™ (COPD assessment test) score at baseline and after end of observation (ca. 12 weeks of treatment, Visit 2)

To address potential confounding due to differences in observed patient demographics (age, sex) and severity of disease, the primary analysis will be adjusted using a propensity score approach. Further details will be provided in a statistical analysis plan.

Secondary endpoints to be determined and compared in an exploratory manner include

- Patients' general condition according to the Physician's Global Evaluation (PGE) score at baseline and end of the observation period,
- Patient satisfaction with inhaler and therapy at end of observation period according to a seven-point ordinal scale (ranging from very dissatisfied to very satisfied as documented in non-interventional BI studies (BI 1237-0042, 1237-0043, 1237-0044, 1237-0045, 1237-0065, 1237-0072),
- Proportion of responders with $\Delta_{mMRC} \geq 1$ and proportion of responders with $\Delta_{CAT} \geq 2$.

Descriptive analyses of handling of the new reusable Respimat® inhaler and user experiences will be performed.

Additional groupwise descriptive statistics will be calculated with respect to

- exacerbations (overall and stratified by levels of eosinophils, where available),
- hospitalizations due to COPD exacerbations,
- adherence,
- levels of eosinophils (if available in patient documentation, where available),
- improvement in dyspnea and responder rates (overall and according to levels of eosinophils), and
- improvement in lung function (overall and stratified by levels of eosinophils)

9. RESEARCH METHODS

9.1 STUDY DESIGN

Open-label comparative multicentre cohort study according to §4, section 23 and §67, section 6 German Medicines Act (NIS), based on newly collected data.

9.2 SETTING

9.2.1 Study sites

Data collection of approximately 900 patients from approximately 150 recruiting sites in Germany is planned. Site selection will be performed to reflect routine COPD care in Germany in order to secure representativeness of the COPD population.

9.2.2 Study population

Inclusion Criteria:

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

- Diagnosis of COPD
- Symptomatic (with regard to dyspnea (mMRC Dyspnea score ≥1) AND with regard to symptoms (CAT Score ≥10) at the same time)
- Patients on LABA/ICS maintenance therapy who are switched to Spiolto® Respimat® in the new reusable inhaler or a free/fixed triple combination of LABA + LAMA + ICS at Visit 1 at the discretion of the treating physician.
- Adults who are contractually capable and mentally able to understand and follow the instructions of the study personnel
- Male or female
- Patients aged ≥40 years of age
- Written informed consent prior to study participation
- The patient is willing and able to follow the procedures outlined in the protocol

Exclusion Criteria:

- Patients with contraindications acc. to SmPC
- Patients not on LABA/ICS maintenance treatment at visit 1, e.g., mono or dual bronchodilation only, ICS only, or a triple combination of LAMA + LABA + ICS (either as a fixed combination product or as separate components)
- Lack of informed consent
- Pregnant and/or lactating females
- Acute exacerbation of COPD (within 4 weeks prior to Visit 1)
- Frequently exacerbating COPD patients, i. e. patients with ≥2 moderate exacerbations within the last 12 months or ≥1 exacerbation leading to hospitalization within the last 12 months[iii]
- Acute respiratory failure (pH <7,35 and/ or respiratory rate >30/min within 3 months prior to Visit 1)
- History or current diagnosis of asthma
- History or current diagnosis of asthma-COPD overlap
- History or current diagnosis of allergic rhinitis within the last 5 years

[iii] Definitions of exacerbation severity according to German Pulmonary Society Guideline (DGP-Leitlinie 2019)[8]

- History or current diagnosis of lung cancer within the last 5 years
- Participation in a parallel interventional clinical trial
- mild exacerbation: additional use of short-acting bronchodilators and treated by the patient without consulting a physician
- moderate exacerbation: treatment includes medical prescription of a systemic corticosteroid and/or antibiotic
- severe exacerbation: exacerbation leading to hospitalization

9.2.3 Study visits

Patients will be enrolled consecutively and will be followed over an observational period of approximately 12 weeks. Two study visits will be performed.

Patients will be attributed to either group (triple therapy or Spiolto® Respimat®) on the investigator's discretion and patient's consent before study start at visit 1 (Baseline).

If possible and manageable and in compliance with the investigator's decision, a 1:1 group distribution of the patients included per site should be aimed at. However, a strict distribution scheme is not given.

At Visit 1 (baseline), after information and signature of the Informed Consent Form, the patient will be included into the NIS. The patient will of course have enough time for considering study participation.
At Visit 2, after approximately 12 weeks of treatment, 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. 12 weeks after baseline visit**
Informed Consent	X	
Specialization of attending physician (GP, pulmonologist, internal specialist)	X	
Inclusion / Exclusion Criteria	X	
Patient demographics (age, gender, height, and weight)	X	
History of COPD	X	
Rationale for changing COPD maintenance therapy	X	
Number and severity of exacerbations in the last 12 months	X	
Number of exacerbations leading to hospitalization in the last 12 months	X	
Device training (yes/no), reason for no training	X	

Table 9.2.3.1 (cont´d): Visit flow chart and data collection parameters

Parameter	**Visit 1; baseline visit**	**Visit 2; approx. 12 weeks after baseline visit**
COPD severity based on GOLD assessment[iv] (GOLD patient groups)	X	
GOLD spirometric classification, if available[v], incl. date of examination	X	
Eosinophils in peripheral blood, if available	X	
Smoking history, current status, pack-years	X	
Concomitant diseases / Comorbidities	X	X
Current COPD related and other relevant concomitant medication	X	X
mMRC breathlessness scale, completed by the patient	X	X
Health and functional status by CAT™ 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 AEs, pregnancy	X	X
Patient satisfaction with inhaler, inhalation and treatment and handling	X	X
Patient's willingness to continue or discontinue treatment with either triple therapy or Spiolto® Respimat® after the study (yes/no)		X
Rationale for treatment discontinuation (if applicable)		X

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
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:

[iv] *GOLD patient group (A, B, C or D) will be automatically calculated within the eCRF based on available exacerbation history, mMRC and CAT*
[v] *GOLD stage 1-4 spirometric classification of airflow limitation based on post-bronchodilator FEV_1*

- Specialization of attending physician (GP, pulmonologist, internal specialist)
- Patient demographics (age, gender, height, weight)
- History of COPD
- Rationale for changing COPD maintenance therapy
- Reported number and severity of exacerbations in the last 12 months
- Number of exacerbations leading to hospitalization in the last 12 months according to medical files
- Device training yes/no, reason for no training
- GOLD patient groups (A, B, C, D, calculated1) based on GOLD guidelines 2019
- GOLD spirometric classifications (1, 2, 3, 4 and date of exam, if available 2)
- Eosinophils in peripheral blood and date of exam, if available
- Smoking history, current 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)
- Current (within the last 6 months) COPD related and other relevant concomitant medication such as beta-blockers, beta-agonists, corticosteroids, or proton pump inhibitors at date of Visit 1
- Assessment of the severity of dyspnea based on the Modified Medical Research Council Questionnaire (mMRC), completed by the patient
- Health and functional status by CAT™ questionnaire, completed by the patient
- General condition of patient based on Physician's Global Evaluation (PGE) at the beginning and at the end of the study
- Safety: ADRs (serious and non-serious), fatal AEs, pregnancies during the study
- Patient satisfaction with inhaler, inhalation, treatment and handling
- Patient's willingness to continue or discontinue treatment with either triple therapy or Spiolto® Respimat® after the study (yes/no)
- Rationale for treatment discontinuation (if applicable)

9.3.1 Exposures

Patients will be treated with Spiolto® Respimat® or triple therapy and be observed for approximately 12 weeks.

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.

Other LAMA, LABA and/or ICS therapy will be performed according to label as described in the respective SmPCs.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

1. Difference between mMRC score at baseline (visit 1) and mMRC score after end of observation (ca. 12 weeks of treatment, Visit 2)
2. Difference between CAT™ score at baseline (visit 1) and CAT™ score after end of observation (ca. 12 weeks of treatment, Visit 2)

The primary outcomes are reported in a descriptive manner, will be compared in an explorative manner and are not safety outcomes.

9.3.2.2 Secondary outcomes

Secondary endpoints to be determined and compared in an exploratory manner include

- patients' general condition according to the Physician's Global Evaluation (PGE) score at baseline and end of the observation period,
- patient satisfaction with inhaler and therapy at end of observation period according to a seven-point ordinal scale (ranging from very dissatisfied to very satisfied as documented in non-interventional BI studies (BI 1237-0042, 1237-0043, 1237-0044, 1237-0045, 1237-0065, 1237-0072),
- proportion of responders with $\Delta_{mMRC} \geq 1$ and the proportion of responders with $\Delta_{CAT} \geq 2$.

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.

9.4.1 PGE

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. 12 weeks after treatment initiation.

9.4.2 Symptomatic Burden: mMRC and CAT™

The modified Medical Research Council (mMRC) scale is a 5-point (0–4) scale based on the severity of dyspnoea. The mMRC will be used to assess the breathlessness state of the patient with just one question: "When do you experience dyspnoea?", covering five everyday activities, potentially leading to dyspnoea and giving an according rate of 0 to 4 points. The MCID is a change of 1.0 point. It will be applied before the treatment and after approximately 12 weeks of treatment

The COPD Assessment Test (CAT™) was developed as a simple instrument to assess health status in patients with COPD[12]. The CAT™ consists of eight items, each formatted as a semantic six-point differential scale, making the tool easy to administer and easy for patients to complete[35]. These eight items cover cough, phlegm, chest tightness, breathlessness when going up hills/stairs, activity limitations at home, confidence leaving home, sleep and energy. Each item is scored from 0 to 5 giving a total score range from 0 to 40, corresponding to the best and worst health status in patients with COPD, respectively[34]. The MCID is a change of 2.0 points[36].

The questionnaire will be filled out by the patient and entered into the database. Patients will be asked to complete the CAT™ in order to evaluate their health and functional status before treatment with Spiolto® Respimat® or triple therapy, respectively, and after approximately 12 weeks.

Additionally, the mMRC stage and CAT™ scores collected from the patient as well as the exacerbation history will be used to automatically calculate the GOLD patient group (A, B, C, or D) in the eCRF.

9.4.3 Patient Satisfaction

The 7-item satisfaction scale with divisions from very dissatisfied to very satisfied to be completed at Visit 1 and Visit 2 to measure patient satisfaction with inhaler use, is a Likert-scale without validation status for the intended use. However, the application of Likert-Scales has been well established in a range of comparable situations[37, 38, 39].

Patient's willingness to continue treatment is assessed by a yes/no question plus reasons for non-willingness.

9.5 STUDY SIZE

9.5.1 Sample size justification

It should be noted that the study is generally to be considered exploratory in design.
It is further recognized that the multivariable, observational setting complicates a realistic and reliable sample size calculation, e.g. due to the influence of potential confounding variables and dropout (both during study conduct and matched analyses). The sample size calculation/justification given below can therefore only provide a rough estimate of statistical power in an exploratory real-world setting. The sample size is based on the assumption that Spiolto® Respimat® is at least non-inferior compared to any triple therapy using two-sample t-tests (one-sided alpha-level 2.5% and 90% power). The respective MCIDs are treated as non-inferiority margins (to the authors knowledge, established non-inferiority margins are lacking with respect to both endpoints).
The MCID regarding mMRC is 1 point. Based on the real world evidence study by Buhl et al. and BI data, a standard deviation (SD) of 1 point is assumed for the mMRC[40].
The MCID regarding CAT™ is 2 points. Based on the real world evidence study by Buhl et al., a SD of 7 points is assumed for the CAT™[40].

44 patients overall (22 per group) are required to assess non-inferiority between Spiolto® Respimat® and triple treatment regarding the mMRC. We expect that data of about 40% of patients will not be available for evaluation at the end of the study: a drop out of 10% is based on experiences with German NIS such as BI 1237-0042. An additional drop out of 30% appears likely due to the need to discard patients which cannot be matched (this is based on similar experiences by Buhl et al.[41]). Thus, when taking into account this dropout, a total number of 74 patients (37 patients per group) is required to evaluate non-inferiority with respect to the mMRC score.

518 patients overall (259 per group) are required to assess non-inferiority between Spiolto® Respimat® and triple treatment regarding the CAT™. For reasons as outlined above, we expect that data of about 40% of patients will not be available for evaluation at the end of the study. Thus, when taking into account this dropout, a total number of 864 patients (432 patients per group) is required to evaluate non-inferiority with respect to the CAT™ score.

Because mMRC and CAT™ are both of interest as primary endpoints here, the required sample size for the NIS equals the higher of the two respective estimates, i.e. 864 patients in total (432 patients per group).

Patients will be attributed to either group (triple therapy or Spiolto® Respimat®) on the investigator's discretion and patient's consent at visit 1. If possible and manageable and in compliance with the investigator's decision, a 1:1 group distribution of the patients included per site should be aimed at. However, a strict distribution scheme is not given.

Measures to be considered in case of substantially unequal recruitment include the early closing one of the treatment arms earlier (i.e., when its target size is reached) and the analysis of unequal group sizes (1:2, 1:3 or 1:4).

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 each recruiting site and further 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 or implausible data entries or 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 [redacted] 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 that 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 thirty 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

Details on the statistical analyses will be given in a statistical analysis plan (SAP).
In brief, the planned analyses will be conducted as follows:

All patients who have received at least one dose of Spiolto® Respimat® or triple combination (free or fixed LAMA + LABA+ ICS) will be included in the analysis; this is the treated set. All analyses will be performed on the treated set (as-treated analysis).

The analyses will relate to the following data:

- primary outcome: Therapeutic success based on mMRC score difference;
- primary outcome: Therapeutic success based on CAT™ score difference;
- secondary outcome: Changes from Visit1 to Visit 2 in the mMRC and CAT™ scores;
- Specialization of attending physician (GP, pulmonologist, internal specialist)

- 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 / current smoking and pack years
- Reported number and severity of exacerbations in the last 12 months
- Dyspnea based on mMRC score at visit 1 and visit 2
- Symptom burden based on CAT™ score at visit 1 and visit 2
- Patient satisfaction with inhaler and therapy at visit 2 only; secondary outcome
- General condition of the patient: evaluated by the physician (Physician´s Global Evaluation (PGE)), secondary outcome
- Patient's willingness to continue, reason for unwillingness; secondary outcome
- Adverse Drug Reactions (ADR and SADR), fatal AEs, pregnancies
- GOLD spirometric classifications (1, 2, 3, 4) and GOLD patient groups (A, B, C, D)
- Details of current treatment with inhaled respiratory agents at Visit 1
- Details of treatment with respiratory agents during the study
- Reasons for ending treatment during the observation period
- Details of treatment continuation / discontinuation

Descriptive statistics for comparison of baseline characteristics and crude outcome analyses comprise N / mean / SD / min / median / max for continuous variables, while for categorical variables tabulations of relative and absolute frequencies will be presented. Incidence rates and 95% CI will be given where appropriate.

All analyses will be carried out using SAS® statistical software, version 9.4 or higher ([redacted]).

9.7.1 Main analysis

For the two primary outcomes, as specified in section 9.3.2.1, the comparative treatment effect will be estimated along with 95% confidence intervals.

The estimation of the treatment effect is subject to potential confounding. Therefore, adjusted analyses are required. Multiple analytical approaches will be applied to allow an assessment of the sensitivity of the results to these approaches:

- Propensity score matching (primary analysis; requires data to be discarded from the analysis)

- Propensity score weighting (uses the complete data set)
- Multivariable regression modeling (uses the complete data set)

Multiple imputation will be applied to estimate the propensity score model and the multivariable regression models.
Covariates for adjustment include patient demographics (age, sex), disease characteristics (baseline CAT™ / mMRC, exacerbation history, pack-years of smoking, FEV_1, eosinophil levels) and health care provider (GP / pulmonologist). Baseline comparability before and after matching will be assessed using standardized differences.
The comparative effectiveness on the primary endpoints will be determined based on model coefficients (along with 95% confidence intervals) and statistical testing of these coefficients. Since the study is exploratory in nature, no multiplicity adjustment is planned.

9.7.3 Handling of missing data

Multiple imputation will be used in the estimation of propensity scores and in multivariable regression analyses. In descriptive analyses, the fraction of missing observations will be reported. 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 every recruiting site of this study. 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

This prospective NIS aims to investigate the comparative effectiveness of Spiolto® Respimat® in the new reusable inhaler vs any free or fixed-dosed triple therapy (LAMA + LABA + ICS) in reducing dyspnoea (as measured via mMRC questionnaire) and symptom burden (as measured via CAT™) in COPD patients who are dyspnoeic despite LABA/ICS maintenance treatment when switched to either Spiolto® Respimat® or to any triple therapy, both in a real-word setting.

A 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 with access to all available and approved treatment options 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.

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 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, source data validation will take place at each recruiting site 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 and [redacted] 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.

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 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

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 that 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 authorization 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 hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

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

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

Adverse Event of Special Interest (AESI)
The term 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 authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason, the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the 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 characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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

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

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event
The intensity of AEs should be classified and recorded according to the NCI-CTCAE criteria (most recent 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.

The report forms are part of the investigator site file.

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 or pregnancy. The Boehringer Ingelheim NIS AE form must be printed from the eCRF and sent per fax. For pregnancy reports the pregnancy monitoring forms A and B must be completed 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. The respective forms are part of the investigator site file. In this case, these data must be entered into the eCRF as soon as possible when electronically available.

All of the above 1-4 to be sent to: Fax: [redacted]

[redacted]

Phone: [redacted]

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 updated 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 finalization of the Study Report.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	Appendix 1	4 June 2019	PGE
2	Appendix 2	4 June 2019	CAT™ Questionnaire
3	Appendix 3	4 June 2019	mMRC Questionnaire
4	Appendix 4	4 June 2019	NIS AE 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

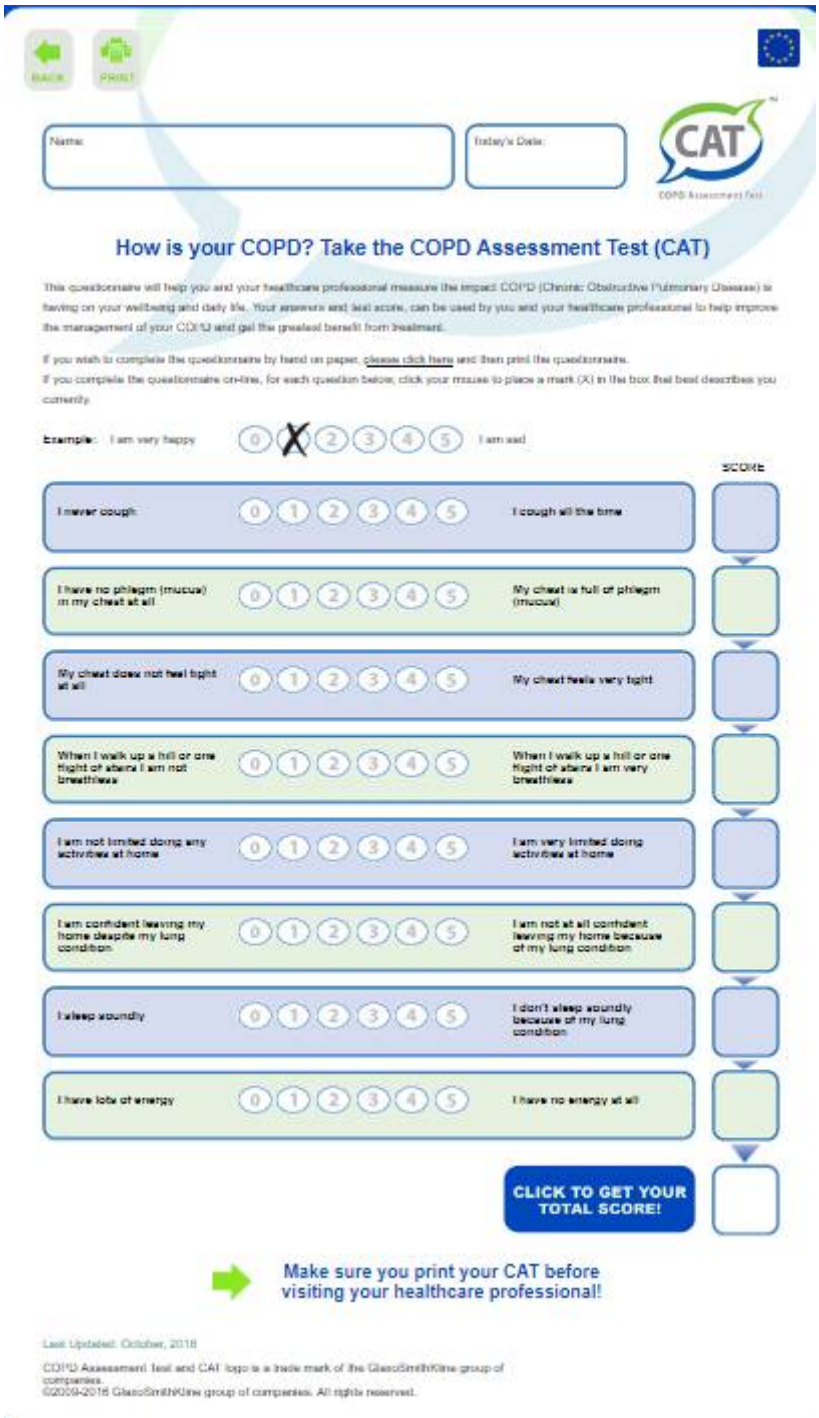
Poor	Satisfactory	Good	Excellent
1 2	3 4	5 6	7 8

General condition of the patient after approximately 12 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: COPD ASSESSMENT TEST (CAT™)

COPD Assessment Test (CAT ™)[vi]



[vi] derived from: http://www.catestonline.org/english/indexEN.htm

APPENDIX 3: 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 4: NIS AE FORM

Boehringer Ingelheim **Non-Interventional Study (NIS) Adverse Event Form**

BI Study No: 1237-0087	Country: GER
Site No:	Subject No:

No. of pages, including this page:

To: Boehringer Ingelheim [*or CRO*]	From:
[Address]	[site stamp]
[Fax number]	

BY SIGNING THIS FORM, YOU ARE CONFIRMING THAT THE INFORMATION CONTAINED HEREIN IS ACCURATE.

Record all dates in ddmmmyyyy format (e.g. 01Jan2016)

Type of report	Date	Investigator's signature	Remarks
☐ Initial	__ __ ____	_____	____
☐ Follow-up	__ __ ____	_____	____
☐ Follow-up	__ __ ____	_____	____
☐ Follow-up	__ __ ____	_____	____
☐ Follow-up	__ __ ____	_____	____
☐ Follow-up	__ __ ____	_____	____
☐ Follow-up	__ __ ____	_____	____

SUBJECT DEMOGRAPHICS

Year of birth: ____ Height ___ (cm) Weight ___ (kg)
If unknown, record 'UNK'

Sex: ☐ ☐ Female Pregnant: ☐ No ☐ Yes weeks
If pregnant, please submit completed Pregnancy Monitoring Form for Studies

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Boehringer Ingelheim **Non-Interventional Study (NIS) Adverse Event Form**

BI Study No: 1237-0087	Country: GER
Site No:	Subject No:

EVENT INFORMATION

Record all dates in ddmmmyyyy format (e.g. 01Jan2016). If ongoing, enter 'CONT.' Record all times in 24-hour (hh:mm) format. If time is unknown, record 'UNK.'

		Event No. [ ]	Event No. [ ]	Event No. [ ]	Event No. [ ]
Adverse Event term (If available, enter the diagnosis)					
Onset date					
Onset time					
End date					
End time					
Was the event serious?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If serious, please mark reason for seriousness	Results in death	☐	☐	☐	☐
	Immediately life-threatening	☐	☐	☐	☐
	Persistent or significant disability/incapacity	☐	☐	☐	☐
	Requires/prolongs hospitalisation	☐	☐	☐	☐
	Congenital anomaly/birth defect	☐	☐	☐	☐
	Other comparable medical criteria (*specify in Description of Event section*)	☐	☐	☐	☐
Was the event a protocol-specified Adverse Event of Special Interest (AESI)?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Is there a reasonable causal relationship between the Adverse Event and: (*provide description of rationale, other possible causes on page 3*)					
BI studied medication or BI product given for the disease in scope of NIS		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Concomitant medications: Please refer to concomitant medication section to document causal relationship.					
Outcome of event (*check only one*)					
Recovered (report AE end date above)		☐	☐	☐	☐
Not yet recovered		☐	☐	☐	☐
Recovered with sequelae (report AE end date above)		☐	☐	☐	☐
Unknown		☐	☐	☐	☐
Fatal		☐	☐	☐	☐
If fatal, was this event the primary cause of death?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If subject died, record date of death:					
Was an autopsy performed?		☐ Yes	☐ No	☐ Unknown	
Was therapy for the event administered?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If yes, specify therapy in Description of Event section.					
Was a dechallenge performed?		☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA
If yes, did the event disappear or significantly decrease in intensity after the BI product was stopped?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Was a rechallenge performed?		☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA
If yes, did the event reappear after reintroduction?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

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Boehringer Ingelheim **Non-Interventional Study (NIS) Adverse Event Form**

BI Study No: 1237-0087	Country: GER
Site No:	Subject No:

RATIONALE FOR CAUSALITY ASSESSMENT

Please document the event(s) and provide your rationale for the causal assessment to BI product and include a rationale for any other causal relationships, which are considered relevant. Rationale may include temporal relationships, confounding factors (i.e. disease/medication), positive dechallenge/rechallenge, interactions with other medications and/or pattern of reaction.

DESCRIPTION OF THE EVENT(S)

Please highlight any additional information (not otherwise provided on this form) which may contribute to the assessment of the case including but not limited to: relevant diagnostic/lab test results (with reference ranges) and therapeutic measures given for event.

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Boehringer Ingelheim **Non-Interventional Study (NIS) Adverse Event Form**

BI Study No: 1237-0087	Country: GER
Site No:	Subject No:

RELEVANT BASELINE CONDITIONS INCLUDING PAST MEDICAL HISTORY

Record all dates in ddmmmyyyy format (e.g. 01Jan 2015). If ongoing, enter 'CONT.'

☐ None ☐ Yes (*specify below*)	If concomitant, provide onset date	Past - Please check box only if ended prior to (S)AE onset
1.		☐
2.		☐
3.		☐
4.		☐
5.		☐
6.		☐

BOEHRINGER-INGELHEIM PRODUCT

Indication Lot Number

Name of BI studied medication or BI product given for the disease in scope of NIS :		
Formulation		
Total daily dose at onset of event (*dose, unit*)		
Route		
Start date		
Start time		
Date of last administration prior to event		
End date		
End time		
Was the administration correct?		☐ Yes ☐ No
If the administration was not correct, check all applicable boxes: overdose, abuse, misuse, medication error, other (i.e. occupational exposure, lack of effect, unexpected benefit)		☐ Misuse / Abuse ☐ Medication error ☐ Overdose ☐ Other:
Action taken with BI studied medication or BI product administered for the disease in scope of NIS as a result of the event (*check one*)	Dose not changed	☐
	Dose reduced	☐
	Dose increased	☐
	Drug withdrawn	☐
	Not applicable	☐

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Boehringer Ingelheim

Non-Interventional Study (NIS) Adverse Event Form

BI Study No: 1237-0087	Country: GER
Site No:	Subject No:

RELEVANT PAST AND CONCOMITANT MEDICATIONS

Please preferably provide trade name. Do not include medications used solely to treat the adverse event(s).

☐ None ☐ Yes (*specify below*)	Indication	Past	Start/end dates *ddmmmyyyy or cont.*	Total daily dose at onset of event (*dose/ unit*)	Route	Is there a reasonable causal relationship between the event and the past or concomitant therapy? If Yes, record event number from page 2
1.		☐	Start:			☐ No ☐ Yes
			End:			Event # ____
2.		☐	Start:			☐ No ☐ Yes
			End:			Event # ____
3.		☐	Start:			☐ No ☐ Yes
			End:			Event # ____
4.		☐	Start:			☐ No ☐ Yes
			End:			Event # ____
5.		☐	Start:			☐ No ☐ Yes
			End:			Event # ____
6.		☐	Start:			☐ No ☐ Yes
			End:			Event # ____
7.		☐	Start:			☐ No ☐ Yes
			End:			Event # ____
8.		☐	Start:			☐ No ☐ Yes
			End:			Event # ____

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ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

APPROVAL / SIGNATURE PAGE

Document Number: c26538106 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-nis-1237-0087

Title: EVELUT: Assessment of dyspnea and other symptoms as patient reported outcomes (PRO) in patients with chronic obstructive pulmonary disease (COPD), symptomatic on LABA/ICS maintenance therapy (now) treated with Spiolto Respimat (tiotropium/olodaterol) in comparison to open or fixed triple combination treatment in routine clinical practice.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	11 Jun 2019 09:56 CEST
Approval-Biostatistics		11 Jun 2019 13:16 CEST
Approval-[redacted] Medical Affairs		11 Jun 2019 17:07 CEST
Approval-[redacted] Safety Evaluation Therapeutic Area		13 Jun 2019 12:48 CEST
Approval-[redacted] of Global Epidemiology		17 Jun 2019 20:51 CEST
Approval-Team Member Medicine		18 Jun 2019 15:58 CEST
Approval-Pharmacovigilance		25 Jun 2019 09:19 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed