# Non-Interventional Study (NIS) Protocol

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| **Document Number:** | **c38251083-01** |
| **BI Study Number:** | 0205-0549 |
| **BI Investigational Product(s):** | Spiriva® HandiHaler® and Spiriva® Respimat® |
| **Title:** | Switching COPD **P**atients from Spiriva® HandiHaler® maintenance therapy to Spiriva® Respimat®: a non-**I**nterventional **R**eal-world clinic**A**l ou**T**come ass**E**ssment: NIS **PIRATE** |
| **Brief lay title:** | Assessment of health-related quality of life after switching COPD patients from a dry powder inhaler to a soft mist inhaler remaining on the same inhalative drug |
| **Protocol version identifier:** | V1.0 |
| **Date of last version of protocol:** | 03 Mar 2022 |
| **PASS:** | No |
| **EU PAS reg. number:** | Not applicable |
| **Active substance:** | Tiotropium bromide |
| **Medicinal product:** | Spiriva® HandiHaler® 18 microgram capsules with powder for inhalation<br>Spiriva® Respimat® 2.5 microgram per puff inhalation solution |
| **Product reference:** | 0205-P03 (Spiriva® Respimat®) |
| **Procedure number:** | Not applicable |
| **Marketing authorization holder(s):** | MAH: [redacted]<br>This study is initiated, managed, and sponsored by: [redacted] |
| **Joint PASS:** | No |
| **Research question and objectives:** | The objective of this NIS is to test whether changing COPD patients from a dry powder inhaler (HandiHaler®) to a soft mist inhaler (Respimat®), without changing the pharmacological compound, will |

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| | lead to an improvement in Clinical COPD Questionnaire (CCQ) overall score and the three subdomains: symptoms (4 items), functional state (4 items) and mental state (2 items) during a study period of approximately 8 weeks.<br><br>**Primary objective:**<br><br>• To assess proportion of patients achieving 0.2 points decrease in the CCQ score* between baseline (visit 1 = visit at the start of the study) and after approximately 8 weeks of treatment (visit 2) in patients with high CCQ baseline score (≥2)<br><br>*CCQ score means the CCQ overall score, unless otherwise stated<br><br>**Secondary objectives**:<br><br>• To assess proportion of patients achieving 0.2 points decrease in the CCQ score between baseline (visit 1) and after approximately 8 weeks of treatment (visit 2) in patients independently from CCQ baseline score<br>• To assess the mean change in CCQ score and in the scores of the 3 CCQ subdomains, symptom, mental state, and functional state domain in all patients independently from CCQ baseline score between baseline (visit 1) and after approximately 8 weeks of treatment (visit 2)<br>• To assess the mean change in CCQ score and in the scores of the CCQ subdomains symptom, mental state, and functional state domain in patients with high CCQ baseline score (≥2) between baseline (visit 1) and after approximately 8 weeks of treatment (visit 2)<br>• To assess patients´ breathlessness based on modified Medical Research Council (mMRC) score at baseline (visit 1) and after approximately 8 weeks of treatment (visit 2)<br>• To assess the change in mMRC score between baseline (visit 1) and after approximately 8 weeks of treatment (visit 2 |
| **Country(-ies) of study:** | Approximately 225 COPD patients from Switzerland |
| Author: | [redacted] |
| **Date:** | 03 Mar 2022 |

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# 1. TABLE OF CONTENTS



[redacted]

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AESI | Adverse Event of special interest |
| AICD | Additional Inhalative COPD Drugs |
| CA | Competent Authority |
| CAT | COPD Assessment Test |
| CI | Confidence Interval |
| CCQ | Clinical COPD Questionnaire |
| CML | Local Clinical Monitor |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRA | Clinical Research Associate |
| CRF | Electronic Case Report Form |
| CRO | Clinical Research Organization |
| D | Diverse |
| DMP | Data Management Plan |
| DPI | Dry Powder Inhaler |
| EDC | Electronic Data Capture |
| e. g. | Exempli Gratia |
| EoT | End of Treatment |
| F | Female |
| FDA | US Food and Drug Administration |
| FEV1 | Forced Expiratory Volume in One Second |
| FU | Follow Up |
| FVC | Forced Vital Capacity |
| GCP | Good Clinical Practice |
| GEP | Good Epidemiological Practice |
| GPP | Good Pharmacoepidemiology Practice |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| HH | HandiHaler |
| HRQoL | Health Related Quality of Life |
| ICH | International Conference on Harmonization |

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|---|---|
| i. e. | Id Est |
| 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 |
| m | Male |
| MAH | Marketing Authorization Holder |
| Max | Maximum |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| Min | Minimum |
| mMRC | Modified Medical Research Council |
| n | Number (quantity) |
| NIS | Non-Interventional Study |
| NIS-DMRP | NIS-Data Management and Review Plan |
| PFIR | Peak Inspiratory Flow Rate |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| SADR | Suspected Adverse Drug Reaction |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SDV | Source Data Verification |
| SMI | Soft Mist Inhaler |
| SmPC | Summary of product characteristics |
| SOP | Standard Operating Procedure |
| w | week |
| WHO | World Health Organization |

# 2. RESPONSIBLE PARTIES

| Function | Name |
|---|---|
| Scientific Coordinator | [redacted] |
| Therapeutic Area [redacted] Respiratory Medicine (TA[redacted] | |
| Team Member Medical Affairs (TM MA) | |
| Scientific Advisor Medical Affairs | na |
| Team Member Epidemiology (TM Epi) | [redacted] |
| Deputy [redacted] Global Epidemiology ([redacted]GEpi) | |
| Therapeutic Area [redacted] Risk Management (TA[redacted] RM), and Pharmacovigilance Working Group (PVWG) [redacted] | |
| Trial Clinical Monitor | |
| TSTAT | |
| Statistical Analysis | Vendor/CRO |
| Data Management | Vendor/CRO |
| Trial Programming | Vendor/CRO |

# 3. ABSTRACT

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|---|---|---|---|
| **Name of company:**<br>Boehringer Ingelheim | | | |
| **Name of finished medicinal product:**<br>*Spiriva® HandiHaler® and Spiriva® Respimat®* | | | |
| **Name of active ingredient:**<br>*Tiotropium bromide* | | | |
| **Protocol date:**<br>03 Mar 2022 | **Study number:** | **Version/Revision:**<br>1.0 | **Version/Revision date:** |
| **Title of study:** | Switching COPD **P**atients from Spiriva® HandiHaler® maintenance therapy to Spiriva® Respimat®: a non-**I**nterventional **R**eal-world clinic**A**l ou**T**come ass**E**ssment: NIS **PIRATE** | | |
| **Rationale and background:** | Chronic obstructive pulmonary disease (COPD) is a common and serious condition, characterized by persistent respiratory symptoms and airflow limitation. Giving to the GOLD 2021 strategy report, long-acting bronchodilators such as long-acting muscarinic antagonists and long-acting β2-agonists are the basis of maintenance therapy for patients with moderate-to-very severe COPD.<br>Beside the pharmacological compound, matching each patient with the most appropriate inhaler is important for an optimal inhaler technique and drug delivery. Previous studies suggested that COPD patients with suboptimal peak inspiratory flow rate (PIFR) may not achieve the greatest possible drug deposition and efficacy when using a dry powder inhaler (DPI) for delivery of inhalative COPD medication.<br>The Respimat®, an active soft-mist inhalation device, allows COPD patients to inhale without effort and can be used irrespective of the PIFR a patient can generate.<br>This NIS aims to evaluate whether patients will benefit from the switch from the DPI Spiriva® HandiHaler® to the Spiriva® Respimat® device, which the physician decides based on the needs of the patient prior to study inclusion using the Clinical COPD Questionnaire (CCQ) and its three domains, changes in clinical control will be assessed.<br>Note: Patients will be included into the study independently of their CCQ* score at baseline.<br>*CCQ score means the CCQ overall score, unless otherwise stated | | |
| **Research question and objectives:** | The objective of this NIS is to test whether changing COPD patients from a dry powder inhaler (HandiHaler®) to a soft mist inhaler (Respimat®), without changing the pharmacological compound, will lead to an improvement in Clinical COPD Questionnaire (CCQ) score (covering last 7 days prior to visit) and in the scores of the three subdomains: symptoms (4 items), functional state (4 items) and mental state (2 items) during a study period of approximately 8 weeks. | | |

The primary objective of the NIS is to assess proportion of patients achieving 0.2 points decrease in the CCQ score between baseline and after approximately 8 weeks of treatment) in patients with high CCQ baseline score (≥2).

Secondary objectives of the NIS are the assessment of the proportion of patients achieving 0.2 points decrease in the CCQ score between baseline and after approximately 8 weeks of treatment independently from CCQ baseline score, the mean change in CCQ score and in the three CCQ domains symptom, mental state, and functional state domain in all patients and in patients with high CCQ baseline score (≥ 2) between baseline and visit 2 (approximately at week 8 after visit 1), breathlessness based on modified Medical Research Council (mMRC) score at baseline, visit 2 (approximately at week 8 after visit 1), change in mMRC score between baseline and visit 2 (approximately at week 8 after visit 1).

Safety data on COPD patients switching from Spiriva® HandiHaler® to Spiriva® Respimat® are collected descriptively and do not represent an objective of the NIS.

Following subgroup analyses will be performed for the primary objective:

- Patients with mMRC score ≥ 2 vs patients with mMRC score <2 at baseline visit
- Patients < 65 years vs patients ≥ 65 years at baseline visit
- Patients with 0-1 exacerbations vs patients with ≥ 2 exacerbations requiring hospitalizations during the 12 months prior study inclusion
- Patients using Spiriva® HandiHaler® ≥ 1 year(s) vs patients on Spiriva® HandiHaler® < 1 year
- Patients with at least one concomitant disease that was classified as mental and/or cognitive disorder vs patients without any concomitant disease that was classified as mental and/or cognitive disorder
- Patients with GOLD spirometric classification 1/2 vs patients with GOLD spirometric classification 3/4 at baseline visit

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| **Study design:** | Open label, observational, non-interventional, national, multicenter study including COPD patients ≥ 40 years switching from Spiriva® HandiHaler® to Spiriva® Respimat® with an observational period of approximately 8 weeks (which is the average time between medical consultations). Patients will be followed-up to either discontinuation of Spiriva® Respimat® or up to week 52, whatever occurs first. |
| **Population:** | COPD patients ≥ 40 years who are planned to be switched from Spiriva® HandiHaler® to Spiriva® Respimat®.<br>The decision to switch is made by the treating physician and patient according to patient´s need and to the standard of best medical practice. This decision is made independently and prior to inclusion in this NIS.<br>Patients who will undergo a switch from Spiriva® HandiHaler® to Spiriva® Respimat® will be informed about the scope of the study and asked whether they would like to participate.<br>**Inclusion criteria:**<br>• Participants ≥ 40 years of age at baseline visit<br>• Patients with confirmed diagnosis of COPD*<br>• Patients who have been on Spiriva® HandiHaler® for ≥ 6 weeks at baseline visit<br>• Patients for whom a switch from Spiriva® HandiHaler® to Spiriva® Respimat® was planned prior to study inclusion. If additional inhalative COPD drugs (AICDs) are used: AICD treatment must have been stable for at least 6 weeks before study inclusion<br>• Signed written informed consent form to participation<br>*Confirmed by spirometry: FEV1/FVC <0.7, (last available FEV1 and FVC including % predicted)<br>**Exclusion criteria:**<br>• Patients who have contraindications to Spiriva® Respimat® according to the current prescribing information label/ summary of product characteristics (SmPCs)<br>• Patients who have signs of a current, acute respiratory tract infection 2 weeks prior visit 1<br>• Patients for whom further follow-up will not be possible at the enrolling site during the planned observational period (of approximately 8 weeks)<br>• Patients with confirmed diagnosis of only asthma<br>• Patients who had > 1 moderate to severe exacerbation(s) within the last 6 weeks prior to study inclusion<br>• Patients who are pregnant or breastfeeding<br>• Patients participating in an ongoing interventional study |

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| **Variables:** | Eligible patients who signed the informed consent form will undergo the baseline visit (= visit 1).<br>Visits are to be scheduled as per standard-of-care. Documentation at the sites is planned at baseline (month 0, visit 1) and after approximately 8 weeks after treatment start (visit 2). Patients will be requested to have an End-of Treatment (EoT) visit (Follow-up visit) if they discontinue Spiriva® Respimat® treatment or if they switch to another inhalative medication. Patients who are still on Spiriva® Respimat® will have a follow-up visit (visit 3) approximately 52 weeks after baseline visit. It is planned that each patient will have 3 visits during the 1-year observational period. Additional visits may be performed as needed, such as when COPD treatment requires adjustment, or whenever otherwise deemed necessary by the study physician based on usual care.<br>**Main data collected:**<br>**At baseline (visit 1):**<br>• Patient demographics (age, gender, height, weight)<br>• Concomitant diseases / comorbidities (relevant comorbidities such as cardiovascular diseases, diabetes mellitus type 2, depression, and diseases affecting the preparing and handling of the device)<br>• Date of confirmed COPD diagnosis<br>• Start with inhalative bronchodilators for COPD treatment [year]<br>• Concomitant COPD medication including additional inhalative COPD drugs (AICDs, dosage, date of onset)<br>• Breathlessness based on mMRC score<br>• Last available FEV1 and FVC including % predicted (value and date measured, closest to the date of baseline visit)<br>• Exacerbation history (number of moderate-to-severe exacerbations in the last 12 months before study inclusion, hospitalizations required)<br>• Smoking history (number of pack years) and status (never, former, current)<br>[redacted]<br>**At visit 2:**<br>• Breathlessness based on mMRC score<br>[redacted] |

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| | • CCQ score and the CCQ symptom, mental state, and functional state domain scores<br>[redacted]<br>• Safety; ADR (serious and non-serious), fatal AEs, pregnancies<br>**At visit 3:**<br>• Changes in COPD treatment scheme (yes/no, date, reason(s), kind of new treatment)<br>• Discontinuation of Spiriva® Respimat® treatment (date, reason(s))<br>• Safety; ADR (serious and non-serious), fatal AEs, pregnancies (including exacerbations) |
| **Data sources:** | **To be completed by the physician:**<br>• Patient demographics<br>• Patient medical files<br>[redacted]<br>**To be completed by the patient:**<br>• mMRC breathlessness scale at baseline (visit 1) and visit 2<br>• Health and functional status by CCQ at baseline (visit 1) and visit 2<br>[redacted] |
| **Study size:** | **Primary endpoint:**<br>Assuming 40% of high CCQ score patients have a 0.2 improvement in CCQ score from baseline at 8 weeks on treatment, then with a sample size of 100, the 95% CI for the response rate will be (0.304, 0.49)6.<br>**Secondary endpoint:**<br>Assuming 30% of all patients have a 0.2 improvement in CCQ score from baseline at 8 weeks on treatment, then with a total sample size of 200, the 95% CI for the response rate will be (0.236, 0,364).<br>With a dropout rate of 10% we would need a total of about 225 patients. |

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| | Sample size assumes that Respimat® is better compared to HandiHaler®. The sample size calculation/justification can only provide a rough estimate of the statistical power in such an exploratory real-world setting. Recruitment will continue until the minimum sample size is achieved. |
| **Data analysis:** | **Primary outcome:**<br>For the primary outcome, the percentage of patients with improvement will be presented together with the 95% confidence interval, whereupon improvement is defined as 0.2 points decrease in the CCQ score from baseline (visit 1) to visit 2.<br>**Secondary outcomes:**<br>For secondary [redacted], the mMRC breathlessness scale at visit 1 and visit 2, [redacted] Changes from visit 1 to visit 2 in the CCQ score and CCQ symptom, mental and functional state score as well as in the [redacted]<br>Subgroup analyses on the primary objective will be performed for several stratifications as described before (see section Research question and objectives). If less than 20 patients are in one subgroup class, classes will be combined in a meaningful way, or the subgroup analysis will be omitted with reason. |
| **Milestones:** | Estimated enrolment duration: 1 year<br>First patient In (FPI): Q2/2022<br>Estimated individual observational period: at least 8 weeks, up to 52 weeks<br>Last patient In (LPI): Q2/2023<br>Last patient Last visit (LPLV): Q2/2024<br>Final study report: July 2024 |

# 4. AMENDMENTS AND UPDATES

None.

# 5. MILESTONES

| Milestone | Planned Date |
|---|---|
| IRB/IEC approval | APR 2022 |
| Start of data collection | APR 2022 |
| End of data collection | APR2024 |
| Study progress report 1 | Not applicable |
| Topline analysis | After visit 2 of the LPI |
| Reg. in the EU PAS register | Not applicable |
| Final report of study results: | JUL 2024 |

# 6. RATIONALE AND BACKGROUND

## 6.1 MEDICAL BACKGROUND

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable, and treatable disease with an estimated global prevalence of almost 300 million in 2017 [I, II]. By 2030, it is predicted that COPD will be the fourth-leading cause of death worldwide [III]. COPD is particularly prevalent in smokers and ex-smokers, people aged ≥ 40 years, and men [IV]. Disease characteristics comprise persistent respiratory symptoms and airflow limitation, usually resulting from significant exposure to noxious particles or gases, like tobacco smoke, air pollution or other environmental exposures [II]. The inhalation of such noxious substances triggers an abnormal inflammatory response in the lung leading to increased mucus production, tissue remodeling, and connected with this, to a narrowing of the air passages in the lower respiratory tract. As a result, the pulmonary parenchyma is destroyed, and pulmonary emphysema is caused. Over time, there are further systemic consequences, such as myopathy, osteoporosis, cor pulmonale, and hypertension with severe restriction of physical functioning. Recurrent acute exacerbations (e.g., due to pulmonary infections) bring about a further deterioration in the condition of the lungs [V]. In COPD patients, physical activity is reduced early in disease progression, as of GOLD Stage 2 [VI]. More recent evidence from large placebo controlled clinical trials indicates that COPD patients are experiencing a steeper absolute decline in lung function with GOLD 2 airflow limitation than with GOLD 3 and 4 [VII]. Those observations suggest the importance of early optimal treatment of the disease.

The main goal in COPD treatment is achievement of disease control and consequently, an improvement of health-related quality of life (HRQoL). Giving to the GOLD 2021 strategy

report, long-acting bronchodilators such as long-acting muscarinic antagonists and long-acting $\beta_2$-agonists are the basis of maintenance therapy for patients with moderate-to-very severe COPD [II].

Beside the pharmacological compound, matching each patient with the most appropriate inhaler is important for an optimal inhaler technique and drug delivery [VIII-XIII]. These days, numerous inhaler devices for maintenance treatment in COPD patients are available on the market, but each class of device has a different approach to inhalation and therefore, requires distinct handling techniques. However, the correct usage of the respective inhaler is a prerequisite for achievement of maximal clinical benefit. Unfortunately, inhalers are often not considered as an important part of the treatment [X]. Discordance especially with prescribed dry powder inhalers (DPIs) was seen in 40% of COPD patients, suggesting that many COPD patients do not generate adequate inspiratory force to overcome prescribed DPIs resistance during normal use [XIII]. Therefore, when using a DPI, COPD patients with suboptimal peak inspiratory flow rate (PIFR) may not achieve the greatest possible drug deposition and efficacy [XIII]. Consequently, maximal clinic benefit might be unattainable for those patients.

The Respimat®, an active soft-mist inhalation device, allows COPD patients to inhale without effort and can be used irrespective of the PIFR a patient can generate [XIV, XV]. It is well accepted by patients due to its easy inhalation and handling characteristics which is an important factor for treatment compliance [XVI, XVII, XVIII]. Additionally, Soft Mist™ Inhaler (SMIs) have a lower intrinsic resistance and do not require a high inspiratory flow rate for optimal drug delivery in comparison to DPIs [XIX].

## 6.2 DRUG PROFILE

Tiotropium bromide is the first once-daily, long-acting anticholinergic bronchodilator for the maintenance therapy of patients with COPD and is available in two formulations in many countries: an aqueous solution (5 µg) delivered via the Respimat® SMI [XX] and a dry powder (18 µg) delivered via the breath-actuated Spiriva® HandiHaler® device (DPI, both formulations: Boehringer Ingelheim Pharma GmbH & Co KG, Ingelheim am Rhein, Germany) [XXI].

Numerous controlled trials, including either or both formulations, have shown that tiotropium provides at least a 24-hour sustained improvement in airflow, reduced hyperinflation, and shortness of breath, as well as a reduced risk of exacerbations and associated hospitalizations, resulting in an increased HRQoL [XXII-XXVIII].

## 6.3 ASSESSMENT OF QUALITY OF LIFE

Various questionnaires on HRQoL are used to try assessing COPD patients' health status and physical state. The Clinical COPD questionnaire (CCQ) has been developed and validated in the Netherlands especially for COPD patients by Jan Kocks et al. in 2006 [XXIX] to categorize

patients' impairments generally and focus patients' treatment on their specific needs. The CCQ is easy to administer, and it takes less than a few minutes to complete. CCQ is used to monitor the clinical control of COPD covering the last 7 days prior to request. It consists of 10 questions, covering 3 domains: symptom domain (4 items [#'s 1,2,5,6]); functional status domain (4 items [#'s 7,8,9,10]) and mental status domain (2 items [#'s 3,4]). The questionnaire is responsive to intervention and has been translated and validated in over 140 languages [XXX]. In a head-to-head comparison of COPD Assessment Test (CAT) and CCQ the patients preferred the latter as it reflected their status better than CAT by giving more details on breathing problems which was more important for them than sleep or energy [XXX]. CCQ has been given maximum ranking in "COPD wellness tools" overview by the International Primary Care Respiratory Group (IPCRG) [XXXI]. The clinical CCQ is a well-established tool to evaluate COPD patients self-reported outcomes [XXIX, XXXII, XXXIII]]. A difference from -0.2 points corresponds to 50% of the minimal clinically important difference for a CCQ of -0.4 points [XXIX, XXXII]. Patients with a worse CCQ (score of ≥2) are expected to have a CCQ score that is on average 0.2 points higher (i.e., worser health status) than patients with an acceptable CCQ score for moderate disease (score of <2) [XXXIV]. Thus, a change of -0.2 points will be used in this NIS to explore whether there is an improvement in CCQ after switching the device without changing the pharmacological compound although the setting in this NIS is different from the validation studies.

## 6.4 SITUATION IN SWITZERLAND

In Switzerland, both devices, the Spiriva® Respimat® SMI as well as the Spiriva® HandiHaler® DPI, are approved treatment options for COPD patients. Beside similar exacerbation and bronchodilator efficacy [XXIV, XXVIII], their safety and pharmacokinetic profiles are similar to each other [XXXV, XXXVI, XXXVII]. However, in Switzerland, life expectancy is one of the highest in Europe [XXXVIII] and therefore, it can be considered that mean age in Swiss COPD patients might be higher than in the other European countries. Thus, Swiss COPD patients might be faced with difficulties in preparation and handling of the device. The Respimat® device was developed to fulfil patients´ and physicians´ needs for an easy usability and might be an appropriate device in older patients who suffer from comorbidities correlated to impaired mobility such as Parkinson´s disease, arthritis/arthrosis, and rheumatism [XXXIX]. In those patients, it seems to be important to follow up the ability for correct usage of their device to ensure adequate COPD maintenance therapy. Since there are no other Tiotropium devices (generic drugs) available on the Swiss market, COPD patients from Switzerland represent an ideal cohort to assess whether there is an improvement in clinical control of COPD when switching the patients from the DPI to the respective SMI without changing the active agent.

## 6.5 RATIONALE

The current non-interventional study (NIS) aims to evaluate whether in a real-world COPD patient setting and by not altering the pharmacological compound the change from the Spiriva® HandiHaler® to the Respimat® will lead to improvements in HRQoL including physical function, and dyspnea.

Based on the previous mentioned background, this NIS has been designed to assess whether changing COPD patients from a dry powder inhaler (HandiHaler®) to a soft mist inhaler (Respimat®), without changing the pharmacological compound, will lead to an improvement in HRQoL. Therapeutic success will be assessed at week 8 which is the mean time between two medical appointments in COPD patients. The well-established and commonly used CCQ will be used to assess changes in HRQoL in switching patients. [redacted] will be collected to characterize the population of COPD patients which is intended for a switch to the SMI device.

# 7. RESEARCH QUESTION AND OBJECTIVES

The objective of this non-interventional, observational study is to assess whether changing COPD patients from a dry powder inhaler (HandiHaler®) to a soft mist inhaler (Respimat®), without changing the pharmacological compound, will lead to an improvement in CCQ score* and in the scores of the three subdomains: symptoms (4 items), functional state (4 items) and mental state (2 items) during a study period of approximately 8 weeks. Each of the 10 CCQ questions is scored by the patient on a 7-point scale between 0 and 6 at baseline and at the end of the observation after approximately 8 weeks. The sum of the scores divided by 10 gives the CCQ score, which measures the health and functional status.

The functional state score is a calculation of the sum of the 4 items (#'s 7, 8, 9, 10) divided by 4, the symptom score is calculation of the sum of the 4 items (#'s 1, 2, 5, 6) divided by 4 and the mental state score is a calculation of the sum of the 2 items (#'s 3, 4) divided by 2. More details, e.g., how to handle missing data, will be described in the statistical analysis plan.

CCQ values can be interpreted as: acceptable (CCQ < 1); acceptable for moderate disease (1 ≤ CCQ <2); instable-severe limited (2 ≤ CCQ < 3); very instable-very severe limited (CCQ ≥ 3) [XVI,XVII]. As a CCQ ≥ 2 is as well associated with an increased mortality [XXVIII], this value will be used as the cut-off for the current non-interventional study.

Our hypothesis is that patients with a worse CCQ (= high CCQ of ≥ 2) at baseline will benefit the most when changing from the DPI Spiriva® HandiHaler® to the SMI Spiriva® Respimat®.

Note: Patients will be included into the study independently of their CCQ at baseline.

*CQQ score means CCQ overall score, unless otherwise stated

**Primary objective:**

The primary objective of the NIS is to assess proportion of patients achieving a 0.2 points decrease in the CCQ score between baseline and after approximately 8 weeks of treatment) in patients with high CCQ baseline score (≥ 2).

**Secondary objectives:**

Secondary objectives of the NIS are the assessment of the proportion of patients achieving a 0.2 points decrease in the CCQ score between baseline and after approximately 8 weeks of treatment independently from CCQ baseline score, the mean change in CCQ score and in the three CCQ domains symptom, mental state, and functional state domain in all patients and in patients with high CCQ baseline score (≥ 2) between baseline and visit 2 (approximately at week 8 after visit 1), breathlessness based on mMRC score at baseline, visit 2 (approximately at week 8 after visit 1), and change in mMRC score between baseline and visit 2 (approximately at week 8 after visit 1),

Safety data of COPD patients switching from Spiriva® HandiHaler® to Spiriva® Respimat® will be collected descriptively and are not a separate objective of the NIS.

# 8. RESEARCH METHODS

## 8.1 STUDY DESIGN

This is a national, multicenter, non-interventional, observational, cohort study based on newly collected data with an observational period of at least 8 weeks until switch or discontinuation of Spiriva® Respimat® treatment or up to 52 weeks after baseline visit whatever occurs first.

This NIS is designed as single-arm study without a specific comparator in a parallel arm. All included patients must have been on treatment with Spiriva® HandiHaler® for at least 6 weeks prior to study inclusion. Therefore, patient could serve as their own control (baseline values) and a parallel arm being on Spiriva® HandiHaler® is not obligatory to address the primary objective of the NIS.

The study is non-interventional on the therapeutic strategy as the decision to switch the patient from Spiriva® HandiHaler® to Spiriva® Respimat® device is made by the treating physician prior to study inclusion due to patient´s individual needs. Patients will be treated within clinical routine practice and according to the current standard of care to assess the real-world situation in Swiss clinical practice. The patients included in the study will be followed for 1 year (approximately 52 weeks) after switching to the Respimat® device with no fixed study visit schedule. The treating physician will be asked to record data for study endpoint assessments in week 8 after baseline to assess therapeutic success of the switch to the Respimat® device. Patients who discontinued Spiriva® Respimat® treatment or who were switched to another treatment will be asked to perform an end-of-treatment (EoT) visit (= follow-up visit).

This national study will be conducted as a multicenter study to collect information on current status, and characteristics of patients switching from HandiHaler® to Respimat® device from

various sites to achieve balanced data with regard to geographic distribution, type of clinical setting (e.g., academic versus community health centers), and prescriber specialty which are representative for the larger patient and prescriber community.

## 8.2 SETTING

### 8.2.1 Study sites

It is planned that data of approximately 225 patients from approximately 40 sites will be collected. Site selection will be performed to reflect routine COPD care to secure representativeness of the Swiss COPD population. As described in section study design, achievement of balanced data regarding geographic distribution, type of clinical setting (e.g., academic versus community health centers), and prescriber specialty which are representative for the larger patient and prescriber community will be considered for site selection.

A log of all patients included into the study (i. e., having given informed consent form) will be maintained in the investigator´s site file at the investigational site irrespective of whether they have been switched or not.

### 8.2.2 Study population

Patients will be enrolled consecutively in the study. The decision to switch the patient from Spiriva® HandiHaler® to Spiriva® Respimat® will be made by the treating physician to the patient's need and to the standard of best medical practice prior to the inclusion into the study.

Patients with COPD planned to be switched according to the respective SmPC and consenting to participate in the study are eligible. To avoid any selection bias, all eligible patients will be invited to participate in this study, in the order in which their eligibility is determined. A time window of 1 years is foreseen for recruitment of the patients. Patients will be treated within clinical routine practice and according to the current standard of care. Patients who discontinue from treatment before the visit at week 52 will be asked to complete an EoT visit.

**Inclusion criteria:**

Patients can be included if all following criteria are met:

- Participants ≥ 40 years of age at baseline visit
- Patients with confirmed diagnosis of COPD*
- Patients who have been on Spiriva® HandiHaler® for ≥ 6 weeks at baseline visit
- Patients for whom a switch from Spiriva® HandiHaler® to Spiriva® Respimat® was planned prior to study inclusion. If additional inhalative COPD drugs (AICDs) are

used: AICD treatment must have been stable for at least 6 weeks before study inclusion

- Signed written informed consent form to participation

*Confirmed by spirometry: FEV1/FVC <0.7 (last available FEV1 and FVC including % predicted)

**Exclusion criteria:**

- Patients who have contraindications to Spiriva® Respimat® according to the current prescribing information label/ summary of product characteristics (SmPC)
- Patients who have signs of a current, acute respiratory tract infection 2 weeks prior visit 1
- Patients for whom further follow-up will not be possible at the enrolling site during the planned observational period (of approximately 8 weeks)
- Patients with confirmed diagnosis of only asthma
- Patients who had > 1 moderate to severe exacerbation(s) within the last 6 weeks prior to study inclusion
- Patients who are pregnant or breastfeeding
- Patients participating in an ongoing interventional study

### 8.2.3 Study visits

Eligible patients who sign the informed consent form (ICF) will undergo the baseline visit.

Patients will be followed up over an observational period of approximately 52 weeks after baseline visit (visit 1). During the observational period, 2 further visits will be performed. Visit 2 will be approximately in week 8, visit 3 will be performed in week 52 as follow-up visit.

Patients who discontinue from the treatment before the visit at week 52 will be asked to complete an EoT visit.

Figure 8.2.3:1 provides a study flow chart. Table 8.2.3:1 gives an overview about the parameters collected during the study.

Figure 8.2.3:1 Study flow chart.

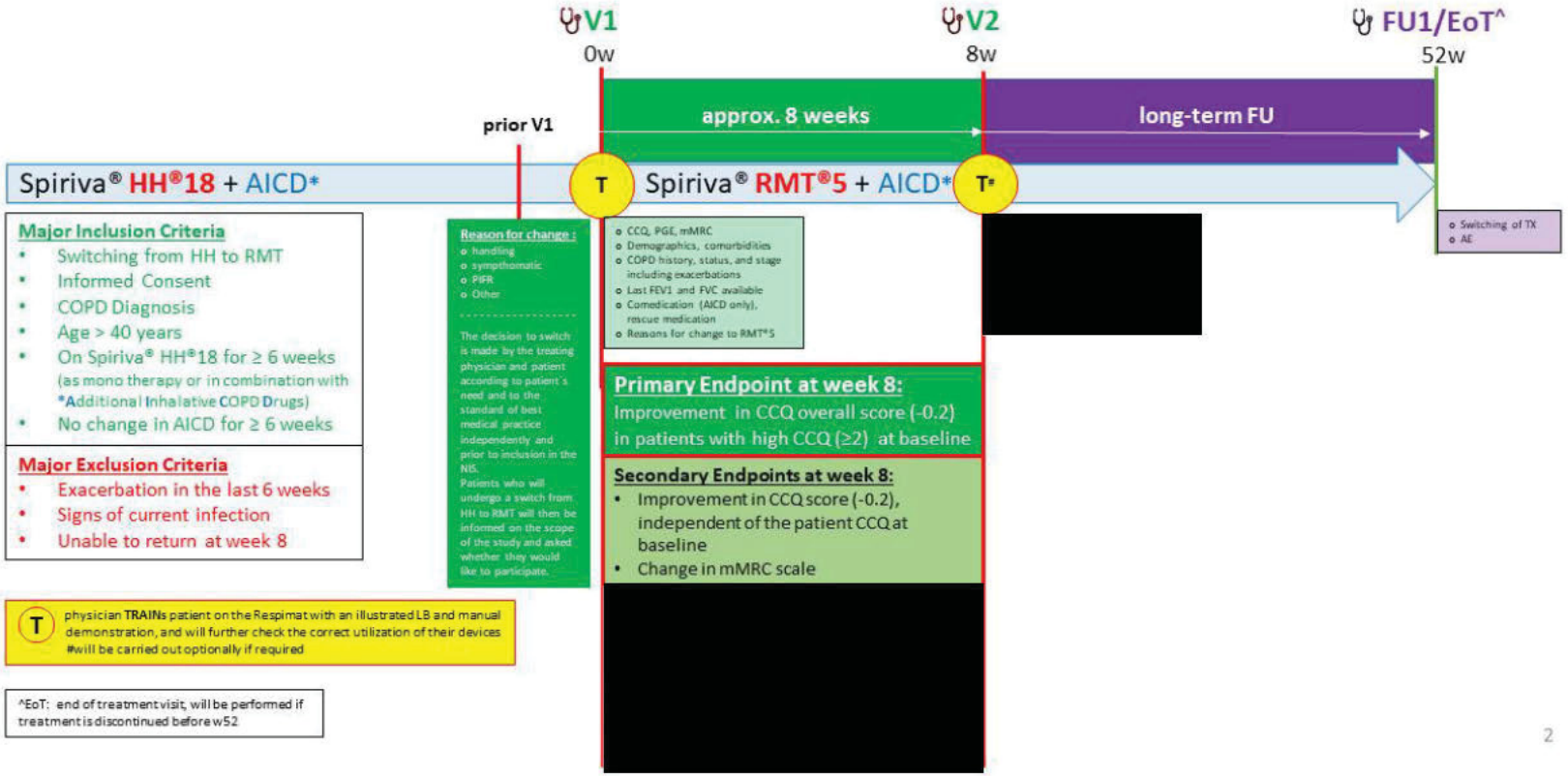


Table 8.2.3:1 Data collection parameters

| Parameter | Baseline visit (Visit 1) | Visit 2 (approx. 8 weeks after baseline visit) | Visit 3 (approx. 52 weeks after baseline visit)/EoT visit (if Spiriva® Respimat® treatment is discontinued or switched) |
|---|---|---|---|
| Informed Consent Form | X | | |
| Inclusion / Exclusion criteria | X | | |
| Patient demographics (age [years], gender [m/f/d], height [cm], and weight [kg]) | X | | |
| Start of COPD (age at onset [years]) | X | | |
| Concomitant diseases / comorbidities (relevant comorbidities such as cardiovascular diseases, diabetes mellitus type 2, depression and diseases affecting the preparing and handling of the Respimat® device) | X | | |
| Start of inhalative bronchodilators for COPD treatment [year] | X | | |
| Concomitant COPD medication including additional inhalative COPD drugs (AICDs, dosage, date of onset [day-month-year]) up to 6 weeks before baseline visit | X | | |
| Changes in COPD treatment scheme (date [day-month-year], reason(s)) | | X | X |
| Reason(s) for change from Spiriva® HandiHaler® to Spiriva® Respimat® | X | | |
| Number of moderate to severe exacerbations in the last 12 months | X | | |
| Number of exacerbations leading to hospitalization in the last 12 months | X | | |
| mMRC breathlessness scale, completed by the patient | X | X | |
| Last available FEV1 and FVC (value and date measured [day-month-year]) | X | | |
| Respimat® training (yes/no) | X | | |

| | | | |
|---|---|---|---|
| COPD severity based on GOLD assessment[1] | X | | |
| GOLD spirometric classification, if available[2] | X | | |
| Smoking status [never/former/current]/history [number of pack years] | X | | |
| Health and functional status by CCQ questionnaire, completed by patient | X | X | |
| [redacted] | [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] | |
| Safety: Adverse Drug Reactions (serious and non-serious), fatal AE, pregnancy | | X | X |
| Assessment of treatment start [yes/no], date of onset of treatment [day-month-year] | | X | |
| [redacted] | | [redacted] | |
| [redacted] | | [redacted] | |
| Rationale for Spiriva® Respimat® treatment discontinuation (if applicable) | | X | X |
| Continuation or discontinuation of treatment with Spiriva® Respimat® after the study [yes/no]/date [day-month-year] | | X | X |

*[1] GOLD patient group (B, C or D) will be automatically calculated based on available exacerbation history and mMRC.*
*[2] GOLD stage 1-4 spirometric classification of airflow limitation based on post-bronchodilator $FEV_1$ and FVC.*

### 8.2.4 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 effectiveness/safety information that could significantly affect continuation of the study, or any other administrative reasons, i.e., lack of recruitment

3. Violation of Good Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by a study site, investigator, or research collaborator, disturbing the appropriate conduct of the study

The investigator/the study site/research collaborator will be reimbursed for reasonable expenses incurred in case of study/site termination (except in case of the third reason).

Patients who discontinue from the study before the visit at week 52 will be asked to complete an EoT visit.

## 8.3 VARIABLES

The following parameters will be collected and assessed at visit 1 and/ or visit 2 and/or visit 3:

- Patient demographics (age, gender, height & weight)
- Concomitant diseases / comorbidities (relevant comorbidities such as cardiovascular diseases, diabetes mellitus type 2, depression and diseases affecting the preparing and handling of the Respimat® device)
- Date of confirmed COPD diagnosis [year]
- Start with inhalative bronchodilators for COPD treatment [year]
- Concomitant COPD medication including AICDs (dosage, date of onset) up to 6 weeks before baseline visit
- Changes in COPD treatment scheme (date, reason(s))
- Last available FEV1 (value and date measured) and FVC including % predicted (value and date measured, closest to the date of baseline visit)
- Reported moderate-to-severe exacerbations based on medical history in the last 12 months and exacerbations leading to hospitalization in the last 12 months
- Smoking history (number of pack years) and status (never, former, current)
- Assessment of the severity of breathlessness based on the mMRC questionnaire
- GOLD spirometric classifications (1, 2, 3, 4) and GOLD patient groups (A, B, C, D) based on GOLD-2022
- Clinical control based on CCQ score and CCQ symptom, mental state, and functional state domain scores

- (Safety Reporting*; Adverse Drug Reactions (serious and non-serious), fatal AEs, and pregnancies at the beginning and at the end of the study)

*Safety data will be collected descriptively and are not a separate objective of the NIS.

### 8.3.1 Exposures

All patients will switch from the Spiriva® HandiHaler® to Spiriva® Respimat® based on physician´s decision which will be made prior to study inclusion basing on patient´s individual medical needs and according to the current SmPC.

Spiriva® Respimat® contains

- the long-acting anticholinergic tiotropium bromide.

The dose dispensed is 2.5 micrograms of tiotropium per puff.

The recommended daily dose of Spiriva® Respimat® for adults is 5 micrograms of tiotropium, equivalent to inhaling 2 puffs from the Respimat® inhaler once daily at the same time of day.

The Summary of Product Characteristics (SmPC) [XX] on Spiriva® Respimat® is contained in the NIS investigator site file in the "Summary of Product Characteristics" section.

Note: The recommended doses stated in the SmPC should not be exceeded.

### 8.3.2 Outcomes

8.3.2.1 Primary outcomes

- Outcome type: primary
- Outcome name: **"Improvement"** defined as 0.2 points decrease in the CCQ score between baseline and visit 2 in patients with high CCQ baseline score (≥ 2)

- Time frame: between baseline (= visit 1) to approximately 8 weeks after switching from Spiriva® HandiHaler® to Spiriva® Respimat® (= visit 2)
- Safety Issue: No

8.3.2.2 Secondary outcomes

- Outcome type: secondary
- Outcome name: **"Improvement"** defined as 0.2 points decrease in the CCQ score between baseline and visit 2 in patients independently from CCQ baseline score
- Time frame: between baseline (= visit 1) to approximately 8 weeks after switching from Spiriva® HandiHaler® to Spiriva® Respimat® (= visit 2)
- Safety Issue: No

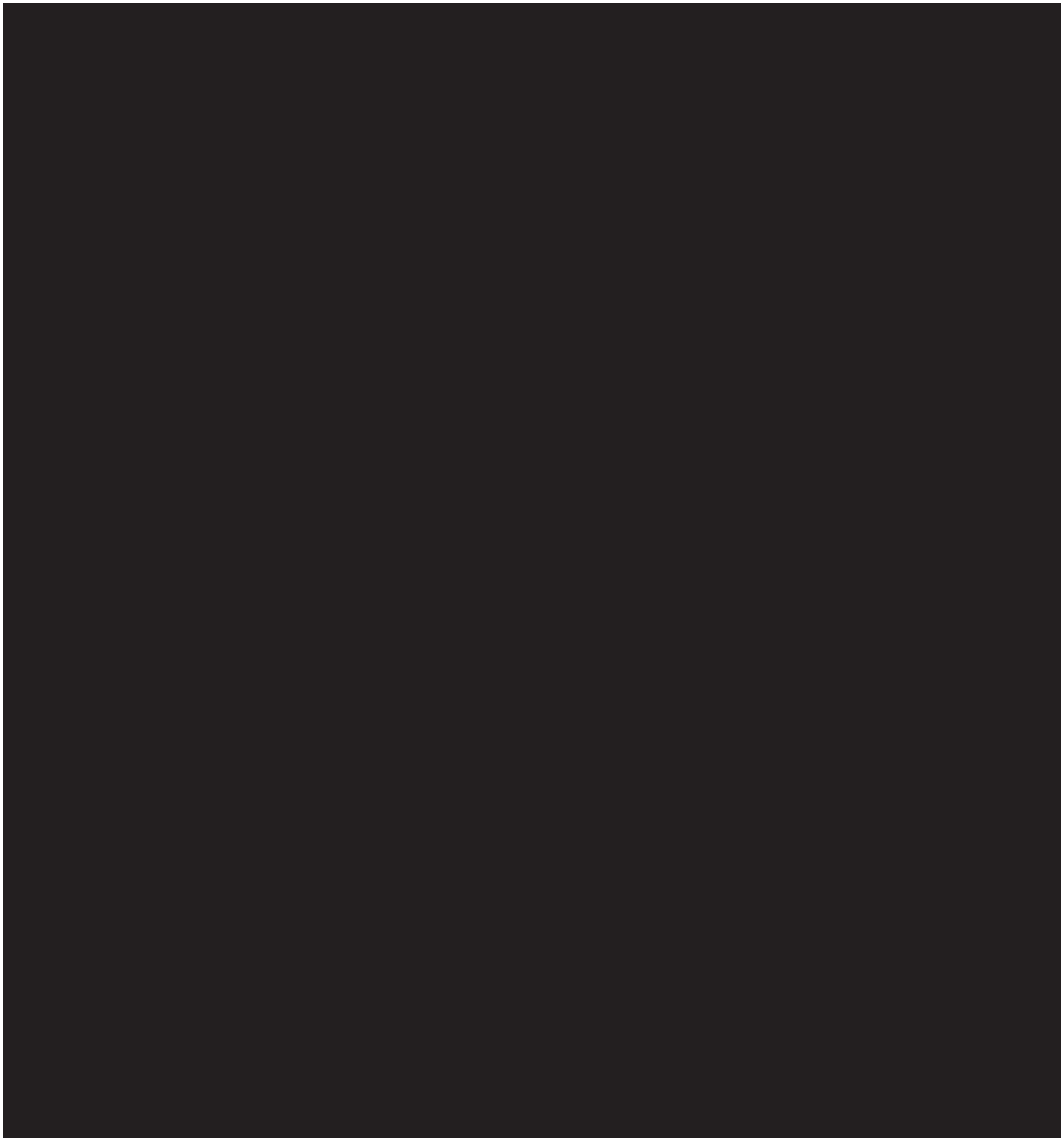
- Outcome type: secondary
- Outcome name: **"Changes in clinical control"** [XXXIII] defined as mean change in the in CCQ score and in the scores of the 3 CCQ subdomains symptom (items 1, 2, 5, 6 of the CCQ), mental state (items 3, 4 of the CCQ), and functional state domain (CCQ-4, items 7, 8, 9 and 10 of the CCQ), in all patients independently from CCQ baseline score
- Time frame:
    - between baseline (= visit 1) and approximately 8 weeks after switching from Spiriva® HandiHaler® to Spiriva® Respimat® (= visit 2)
- Safety Issue: No

- Outcome type: secondary
- Outcome name: **"Changes in clinical control"** defined as mean change in the in CCQ score and in the scores of the 3 CCQ subdomains symptom (items 1, 2, 5, 6 of the CCQ), mental state (items 3, 4 of the CCQ), and functional state domain (CCQ-4, items 7, 8, 9 and 10 of the CCQ), in patients with high CCQ baseline score (≥ 2)
- Time frame:
    - between baseline (= visit 1) and approximately 8 weeks after switching from Spiriva® HandiHaler® to Spiriva® Respimat® (= visit 2)
- Safety Issue: No

- Outcome type: secondary
- Outcome name: **"Breathlessness of the patients"** assessed by the mMRC scale completed by all patients
- Time frame: Assessment will be performed at baseline (= visit 1), approximately 8 weeks after switching from Spiriva® HandiHaler® to Spiriva® Respimat® (= visit 2)
- Safety Issue: No

- Outcome type: secondary
- Outcome name: **"Changes in breathlessness of the patients"** assessed by the mMRC scale completed by all patients
    - Time frame: between baseline (= visit 1) to approximately 8 weeks after switching from Spiriva® HandiHaler® to Spiriva® Respimat® (= visit 2)
- Safety Issue: No

[redacted]



### 8.3.3 Covariates

Not applicable.

## 8.4 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 previous exacerbation history.

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

Start of treatment will be assessed by a yes/no question at visit 2. If treatment was started, date of treatment onset will be asked by the physician.

The CCQ comprises 10 items. Each question can be scored by patients on a 7-point scale between 0 and 6. The sum of the scores divided by 10 gives the CCQ score. For the functional status calculation, the sum of the 4 items (# 7, 8, 9, 10) is divided by 4, for the symptom domain the sum of the 4 items (# 1, 2, 5, 6) is divided by 4, and for the mental state domain the sum of the 2 items (# 3, 4) is divided by 2. This questionnaire will be filled out by the patient and entered in the database by trained personnel from the Clinical Research Organization. Patients will be asked to complete the CCQ to evaluate their clinical control before, approximately 8 weeks after treatment with Spiriva® Respimat®.

[redacted]

The modified Medical Research Council (mMRC) scale will be used to assess the breathlessness state of the patient before switching the device, and approximately 8 weeks after device switch. The mMRC stage (0 to 4) collected from the patient as well as the exacerbation history will be used to calculate the GOLD patient group (B, C, or D) in the CRF.

[redacted]

## 8.5 STUDY SIZE

It is expected that half of the patients included will have CCQ score of ≥ 2 (high CCQ).

**Primary endpoint**: Assuming 40% of high CCQ score patients have a 0.2 improvement in CCQ score from baseline at 8 weeks on treatment, then with a sample size of 100, the 95% CI for the response rate will be: (0.304, 0.496).

**Secondary endpoint**: Assuming 30% of all patients have a 0.2 improvement in CCQ score from baseline at 8 weeks on treatment, then with a total sample size of 200, the 95% CI for the response rate will be (0.236, 0,364).

With a dropout rate of 10%, a total of about 225 patients will be needed.

Sample size assumes that Respimat® is better compared to HandiHaler® and patients will improve their CCQ scores once switched to Respimat®. The sample size calculation/justification can only provide a rough estimate of the statistical power in such an exploratory real-world setting. Recruitment will continue until the minimum sample size is achieved.

## 8.6 DATA MANAGEMENT

The data management plan is summarized below. Full details of the data management plan are documented in a separate NIS-Data Management and Review Plan (NIS-DMRP).

A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning, and validation. Boehringer-Ingelheim will check CRFs for correctness at date of collection. The CRFs will be sent to the vendor or Clinical Research Organization (CRO) and will be computed by trained staff from the vendor/CRO including programmable edits to obtain immediate feedback if data are missing (also negative answers, unknown), out of range, illogical or potentially erroneous. These rules may encompass simple checks such as range validation or presence/absence of data.

Concurrent manual data review may be performed based on parameters dictated by the DMP. Ad hoc queries to the sites may be generated and followed up for resolution. A source data quality audit may be initiated to ensure that the data in the database is accurate. Source data verification (SDV) will be performed at sites identified by a risk-based approach as needed.

The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system will meet the standards of the International Committee on Harmonization guideline E6R1 regarding electronic study data handling and the safety requirements of the FDA (US Food & Drug Administration) concerning systems for the data acquisition of clinical studies in accordance with "Title 21 Code of Federal Regulations (21 CFR Part 11): Electronic Records; Electronic Signatures". Patient confidentiality will be strictly maintained.

## 8.7 DATA ANALYSIS

This section provides specifications for the preparation of the final statistical analysis plan (SAP), which will be issued prior to database lock. Any differences compared to this statistical section should be identified and documented in the final SAP.

The following data handling conventions will be followed:

- Baseline assessments are those that were completed at the baseline visit (visit 1).
- The following analysis time windows will be utilized in the analysis:
    - Assessments scheduled to be done:
    - Approximately 8 weeks after treatment start (= visit 2): 8 weeks ± 2 weeks
    - Approximately 52 weeks after treatment start (= visit 3, follow-up visit): 52 weeks ± 4 weeks
    - If patients discontinue or switched from Spiriva® Respimat® treatment, they will be asked to perform an EoT visit (= visit 3) nearby to the date of stopping Spiriva® Respimat® treatment

No formal hypothesis testing will be performed since this is a self-controlled study. The analysis of the data will be of descriptive and explorative character. Variables will be summarized using appropriate statistical methods

The statistical characteristics presented in the end-of-text tables will be N / mean / SD / min / median / max for continuous variables. Tabulations of relative and absolute frequencies will be presented for categorical variables. Proportions and 95% CI will be given when appropriate.

At baseline, the following data will be collected as available in routine clinical practice:

Patient demographics and medical history:

- Patient demographics (gender, age, height, weight)
- Comorbidities (main diagnosis and concurrent diagnosis according to MedDRA, version valid at the time of database closure)
- COPD related concomitant medication (according to the WHO classification, version valid at the time of database closure)
- Details of treatment with inhaled respiratory agents before the study
- History of smoking
- GOLD spirometric classifications (1, 2, 3, 4) and GOLD patient groups (A, B, C, D), date of confirmed COPD diagnosis

Data collection at baseline:

- Breathlessness based on mMRC score at visit 1; secondary endpoint

- CCQ score and CCQ symptom, mental state, and functional state scores; secondary endpoint

[redacted]

The following data will be collected as available in routine clinical practice at visit 2:

- Assessment of treatment start with date of onset, if applicable
- Breathlessness based on mMRC score, secondary endpoint
- CCQ score and CCQ symptom, mental state, and functional state scores; secondary endpoint

[redacted]

- Reasons for ending treatment during the observational period
- Details of treatment continuation / discontinuation
- Adverse Drug Reactions (ADR & SADR), fatal AEs, pregnancies (descriptive collection, no endpoint of the current study).

The following data will be collected as available in routine clinical practice at visit 3 (follow-up visit)/EoT vis:

- Details of treatment with respiratory agents during the study and changes (if applicable)
- Reasons for ending treatment during the observational period
- Details of treatment continuation / discontinuation

- Adverse Drug Reactions (ADR & SADR), fatal AEs, pregnancies (descriptive collection, no endpoint of the current study).

All statistical analyses will be pre-specified in the SAP. Statistical analysis will be performed by using SAS Version 9.4 or higher.

### 8.7.1 Main analysis

For the primary outcome, the proportion of patients (%) with a CCQ decrease of at least 0.2 points and a high CCQ baseline score of ≥ 2 will be presented together with the 95% confidence interval.

[redacted]

### 8.7.3 Safety Analysis

All adverse events and adverse drug reactions collected per study protocol will be included and summarized in the in the final study report according to local requirements.

## 8.8 QUALITY CONTROL

All details are documented in the NIS-DMRP.

Every physician shall allow an authorized personal or staff from Boehringer Ingelheim (Schweiz) GmbH to make regular visits to monitor the study. The monitor will either use interviewing techniques for monitoring or perform source data verification. The CRF entries will be compared with the data given in the patient files. Therefore, in order to perform an extend source data verification the monitor shall have access to the patient files. Furthermore, the CRFs will be controlled for completeness and accuracy.

Visiting of the study and laboratory facilities will likewise be allowed.

During data entry, incomplete or non-valid data will be identified, and data clarification requests will be sent to the physician.

Completed CRFs should be returned at the end of each month to the responsible study manager to accelerate the process of data entry and evaluation. In case of return after more than 3 months after completion acceptance of the CRF cannot be ensured. The physician/investigator or a qualified designee will be responsible for recording and verifying the accuracy and correctness of patient data within the CRF via signature.

Data will be entered and verified for accuracy by trained personal from Boehringer Ingelheim (Schweiz) GmbH / CRO /vendor according to the data entry manual. A sample of 10% of all CRFs will be double-checked by an independent person. Data will be checked during patient enrolment for consistency, plausibility, and out-of-range values by responsible Data Management staff. These checks will be performed through programs and range checks within the EDC system.

## 8.9 LIMITATIONS OF THE RESEARCH METHODS

The intention of this NIS is to collect data on the changes in HRQoL in patients with COPD after switching from Spiriva® HandiHaler® to Spiriva® Respimat® in a real-world setting.

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

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

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

## 8.10 OTHER ASPECTS

### 8.10.1 Data quality assurance

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

### 8.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, in paper or electronic Form.

#### 8.10.2.1 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 reported on the CRFs 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 CRFs, the following data need to be derived from source documents:

- Patient identification (gender, date of birth)
- Patient participation in the study (substance, study number, patient number, date patient was informed)

- Dates of patient's visits, including prescription of study medication
- Medical history (including study indication and concomitant diseases, if applicable)
- COPD medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (SAEs) (onset date (mandatory), and end date (if available))
- Originals or copies of laboratory results (in validated electronic format, if available)
- Conclusion of patient's participation in the study
- Questionnaires and surveys completed by the patient
- [redacted]

8.10.2.2 Direct access to source data and documents

The investigator/institution will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs 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., Swissmedic). BI study staff and auditor may review all CRFs and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.10.2.1.

### 8.10.3 Completion of study

The IEC/competent authority in Switzerland needs to be notified about the end of the study (last patient/patient out, unless specified differently in Section 9.1) or early termination of the study.

### 8.10.4 Protocol deviations

Protocol deviations will be specified in the SAP. Patients with protocol deviations will be excluded from the full analysis set.

## 9. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, Guidelines for Good Pharmacoepidemiology Practice (GPP), and the relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic,

diagnostic and therapeutic procedures) remains 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.

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).

## 9.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

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

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient. The patient must be informed that his / her medical records may be examined by authorized monitors (CML/CRA) or Quality Medicine auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

## 9.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained because 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 because 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*.

# 10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

## 10.1 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 unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether, or not considered related to the medicinal product.

Adverse drug reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an 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 judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or 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.

## 10.2 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 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 the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated

Moderate: Enough discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities

Pregnancy:

In rare cases, pregnancy might occur in a NIS. Once a patient has been enrolled in the study and has taken study medication, the investigator must report any drug exposure during pregnancy in a study participant within 7 days by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form (Part B).

The ISF will contain the Pregnancy Monitoring Form (Part A and B). As pregnancy itself is not to be reported as an AE, in the absence of an accompanying serious ADR and/or AESI, only the Pregnancy Monitoring Form and not the NIS AE form is to be completed. If there is a serious ADR and/or AESI associated with the pregnancy a NIS AE form must be completed in addition.

The following must be reported on the NIS AE Form and/or Pregnancy Monitoring Form for Studies in case such AE/drug exposure during pregnancy information is identified during the review of the individual records:

| | |
|---|---|
| All **serious ADRs** associated with the Spiriva® Respimat® | immediately within 24 hours |
| All **AEs with fatal outcome** in patients exposed to Spiriva® Respimat® | immediately within 24 hours |
| All **protocol specified AESIs** Spiriva® Respimat® | immediately within 24 hours |
| All **non-serious ADRs** associated with the Spiriva® Respimat® | 7 calendar days |
| Drug exposure during pregnancy | 7 calendar days |

The same timelines apply if follow-up information becomes available for the respective events.

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 CRF from signing the informed consent onwards until the end of the study:

- all adverse drug reactions (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.

Information required

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

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than the Spiriva® 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.

Expedited Reporting of AEs and Drug Exposure during Pregnancy to BI Pharmacovigilance

The following must be reported by the investigator on the NIS AE form and/or Pregnancy Monitoring Form from signing the informed consent onwards until the end of the study and provide to BI unique entry point:

| Type of Report | Timeline |
|---|---|
| All **serious ADRs** associated with the Spiriva® Respimat® | immediately within 24 hours |
| All **AEs with fatal outcome** in patients exposed to Spiriva® Respimat® | immediately within 24 hours |
| All **protocol specified AESIs** Spiriva® Respimat® | Immediately within 24 hours |
| All **non-serious ADRs** associated with the Spiriva® Respimat® | 7 calendar days |
| Drug exposure during pregnancy | 7 calendar days |

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

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate CRF page and the NIS AE form.

### 10.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the Marketing Authorization Holder (MAH) according to local and international regulatory requirements.

## 11. 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.

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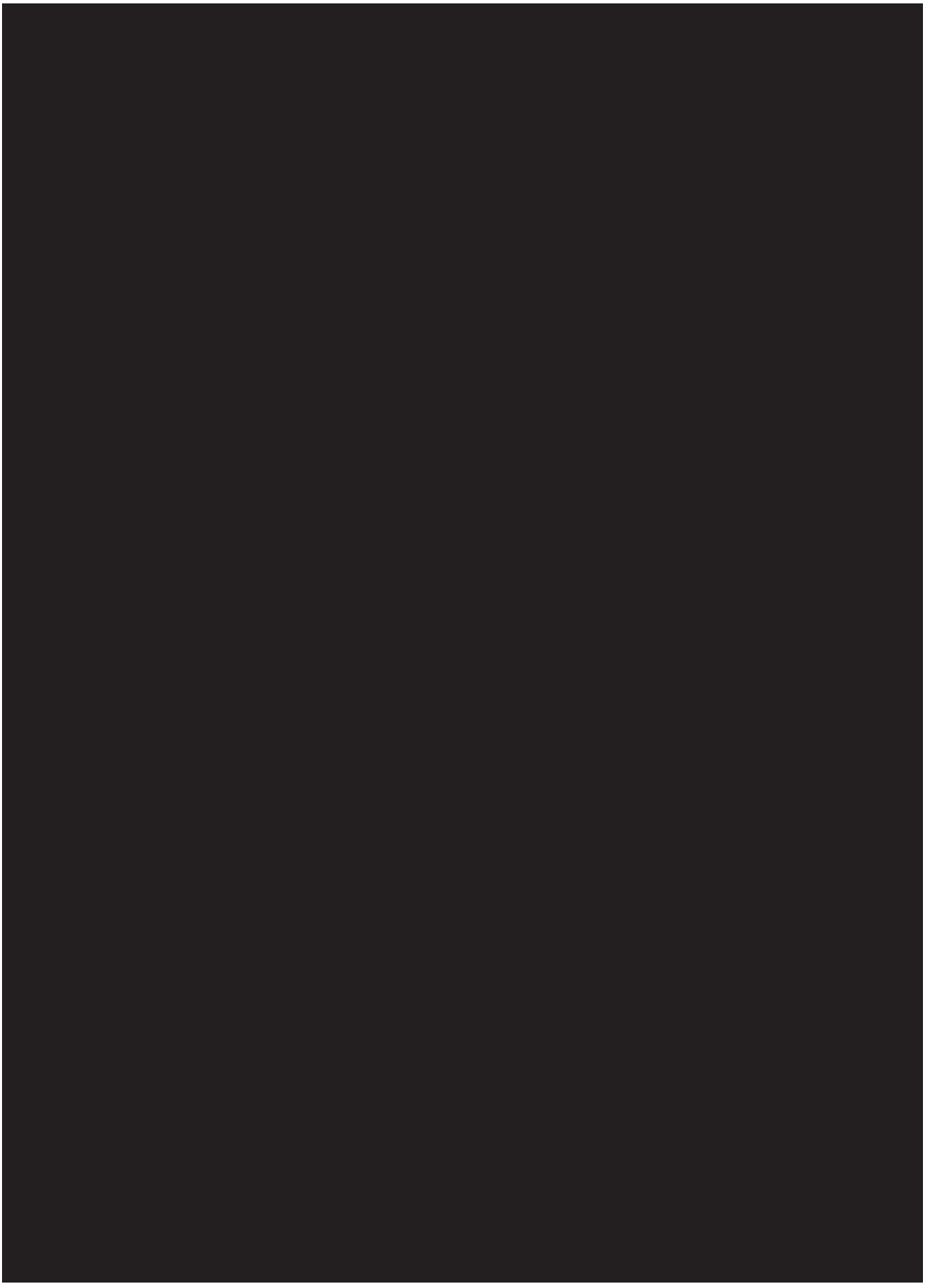

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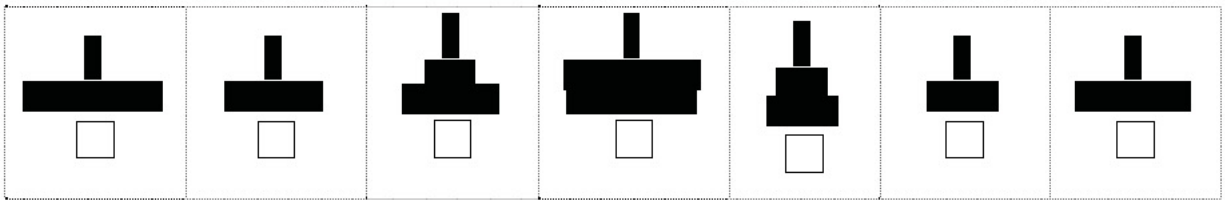

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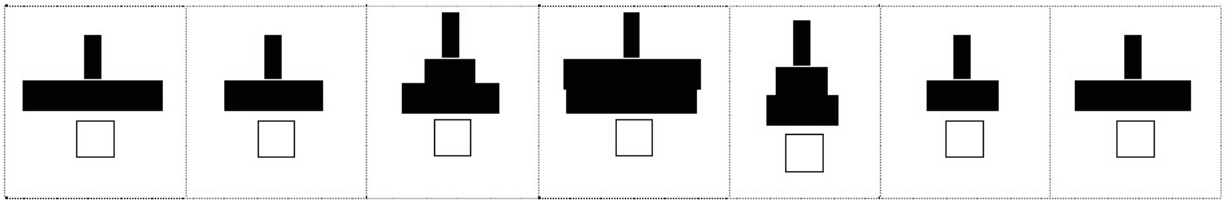

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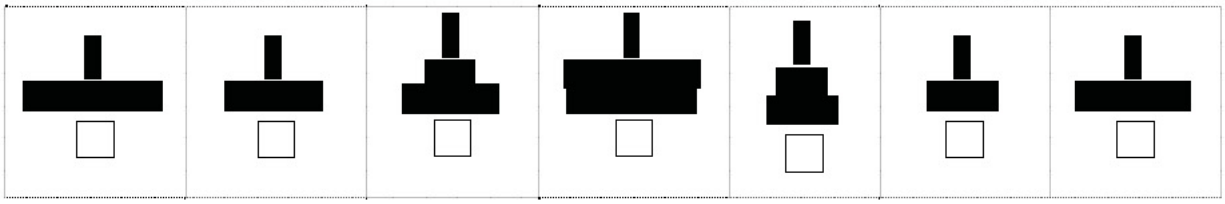

## 3. Clinical COPD Questionnaire

Patient number:_____
Date:_____

**CLINICAL COPD QUESTIONNAIRE**

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

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

**APPROVAL / SIGNATURE PAGE**

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**Document Name:** clinical-trial-protocol-version-01

**Title:** Switching COPD Patients from Spiriva® HandiHaler® maintenance therapy to Spiriva® Respimat®: a non-Interventional Real-world clinicAl ouTcome assEssment: NIS PIRATE

**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Approval-Clinical Trial Leader | [redacted] | 04 Mar 2022 15:17 CET |
| Approval-Team Member Medicine | | 04 Mar 2022 16:24 CET |
| Approval-Team Member Drug Safety | | 07 Mar 2022 16:19 CET |
| Approval-On behalf of [redacted] or [redacted] or [redacted] | | 08 Mar 2022 18:13 CET |
| Approval | | 11 Mar 2022 15:25 CET |
| Approval-Biostatistics | | 14 Mar 2022 13:45 CET |

**(Continued) Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|