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Non-interventional Study Protocol

Document Number:	**c28180323-01**
BI Study Number:	1237-0097
BI Investigational Product(s):	Re-usable Respimat® Soft Mist™ inhaler
Title:	A real-world non-interventional study to assess patient satisfaction with and preference for re-usable Respimat Soft Mist inhaler in patients with chronic obstructive pulmonary disease.
Brief lay title	Re-usable Respimat® Soft Mist™ inhaler study
Protocol version identifier:	1.0
Date of last version of protocol:	N/A
PASS:	No
EU PAS register number:	Study not registered
Active substance:	(1) Tiotropium; (2) Olodaterol; and (3) Tiotropium / Olodaterol
Medicinal product:	Re-usable (1) Spiriva® Respimat® 2.5 microgram, inhalation solution; (2) Striverdi® Respimat® 2.5 microgram, inhalation solution; and (3) Spiolto® Respimat® 2.5 microgram / 2.5 microgram, inhalation solution
Product reference:	(1) Spiriva® Respimat®: NL/H/0718/001; (2) Striverdi® Respimat®: NL/H/2498/001; and (3) Spiolto® Respimat®: NL/H/3157/001
Procedure number:	N/A
Marketing authorisation holder(s):	
Study Sponsor	
Joint PASS:	No
Research question and objectives:	The overall aim of this study is to assess patient satisfaction with inhaler attributes of the re-usable Respimat® Soft Mist™ Inhaler (SMI) in adult patients

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	with chronic obstructive pulmonary disease (COPD), including patients who are Respimat SMI-experienced and Respimat SMI-naïve. This study also aims to examine patient preference for the re-usable Respimat SMI compared to the disposable Respimat SMI in Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry. Primary Objective: The primary objective of the study is to assess patient satisfaction with the re-usable Respimat SMI, assessing the mean total score of the validated Patient Satisfaction and Preference Questionnaire (PASAPQ) at study end. Secondary Objectives: *For all patients* 1. To examine the individual domains of the PASAPQ: total performance score, total convenience score, the overall satisfaction question and the question on willingness to continue with inhaler at study end 2. To examine ease of handling of the re-usable Respimat SMI at study end *Additionally, for Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI at study entry* 3. To compare the difference in mean total PASAPQ score between baseline and study end 4. To examine patient preference for the re-usable Respimat SMI, through single question asking patients their preference for the re-usable compared to the disposable Respimat SMI at study end
Countries of study:	Up to 10 European countries using Respimat SMI to treat COPD, including but not restricted to Belgium, Denmark, Finland, Germany, Netherlands, Norway, Romania and Sweden.
Author:	
Date:	11 Jun 2019
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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
BI	Boehringer Ingelheim
CA	Competent Authority
CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FAS	Full Analysis Set
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LABA	Long-Acting Beta-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LPCO	Local Pharmaceutical Complaint Officer
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
PASAPQ	Patient Satisfaction and Preference Questionnaire
PRO	Patient Reported Outcome
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMI	Soft Mist™ Inhaler
SOC	System Organ Class
TM	Team Member
TPC	Technical Product Complaint

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3. RESPONSIBLE PARTIES

Name	Role in Study	Affiliation	Email Address
	Team Member Medical Affairs (TM MA) global		
	Team Member Epidemiology (TM Epi)		
	GPV study coordination		
	Trial Statistician (TSTAT)		
	Coordinating investigator		
	Project Oversight		
	Project		
	Evidence Strategy		
	Epidemiology		
	Senior Epidemiology Oversight		
	Biostatistician		
	Pharmacovigilance		

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Name	Role in Study	Affiliation	Email Address
	Site Strategy		

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4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Re-usable (1) Spiriva® Respimat® 2.5 microgram inhalation solution; (2) Striverdi® Respimat® 2.5 microgram inhalation solution; and (3) Spiolto® Respimat® 2.5 microgram / 2.5 microgram inhalation solution			
Name of active ingredient: (1) Tiotropium; (2) olodaterol; and (3) tiotropium/olodaterol			
Protocol date: 11 Jun 2019	**Study number:** 1237-0097	**Version/Revision:** 1.0	**Version/Revision date:** N/A
Title of study:	A real-world non-interventional study to assess patient satisfaction with and preference for re-usable Respimat Soft Mist inhaler in patients with chronic obstructive pulmonary disease.		
Rationale and background:	Inhaled medications are the mainstay of pharmacological treatment (both rescue therapy and maintenance treatment) for patients with chronic obstructive pulmonary disease (COPD). A number of inhaler devices are available, and their selection is based on patients' needs and preferences, depending on device characteristics and patient capabilities. The Respimat® Soft Mist™ inhaler (SMI) (Spiriva®, Striverdi® or Spiolto®) has been available since 2004 for the delivery of treatments to patients with COPD or asthma and has gained widespread use. While Respimat SMI was initially available as a 'disposable' inhaler that patients were only able to use for the labelled number of doses following insertion of the cartridge, feedback from patients and physicians resulted in modification of the disposable Respimat SMI to become an environmentally friendly re-usable inhaler. Studies have shown that greater treatment satisfaction is associated with improved adherence and persistence with medication; critical to improving health outcomes for patients. Therefore, as part of the post-marketing evaluation of the re-usable Respimat SMI, it is important to assess patients' satisfaction and preference for the re-usable features of the device in the real-world setting.		

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Name of active ingredient: (1) Tiotropium; (2) olodaterol; and (3) tiotropium/olodaterol			
Protocol date: 11 Jun 2019	**Study number:** 1237-0097	**Version/Revision:** 1.0	**Version/Revision date:** N/A
Study design:	A multi-centre, open-label, prospective, real-world non-interventional study will be conducted over a 6 month period on patients with COPD who receive the re-usable Respimat SMI. It will include two patient cohorts: (1) Respimat SMI-experienced, defined as patients who have been on maintenance treatment with a Respimat SMI product (Spiriva, Striverdi or Spiolto) and receive a refill prescription at study entry; and (2) Respimat SMI-naïve, defined as patients who have not previously used a Respimat SMI product and receive their first prescription at study entry. The prescription at study entry for both cohorts should be for a re-usable Respimat SMI product. The Respimat SMI-experienced patient cohort will further be divided into two subgroups: (1a) patients on maintenance treatment with a re-usable Respimat SMI at study entry; and (1b) patients on maintenance treatment with a disposable Respimat and switching to a re-usable Respimat SMI at study entry. Patients will be followed from study entry (enrolment visit) for a period of approximately 4-6 weeks (follow-up assessment, study end). The minimum pack size for the re-usable Respimat SMI is 30 days (4 weeks), after which the follow-up assessment will be conducted. An additional 2 week follow-up window has been included to account for scheduling of clinic visits and/or provision of time for the patient to complete the PASAPQ and the questions on the ease of handling of the re-usable Respimat SMI. All patients will complete the PASAPQ and ease of handling questions at the follow-up assessment (study end). Additionally, Respimat-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry will complete the PASAPQ at baseline and the individual question on patient preference for the re-usable or disposable Respimat SMI at follow-up assessment. PASAPQ, ease of handling questions and the patient preference question will be administered electronically, with the provision for administration in paper format, if required, providing the ability to be completed offsite (remotely). Safety data (serious and non-serious adverse drug reactions [ADR], adverse events [AE] with a fatal outcome and other reportable safety events) will be collected for all patients throughout the study period.		

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Name of active ingredient: (1) Tiotropium; (2) olodaterol; and (3) tiotropium/olodaterol			
Protocol date: 11 Jun 2019	**Study number:** 1237-0097	**Version/Revision:** 1.0	**Version/Revision date:** N/A
Population:	Patients aged 40 years or older with COPD residing in one of the target countries, who have been prescribed a re-usable Respimat SMI during the study period, in the course of standard clinical practice. <u>Inclusion criteria:</u> Patients fulfilling all the following inclusion criteria will be eligible for participation in the study: - Provision of signed informed consent prior to study data collection - Patient with COPD aged 40 years or older - Patient prescribed (or already receiving the disposable Respimat SMI and switched to) one of the following re-usable Respimat SMI products per the standard clinical practice: Spiriva 2.5 microgram inhalation solution; (2) Striverdi 2.5 microgram inhalation solution; and (3) Spiolto 2.5 microgram / 2.5 microgram inhalation solution - Patient unlikely to change their Respimat therapy during the observation period (in the opinion of the investigator) <u>Exclusion criteria:</u> Patients fulfilling any of the following exclusion criteria will not be eligible for participation in the study: - Patient using a disposable Respimat SMI product during the study period, after study entry - Patient who have had a severe COPD exacerbation requiring hospitalisation in the immediate 3 months prior to study entry - Patient participating in a clinical trial or any other non-interventional study of a drug or device at the time of enrolment - Visual, cognitive, motor or health impairment that, as judged by the investigator, may cause concern regarding the patient's ability to complete the questionnaires - Patient not fluent and literate in one of the main languages of the country		

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Protocol date: 11 Jun 2019	**Study number:** 1237-0097	**Version/Revision:** 1.0	**Version/Revision date:** N/A
Variables:	Exposures: The re-usable Respimat SMI administered with one of the 3 products: Spiriva 2.5 microgram inhalation solution (tiotropium), Striverdi 2.5 microgram inhalation solution (olodaterol) or Spiolto 2.5 microgram / 2.5 microgram inhalation solution (tiotropium / olodaterol). The Respimat SMI product prescribed to the patient (Spiriva, Striverdi or Spiolto) and the inhaler version (disposable or re-usable) will be recorded. Outcomes: *Primary outcome* The primary outcome of the study is the mean total PASAPQ score with re-usable Respimat SMI at study end (follow-up assessment) *Secondary outcomes* - Total performance PASAPQ score for all patients at study end (follow-up assessment) - Total convenience PASAPQ score for all patients at study end (follow-up assessment) - Overall satisfaction question for all patients at study end (follow-up assessment) - Question on willingness to continue with inhaler for all patients at study end (follow-up assessment) - Questions on ease of handling re-usable Respimat SMI for all patients at study end (follow-up assessment) - Difference in the mean total PASAPQ score between study entry (baseline visit) and study end (follow-up assessment) in the Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry - Question on preference for re-usable or disposable Respimat SMI at study end (follow-up assessment) in Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry		

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Protocol date: 11 Jun 2019	**Study number:** 1237-0097	**Version/Revision:** 1.0	**Version/Revision date:** N/A
	Covariates: - Patient demographics (e.g. age, gender, height, weight, highest level of educational attainment), at study entry - Duration of COPD, at study entry - Number of COPD exacerbations, based on medical history, in the 12 months prior to study entry and during study period - Pulmonary function (post-bronchodilator forced expiratory volume in one second [FEV_1] and forced vital capacity [FVC]), based on most recent spirometry test in the 12 months prior to study entry (if available) - COPD Assessment Test (CAT) or Modified Medical Research Council (mMRC) score, at study entry (if available) - COPD severity (grade [1-4] and patient group [A, B, C or D]), based on the 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade and group, at study entry - Respimat SMI type used during study period (disposable or re-usable) - Duration of treatment with disposable Respimat SMI (for Respimat SMI-experienced patients), at study entry (if available) - Last day of use of disposable Respimat SMI (for Respimat SMI-experienced patients), at study entry - Date of first prescription of re-usable Respimat SMI, at study entry - COPD-related and other concomitant medications, based on medical prescription history, in the 6 months prior to study entry and during the study period - Comorbidities, at study entry and during the study period - Serious and non-serious ADRs, AEs with a fatal outcome and other reportable safety events during the study period - Smoking status/history (current smokers, former smokers, and never smokers) and pack-years (for current smokers), at study entry and at study end - Details of discontinuation of the re-usable Respimat SMI during the study period (if applicable)		

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Protocol date: 11 Jun 2019	**Study number:** 1237-0097	**Version/Revision:** 1.0	**Version/Revision date:** N/A
Data sources:	Patient medical records, collected through the routine clinical care, will be used to assess the eligibility criteria of patients and to collect information on patient demographics, smoking history, COPD duration, exacerbation history, pulmonary function, the Respimat SMI prescribed and duration of treatment with Respimat SMI (in Respimat SMI-experienced patients), COPD-related concomitant medications and comorbidities, where available. If available, the CAT or mMRC score, along with the exacerbation history and the post-bronchodilator spirometry measurement, will be used to sappraise the COPD severity using the GOLD criteria. The validation question to confirm patients' use of the re-usable Respimat SMI will be asked at study end to all patients. The patients' satisfaction with the re-usable Respimat SMI (measured by the self-administered PASAPQ) and the questions on ease of handling of the re-usable Respimat SMI will be completed by all patients at study end (follow-up assessment). Additionally, for the Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry, PASAPQ will be administered at study enrolment (baseline visit) to assess the difference in the mean total PASAPQ score between study enrolment and study end. The patient preference question for the re-usable or disposable Respimat SMI will be administered at the follow-up assessment (study end) to the Respimat-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry. The safety data will be extracted from the medical records and/or collected from a telephone interview (held by the Investigator's staff) at the time of the follow-up assessment and entered into the electronic case report form (eCRF) where it will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class (SOC) and preferred term (PT).		
Study size:	It is planned that approximately 250 COPD patients (Respimat SMI-experienced and Respimat SMI-naïve) from Europe will be enrolled in this study. It is anticipated that at least half the patients will be Respimat SMI-experienced.		

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Name of active ingredient: (1) Tiotropium; (2) olodaterol; and (3) tiotropium/olodaterol			
Protocol date: 11 Jun 2019	**Study number:** 1237-0097	**Version/Revision:** 1.0	**Version/Revision date:** N/A
Data analysis:	The total PASAPQ and the domain scores (total performance score, total convenience score, overall patient satisfaction score and the rating of willingness to continue with the inhaler) will be summarised using descriptive statistics for continuous variables. The difference in the mean total PASAPQ score between baseline and study end, in Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry, will be compared using a two-tailed paired *t*-test or an appropriate non-parametric test (e.g. Wilcoxon signed ranks test), depending on the distributions of the count / score data.Responses to the questions on the ease of handling of the re-usable Respimat SMI will be summarised using descriptive statistics for categorical or continuous variables, as appropriate. Results for both primary and secondary outcomes will be presented as the total study population, Respimat SMI-experienced and Respimat SMI-naïve patients (where applicable). Additional subgroup analyses by key patient characteristics (e.g. age, GOLD patient group, type of re-usable Respimat SMI prescribed, smoking status, etc.) may be performed, provided the subgroups of interest include more than 20% of all patients. The safety data will be reported by summarising counts and frequencies of non-serious ADRs, serious ADRs, AEs with a fatal outcome, other reportable safety events, grouped by MedDRA SOC and PT.		
Milestones:	Final protocol: May 2019 Planned first patient in: August-2019 Planned last patient in: December-2019 Planned last patient out: February-2020 Planned final study report: June-2020		

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5. AMENDMENTS AND UPDATES

None.

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6. MILESTONES

Milestone	Planned Date
Final protocol	May 2019
Planned first patient in	August 2019
Planned last patient in	December 2019
Planned last patient out	February 2020
Planned final study report	June 2020

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7. RATIONALE AND BACKGROUND

Chronic obstructive pulmonary disease (COPD) is the third-leading cause of mortality worldwide and is associated with significant morbidity (Rabe and Watz 2017). The 2017 global prevalence of COPD is estimated to be 299 million cases, with a 23.8% increase in prevalence between 2007 to 2017 (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators 2018). COPD is more prevalent in the older population and in men than in women, with tobacco smoking as the main cause, particularly in high-income countries (Rabe and Watz 2017).

Inhaled medications are the mainstay of pharmacological treatment (both rescue therapy and maintenance treatment) for patients with COPD (Mirza et al. 2018). This provides efficient and targeted drug delivery to the site of action, providing increased efficacy and safety. Lower doses are required, with fewer systemic adverse effects than oral therapy (Dhand et al. 2018). An important component of treatment selection includes appropriate inhaler device selection. A number of inhaler devices are available, and selection should be based on patients' needs and preferences, depending on inhaler characteristics and patient capabilities (Dhand et al. 2018).

Since 2004, the Respimat® Soft Mist™ inhaler (SMI) has been available across many regions worldwide, for the delivery of treatments for patients with COPD or asthma and has gained widespread use (over 10 million patient-years across all products) (Dhand et al. 2019). The range of drugs and drug combinations available in Respimat SMI include Spiriva® (tiotropium; long-acting muscarinic receptor antagonist [LAMA]), Striverdi® (olodaterol; long-acting beta-agonist [LABA]), Spiolto® (tiotropium–olodaterol), Berodual® (ipratropium–fenoterol hydrobromide) and Combivent® (albuterol; short-acting beta-agonist [SABA])–ipratropium; short-acting muscarinic receptor antagonist [SAMA]). Respimat SMI is a hand-held, propellant-free inhaler that provides a slow-moving, long-lasting mist of drug for inhalation, featuring a high fine-particle fraction independent of inspiratory airflow, with optimal aerosol velocity and generation time. These features result in ease of inhalation and higher drug deposition compared to dry-powder or pressurised metered-dose inhalers (Dalby et al. 2011). To date, the Respimat SMI has been well received by patients, with high acceptance and satisfaction (Schürmann et al. 2005), largely as a result of its higher drug delivery capabilities requiring lower doses, and providing increased control of symptoms and increased therapeutic ratio (Caillaud et al. 2007).

Respimat was initially available as a 'disposable' inhaler that patients were able to use only for the labelled number of doses following insertion of the cartridge. However, feedback from patients and physicians resulted in modification of the disposable Respimat SMI into a next-generation, environmentally friendly re-usable inhaler. The enhanced features include simplified assembly and daily use, optimisation of the dose indicator, and use with up to 6

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cartridges together with an intuitive cartridge exchange mechanism, that aim to improve both the usability and environmental impact of the Respimat SMI product. At the same time, the basic functions of the inhaler, such as its unique pharmaceutical performance and reliable drug delivery are preserved (Dhand et al. 2019). A recently published study reported comparable average delivered dose and fine-particle dose between the re-usable and disposable Respimat SMI (Dhand et al. 2019). Further, in study of 65 people, which included 11 healthcare professionals and 54 patients with COPD, asthma or mixed airway disease, usability of the re-usable Respimat SMI was reported to be improved, with regard to assembly and daily use (Dhand et al. 2019). In addition, a sub-sample of patients who had previously used the disposable Respimat SMI, 81% (n=13/16) reported preferring the re-usable inhaler (Dhand et al. 2019).

Studies have shown that greater treatment satisfaction is associated with improved adherence and persistence with medication; critical to improving health outcomes for patients (Dias Barbosa et al. 2012, Chrystyn et al. 2014). In a study by Chrystyn et al., the satisfaction of 1443 patients with COPD with their inhaler, was shown to be associated with increased treatment compliance, increased health status and less frequent exacerbations (Chrystyn et al. 2014). Therefore, as part of the post-marketing evaluation of the re-usable Respimat SMI, it is important to assess patients' satisfaction and preference for the re-usable SMI features, in the real-world setting.

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8. RESEARCH QUESTION AND OBJECTIVES

The overall aim of this study is to assess patient satisfaction with the inhaler attributes of the re-usable Respimat SMI (Spiriva® 2.5 microgram inhalation solution, Striverdi® 2.5 microgram inhalation solution or Spiolto® 2.5 microgram / 2.5 microgram inhalation solution) in adult patients with COPD, including patients who are Respimat SMI-experienced and Respimat SMI-naïve (see **Section 9.1** for definitions of Respimat SMI-experienced and Respimat SMI-naïve cohorts). This study also aims to examine patient preference for the re-usable Respimat SMI compared to the disposable Respimat SMI in Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry.

8.1 STUDY OBJECTIVES

Primary Objective:

The primary objective of the study is to assess patient satisfaction with the re-usable Respimat SMI, assessing the mean total score of the validated Patient Satisfaction and Preference Questionnaire (PASAPQ) at study end.

The PASAPQ is a self-administered multi-item instrument, which includes a performance domain (7 items), a convenience domain (6 items), an overall satisfaction question (Item 14) and a question on willingness to continue with inhaler (Item 15). It has been developed and validated to measure respiratory inhalation device satisfaction and preference in patients with asthma and COPD (Kozma et al. 2005).

Secondary Objectives: The secondary objectives of the study are:

For all patients

1. To examine the individual domains of the PASAPQ: total performance score, total convenience score, the overall satisfaction question and the question on willingness to continue with inhaler at study end
2. To examine the ease of handling of the re-usable Respimat SMI at study end

Additionally, for Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI at study entry

3. To compare the difference in the mean total PASAPQ score between study entry and study end
4. To examine patient preference for the re-usable Respimat SMI, through a single question asking patients their preference for the re-usable compared to the disposable Respimat SMI at study end

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9. RESEARCH METHODS

9.1 STUDY DESIGN

A multi-centre, open-label, prospective, real-world non-interventional study over a 6 month period of patients with COPD prescribed re-usable Respimat® SMI, will be conducted.

It will include two patient cohorts: (1) Respimat SMI-experienced, defined as patients who have been on maintenance treatment with a Respimat SMI product (Spiriva®, Striverdi® or Spiolto®) and receive a refill prescription at study entry and (2) Respimat SMI-naïve, defined as patients who have not previously used a Respimat SMI product and receive their first prescription at study entry. The prescription at study entry for both cohorts should be for a re-usable Respimat SMI product.

The Respimat SMI-experienced patient cohort will further be divided into two subgroups: (1a) patients on maintenance treatment with a re-usable Respimat SMI at study entry; and (1b) patients on maintenance treatment with a disposable Respimat and switching to a re-usable Respimat SMI at study entry (**Figure 1**).

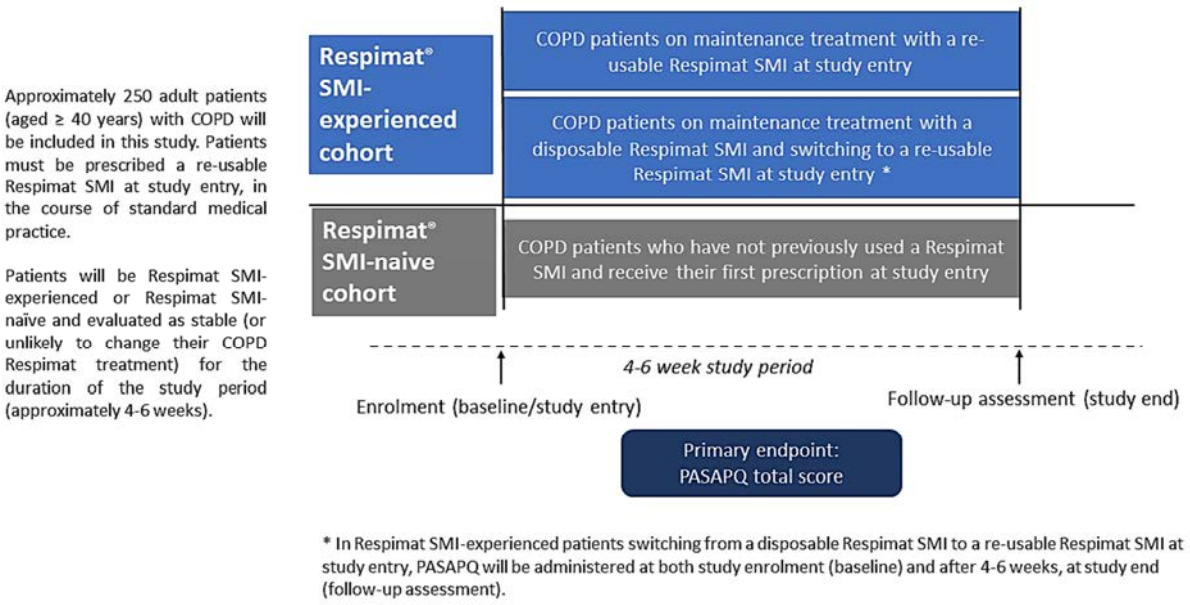
Patients will be followed from the time of study entry (enrolment visit) for a period of approximately 4-6 weeks (study period) (**Figure 1**). The minimum pack size for the re-usable Respimat SMI is 30 days (4 weeks), after which the follow-up assessment will be conducted. An additional 2 week follow-up window has been included to account for scheduling of clinic visits and/or provision of time for the patient to complete the PASAPQ and the questions on the ease of handling of the re-usable Respimat SMI.

The primary outcome is satisfaction with the re-usable Respimat SMI attributes in patients with COPD, which will be measured by the PASAPQ total score (from 13 questions) at the end of the study period (follow-up assessment, **Figure 1**) for all patients.

Secondary outcomes will include individual domains of the PASAPQ: total performance score (from 7 individual questions), total convenience score (from 6 individual questions), the overall satisfaction question and the question on willingness to continue with inhaler. The ease of handling of the re-usable Respimat SMI will also be assessed in all patients at the end of the study period. Additionally, the study will compare the PASAPQ total score at study enrolment (baseline visit) with the PASAPQ score during the follow-up assessment in the Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry; and assess patient preference for the re-usable Respimat SMI through a single question asking patients their preference for the re-usable compared to the disposable Respimat SMI (**Figure 2**).

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Safety data (serious and non-serious adverse drug reactions [ADR], adverse events [AE] with a fatal outcome and other reportable safety events) of the re-usable Respimat SMI will be collected for all patients throughout the study period.



COPD: Chronic Obstructive Pulmonary Disease; PASAPQ: Patient Satisfaction and Preference Questionnaire; SMI: Soft Mist Inhaler.

Figure 1. Study design

The study population will be identified by the participating physicians involved in the diagnosis, treatment and management of COPD patients (general practitioners and/or specialist physicians including pneumologists). Eligible patients must be prescribed and use a re-usable Respimat SMI product (as per the routine clinical practice of the participant sites). Patients will be Respimat SMI-experienced or Respimat SMI-naïve (see **Section** 9.1 for definitions of Respimat SMI-experienced and Respimat SMI-naïve cohorts) and evaluated as stable (or unlikely to change their COPD Respimat treatment) for the duration of the study period (approximately 4-6 weeks). Eligible patients will be asked to provide written informed consent prior to inclusion in the study.

Patients will be enrolled consecutively, following informed consent, and followed over the 4-6 weeks (approximately) study period. The enrolment will be competitive, i.e. the sites are free to enrol as many Respimat SMI-experienced and Respimat SMI-naïve patients as available. It is not required that all countries will have both cohorts represented at the site or at the country level. It is, however, anticipated that at least half the patients will be Respimat SMI-experienced. This will be monitored throughout patient recruitment and capped where necessary.

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Patients will be followed prospectively from the time of enrolment until the earliest of: death, loss to follow-up or end of the study period (i.e. approximately 4-6 weeks after the enrolment visit). Patients who are alive and not lost to follow-up, will have a follow-up assessment at the end of the study period (**Figure 1**).

9.2 SETTING

9.2.1 Study period

Patient enrolment will commence in August 2019 and is expected to end in December 2019 (see **Section 6** for details of study milestones). The last patient last assessment is expected in February 2020.

9.2.2 Study sites

It is planned that approximately 250 patients (Respimat SMI-experienced and Respimat SMI-naïve) from approximately 32 sites in up to 10 European countries, potentially including (but not limited to) Belgium, Denmark, Finland, Germany, Netherlands, Norway, Romania and Sweden, will be enrolled in this study. Site selection will be performed to reflect the distribution of routine COPD care in the participating countries in order to secure a representative population of COPD patients. This may include public and private hospitals and clinics, university hospitals, specialist medical centres, and community-dwelling general practitioners and specialists. Patients may be treated by general practitioners or specialist physicians, including pneumologists.

9.2.3 Study population

The study population will include patients (aged 40 and above) with COPD, who are residing in one of the target countries and follow the routine clinical practice of the participant sites (see **Section 9.2.2** for list of target countries). Patients should be prescribed a re-usable Respimat SMI product, during the study period (see **Section 9.2.1**), in the course of standard medical practice. Patients must be able to inhale the medication in a competent manner from the Respimat SMI according to the Clinical investigator's judgement, which will be recorded in the electronic case report form (eCRF) as per standard clinical practice.

Inclusion criteria:

Patients fulfilling all the following inclusion criteria will be eligible for participation in the study:

- Provision of signed informed consent prior to study data collection

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- Patient with COPD aged 40 years or older
- Patient prescribed (or already receiving the disposable Respimat SMI and switched to) 1 of the following re-usable Respimat SMI products per the standard clinical practice: Spiriva 2.5 microgram inhalation solution, Striverdi 2.5 microgram inhalation solution or Spiolto 2.5 microgram / 2.5 microgram inhalation solution
- Patient unlikely to change their Respimat therapy during the observation period (in the opinion of the investigator)

Exclusion criteria:

Patients fulfilling any of the following exclusion criteria will not be eligible for participation in the study:

- Patient using a disposable Respimat SMI product during the study period, after study entry
- Patient who have had a severe COPD exacerbation requiring hospitalisation in the immediate 3 months prior to study entry
- Patient participating in a clinical trial or any other non-interventional study of a drug or inhaler at the time of enrolment
- Visual, cognitive, motor or health impairment that, as judged by the investigator, may cause concern regarding the patient's ability to complete the questionnaires
- Patient not fluent and literate in one of the main languages of the country

Where allowed by local regulations, a patient screening log will be kept at each site, recording basic information such as age at COPD diagnosis, gender, information on the eligibility (or reasons for non-eligibility/non-enrolment, including a reason for refusal [if known]). In addition, a log of all patients included into the study (i.e. having provided informed consent) will be maintained in the Investigator Site File irrespective of whether they have completed the study or not.

9.2.4 Study visits / assessments

Patients will have two assessments: one at study enrolment (baseline visit) corresponding to their routine clinic visits for treatment of COPD, and one at end of the study period (follow-up assessment), which will occur approximately 4-6 weeks after the baseline visit. The follow-up assessment can be completed during the routine clinic visit or remotely (by telephone) if the patient does not visit the site (clinic) within 4-6 weeks of the baseline visit. No additional clinic visits or assessments are mandated or recommended for this study.

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All patients will have the PASAPQ administered at study end (follow-up assessment). The PASAPQ will be administered in electronic format, with the provision for administration in paper format, if required. For the Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry, the PASAPQ will be administered twice: (1) at study enrolment (baseline visit); and (2) at study end (follow-up assessment).

The pack size for the re-usable Respimat will cover 30 days (1 month), or 90 days (3 months), depending on the country. It is therefore anticipated that patients prescribed larger pack sizes may not return to the clinic at the time of follow-up assessment. Therefore, the PASAPQ, as well as the questions on the ease of handling of the re-usable Respimat SMI and patient preference, will be administered either electronically or mailed to patients (depending on patient preference) to be completed offsite (remotely) (see **Section 9.4.2.1**).

9.2.5 Patient withdrawal

Patients are free to discontinue or withdraw from the study at any time. Reason for discontinuation or withdrawal will be collected; however, reasons for withdrawal of consent do not have to be disclosed. Unless otherwise requested by the participant, all data obtained up to that point (i.e. before the consent withdrawal) will be retained.

9.2.6 Study discontinuation

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

- Failure to meet expected enrolment goals overall or at a particular study site
- Emergence of any efficacy/safety information that could significantly affect the continuation of the study, or any other administrative reasons, i.e. lack of recruitment
- Violation of the study protocol, or the contract by a study site or investigator, or applicable laws and regulations for non-interventional studies, which could disturb the appropriate conduct of the study

9.3 VARIABLES

This is a non-interventional study design enrolling consented patients with COPD who will be treated with a re-usable Respimat product (Spiriva, Striverdi or Spiolto), according to their approved summary of product characteristics. Patients will be enrolled consecutively and will be followed over a period of approximately 4-6 weeks (**Figure 1**). Data, as listed in **Table 1**, will be collected, where available.

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Table 1: Visit flow chart and data variables to be collected

	Study entry (Baseline)	**Follow-up assessment (4-6 weeks after baseline)**
Informed Consent	X	
Inclusion / Exclusion Criteria	X	
Patient demographics (e.g. age, gender, height, weight)	X	
Duration of COPD	X	
CAT or mMRC score (if available)	X	
Pulmonary function (based on most recent spirometry test in the 12 months prior to study entry[1]) (if available)	X	
Disease severity based on 2019 GOLD grade and group[2]	X	
Respimat® SMI product prescribed (Spiriva®, Striverdi® or Spiolto®)	X	
Duration of treatment with disposable Respimat SMI[3]	X	
Last day of use of disposable Respimat SMI[3]	X	
Date of first prescription of re-usable Respimat SMI	X	
Number of COPD exacerbations (in the 12 months prior to study entry) and during the study period	X	X
COPD-related and other concomitant medications (in the 6 months prior to study entry and during the study period[4])	X	X
Comorbidities	X	X
Smoking status / history	X	X
PASAPQ completed by the patient[5]	X	X
Respimat SMI type used during study period (disposable or re-usable)		X
Questions on the ease of handling of re-usable Respimat SMI		X
Question on Respimat SMI preference (disposable vs re-usable)[5]		X
Safety: Serious and non-serious ADRs, AEs with a fatal outcome and other reportable safety events		X
Details of discontinuation of the re-usable Respimat SMI during the study period[4] (if applicable)		X

[1] If more than one measurement is available in the 12-month period prior to study entry, the measurement closest to the study entry will be included.
[2] GOLD grade (1-4) and patient group (A, B, C or D) will be appraised based on available exacerbation history, assessment of symptoms based on CAT, and GOLD spirometry classification of airflow limitation based on post-bronchodilator spirometry results, if available (GOLD 2019).
[3] This will be assessed in Respimat SMI-experienced patients only.
[4] The study period starts with the baseline visit and ends with the follow-up assessment, which is approximately 4-6 weeks.
[5] PASAPQ at study enrolment (baseline visit) and the question on Respimat SMI preference (disposable vs re-usable) will be administered only to the Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry.

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ADR: Adverse Drug Reaction; AE: Adverse Event; CAT: COPD Assessment Test; COPD: Chronic Obstructive Lung Disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council PASAPQ: Patient Satisfaction and Preference Questionnaire; SMI: Soft Mist™ Inhaler.

9.3.1 Exposures

The exposures of interest in this study are the re-usable Respimat SMI administered with one of the 3 products: Spiriva 2.5 microgram inhalation solution (tiotropium), Striverdi 2.5 microgram inhalation solution (olodaterol) or Spiolto 2.5 microgram / 2.5 microgram inhalation solution (tiotropium / olodaterol).

In this study, all patients will follow the usual clinical practice of the participating sites and will receive their treatment (Spiriva, Striverdi or Spiolto) in a re-usable Respimat SMI after being prescribed a Respimat SMI product for the first time in the course of standard clinical practice (Respimat SMI-naïve patients) or after having been on maintenance treatment with a Respimat SMI product and receive a refill prescription at study entry (Respimat SMI-experienced patients).

The Respimat SMI product prescribed to the patient (Spiriva, Striverdi or Spiolto) and the inhaler version (disposable or re-usable) will be recorded in the eCRF.

9.3.2 Outcomes

9.3.2.1 Primary outcome

The primary outcome of the study is the mean total PASAPQ score with re-usable Respimat SMI at study end (follow-up assessment) (see **Section** 9.4.2.1 and **Table** 3 for the PASAPQ questions and scoring).

9.3.2.2 Secondary outcomes

- Total performance PASAPQ score for all patients at study end (follow-up assessment) (see **Table** 3)
- Total convenience PASAPQ score for all patients at study end (follow-up assessment) (see **Table** 3)
- Overall satisfaction question with inhaler for all patients at study end (follow-up assessment) (see **Table** 3)
- Question on willingness to continue with inhaler for all patients at study end (follow-up assessment) (see **Table** 3)
- Questions on ease of handling of the re-usable Respimat SMI for all patients at study end (follow-up assessment) (see **Table** 4)

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- Difference in the mean total PASAPQ score between study entry (baseline visit) and study end (follow-up assessment) in Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry
- Question on preference for re-usable or disposable Respimat SMI at study end (follow-up assessment) in Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry (see **Section 9.4.2.3**)

9.3.3 Covariates

The following covariates, where available, will be collected and assessed at study enrolment (baseline visit) and/or study end (follow-up assessment). See **Table 1** for the timing of data collection:

- Patient demographics (e.g. age, gender, height, weight, highest level of educational attainment)
- Duration of COPD
- Number of COPD exacerbations, based on medical history, in the 12 months prior to study entry or in the study period
- Pulmonary function (post-bronchodilator expiratory volume in one second [FEV_1] and forced vital capacity [FVC]), based on most recent spirometry test in the 12 months prior to study entry (if available)
- COPD Assessment Test (CAT) score or modified Medical Research Council (mMRC) dyspnoea scale (if available)
- COPD severity (grade [1-4] and patient group [A, B, C or D]) based on the 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade (GOLD 2019)
- Respimat SMI type used during study period (disposable or re-usable)
- Duration of treatment with Respimat SMI (for Respimat SMI-experienced patients) (if available)
- Last day of use of disposable Respimat SMI (for Respimat SMI-experienced patients)
- Date of first prescription of re-usable Respimat SMI
- COPD-related and other concomitant medications, based on medical prescription history, in the 6 months prior to study entry and during the study period
- Comorbidities such as cardiovascular diseases, malignancies (e.g. lung cancer), diabetes mellitus, musculoskeletal diseases, renal diseases, liver diseases, osteoporosis, gastroesophageal reflux, other respiratory diseases (e.g. asthma, pulmonary fibrosis, pneumonia), or mental health conditions (e.g. depression, anxiety)

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- Serious and non-serious ADRs, AEs with a fatal outcome, pregnancies and other reportable safety events (as outlined in **Section 10.2**) during the study period
- Smoking status/history (current smokers, former smokers, and never smokers) and pack-years (for current smokers)
- Details of discontinuation of the re-usable Respimat SMI during the study period (if applicable)

9.4 DATA SOURCES

9.4.1 Demographic and clinical details

Patient medical records, collected through the routine clinical care, will be used to assess the eligibility criteria of patients (see **Section 9.2.3** for the details of the study inclusion and exclusion criteria). Medical records will also be used to collect information on patient demographics, smoking history, COPD duration, exacerbation history, post-bronchodilator FEV_1, FVC, the Respimat product prescribed, COPD-related and other concomitant medications, and comorbid conditions (where available).

The GOLD criteria of COPD severity (GOLD Grade 1-4 and Stage A, B, C and D) will be appraised based on available exacerbation history, assessment of symptoms based on the CAT score or mMRC dyspnoea scale (where available) and GOLD spirometry classification of airflow limitation based on the most recent post-bronchodilator spirometry measurement, if available (GOLD 2019).

The CAT consists of 8 items, covering a wide range of disease severity. Each of the 8 items is formatted into a semantic 6-point differential scale, which makes it easy for the patients to complete the overall score ranges from 0-40 (Jones et al. 2009).

The mMRC assesses the grading of severity of breathlessness during daily activities. The scores range from 0-4, with a score of 0 representing 'I only get breathless with strenuous exercise' and a score of 4 representing 'I am too breathless to leave the house or I am breathless when dressing or undressing' (Fletcher 1960).

9.4.1.1 Validation of receipt of re-usable Respimat SMI Question

The re-usable Respimat SMI can be differentiated from the disposable Respimat SMI through the position of the dose indicator. In the re-usable Respimat SMI the dose indicator is attached to the base of the cartridge and in the disposable Respimat SMI, the dose indicator is located on the side of the inhaler. Patients will be advised to contact the sites if they are not dispensed a re-usable Respimat SMI product at study entry.

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Additionally, at the time of the follow-up visit, single question will be asked to all patients to confirm the re-usable version of Respimat SMI was being used during the study period (Table 2).

Table 2: Validation of receipt of re-usable Respimat SMI

Validation of receipt of re-usable Respimat SMI		**Scoring**
Type of inhaler	What type of inhaler have you been using since commencing the study?	- Re-usable inhaler - Disposable inhaler

9.4.2 Patient Reported Outcome (PRO) assessment

9.4.2.1 Patient Satisfaction and Preference Questionnaire (PASAPQ)

The patients' satisfaction with regard to the handling of the re-usable Respimat SMI will be measured by the self-administered, 15-item PASAPQ that includes a performance domain (7 items), a convenience domain (6 items), an overall satisfaction question (Item 14) and a question on willingness to continue with inhaler (Item 15). Only the questions in the performance and convenience domains count towards the total score. Questions 1-14 are answered using a 7-point ordinal scale with divisions from very dissatisfied to very satisfied; question 15 is answered using a value from 0-100, with zero indicating that the patient would not be willing to continue using the inhaler and 100 indicating that the patient would definitely be willing to continue using the inhaler (Kozma et al. 2005). The PASAPQ has been translated and validated for use in all the main languages of the study countries.

To calculate the total score, the sum of the 13 items of the two domains (performance and convenience; items 1-13) are transformed to a 0- (least) to 100- (most) point scale, with higher scores indicating greater satisfaction. Missing data in the PASAPQ is handled as follows (Miravitlles et al. 2016):

- If half or more than half of the questions in the individual domains (performance and convenience) of the PASAPQ are missing for a patient, no score is calculated and the PASAPQ domain score is marked as missing.
- If a patient answers at least half of the questions in the domain, values for missing questions will be imputed using the mean of the remaining, non-missing questions in that domain.

The PASAPQ will be administered to all patients (Respimat SMI-experienced and Respimat SMI-naïve) at the follow-up assessment. Additionally, for the Respimat SMI-experienced

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patients switching from a disposable to a re-usable Respimat SMI product at study entry, PASAPQ will be administered at the baseline visit (see **Figure 2**).

The PASAPQ will be administered in electronic format, with the provision for administration in paper format, if required. The electronic questionnaire will be designed using a mobile-first approach. The patients will receive a link to the PASAPQ via email, which they can complete using their hand-held electronic devices (such as smartphone, iPad or tablet), laptop or desktop computer. The link will be provided as follows:

- At baseline visit (study entry): to the Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry – the link will be valid for up to 3 days after the baseline visit.
- At study end (i.e. 4 weeks after the baseline visit): to all patients (Respimat SMI-experienced and Respimat SMI-naïve) – the link be valid for up to 2 weeks after study end.

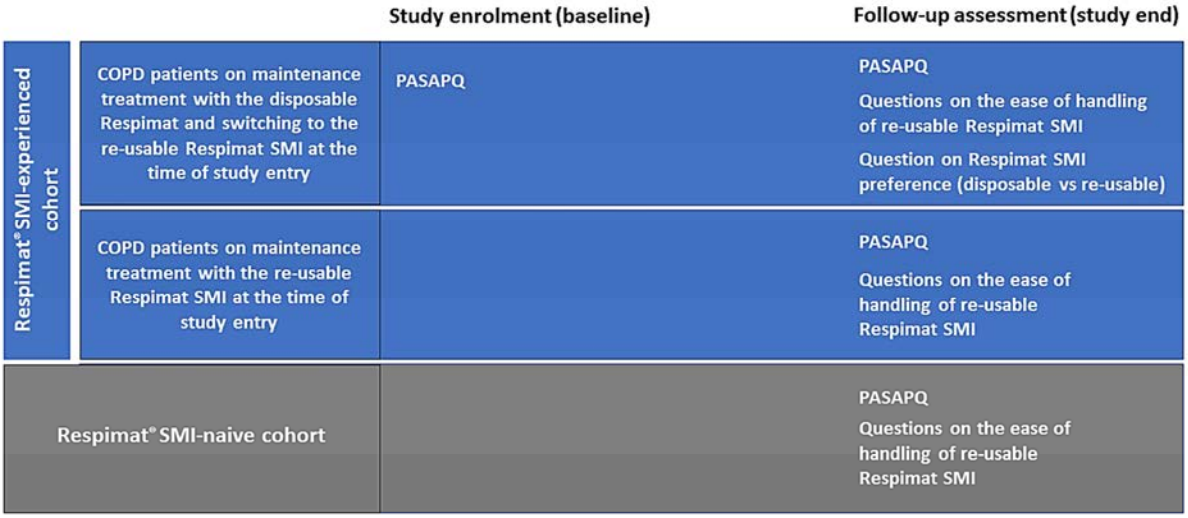
Patients unable to complete the PASAPQ electronically may be provided with a paper version of the PASAPQ at study enrolment (baseline visit), if applicable. It can also be mailed (with a pre-paid return envelope) to patients to be completed up to 2 weeks after study completion (follow-up assessment).

Table 3: PASAPQ questions and scoring

	Domain	Question	Scoring
Total Score	**Performance**	Q1: Overall feeling of inhaling your medicine	Items scored on a 7-point Likert scale: 1 = Very dissatisfied 2 = Dissatisfied 3 = Somewhat dissatisfied 4 = Neither satisfied nor dissatisfied 5 = Somewhat satisfied 6 = Satisfied 7 = Very satisfied
		Q2: Inhaled dose goes to lungs	
		Q3: Amount of medication left	
		Q4: Works reliably	
		Q5: Ease of inhaling a dose	
		Q10: Using the inhaler	
		Q11: Speed medicine comes out	
	Convenience	Q6: Instructions for use	
		Q7: Size of inhaler	
		Q8: Durability of inhaler	
		Q9: Ease of cleaning inhaler	
		Q12: Ease of holding during use	
		Q13: Convenience of carrying	
	Overall	Q14: Overall satisfaction with the inhaler	

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	Domain	Question	Scoring
	satisfaction question		
	Question on willingness to continue with inhaler	Q15: Willingness to continue using the inhaler that was used during the study	Score ranges from 0-100, with 0 indicating that the patient would not be willing to continue using this inhaler and 100 indicating that the patient would definitely be willing to continue



COPD: Chronic Obstructive Pulmonary Disease; PASAPQ: Patient Satisfaction and Preference Questionnaire; SMI: Soft Mist Inhaler.

Figure 2. Timing of the PRO data collection

9.4.2.2 Ease of handling questions

For all patients, the ease of handling of the re-usable Respimat SMI will be completed at the time of follow-up assessment, using a set of individual questions with answers to each question scored on a 7-point ordinal scale, with divisions from very dissatisfied to very satisfied (see **Table 4** for details).

9.4.2.3 Question on patient preference for re-usable or disposable in Respimat SMI-experienced patients

A single question will be asked only to the Respimat-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry, to determine their preference

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for the type of Respimat SMI: re-usable vs the disposable Respimat SMI (see Table 4 for details).

Table 4: Ease of handling questions and patient preference (for Respimat SMI-experienced patients switching from disposable to re-usable Respimat SMI at the time of study entry)

For all patients		**Scoring**
Ease of handling	Q1: How satisfied are you with the ease of removing the clear base?	All items scored on a 7-point Likert scale: 1 = Very dissatisfied 2 = Dissatisfied 3 = Somewhat dissatisfied 4 = Neither satisfied nor dissatisfied 5 = Somewhat satisfied 6 = Satisfied 7 = Very satisfied
	Q2: How satisfied are you with the grip of the cartridge?	
	Q3: How satisfied are you with inserting a new cartridge?	
	Q4: How satisfied are you with the readability of the dose indicator?	
	Q5: How satisfied are you with recognising when you need to replace the cartridge?	
	Q6: How satisfied are you with automatic detachment of the clear base when the cartridge is empty?	
	Q7: How satisfied are you with automatic return to the start-use position when replacing the clear base?	
	Q8: How satisfied are you with the overall ease of handling the inhaler?	
	Q9: How satisfied are you with the sustainability (eco-friendly) concept of the inhaler, due to re-use ability?	
	Q10: How satisfied are you with recognising when to replace the inhaler?	1 = Very dissatisfied 2 = Dissatisfied 3 = Somewhat dissatisfied 4 = Neither satisfied nor dissatisfied 5 = Somewhat satisfied 6 = Satisfied 7 = Very satisfied 8 = Not applicable
Only for Respimat SMI-Experienced patients switching from disposable to re-usable Respimat SMI at the time of study entry		
Rating of inhaler preference	Q1: Comparing the re-usable with disposable inhaler, please indicate which inhaler do you prefer to use?	- Re-usable inhaler - Disposable inhaler - No preference

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9.4.3 Adverse events

The safety data including serious and non-serious ADRs, AEs with a fatal outcome and other reportable safety events (see **Table 6** and **Section 10.2** for further details) will be extracted from the medical records and/or collected from a telephone interview (held by the Investigator's staff) at the time of the follow-up assessment and entered into the eCRF where it will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class (SOC) and preferred term (PT).

9.5 STUDY SIZE

The primary objective of this study is to assess patient satisfaction for the re-usable Respimat SMI, measured by the total mean score of PASAPQ. Assuming a population standard deviation (SD) of 18 points, and a 95% confidence interval (CI), a sample size of at least 50 patients will enable the estimation of a population mean total PASAPQ score within a margin of error (precision) of ±5.0 points. Assuming that 10% of patients will not have evaluable data (i.e. loss to follow-up), a total number of 56 patients is required.

To test for differences in the mean total PASAPQ score in Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry, the minimum clinically important difference for PASAPQ, which has been previously reported as 8-10 points, will be used (Hodder and Price 2009). A sample size of 56 patients will have a 90% power to detect a minimum 8-point difference in total PASAPQ score means assuming SD of differences of 18 points, using a paired t-test with a 5% two-sided significance level. To account for potential 10% of patients with no evaluable data, a total sample size of minimum 63 patients is required. If the difference in the mean total PASAPQ score is further reduced to 6 points, the sample size will increase to 107 patients, accounting for a potential 10% patients with no evaluable data at follow-up assessment. Different scenarios, depending on the desired power (80% or 90%) and mean difference of total PASAPQ score (6-, 8- and 10-point difference) and considering an 18-point SD of differences are presented in Table 5.

Table 5: Sample size scenarios for detecting difference in total PASAPQ score means

	Scenario 1	**Scenario 2**	**Scenario 3**	**Scenario 4**	**Scenario 5**	**Scenario 6**
Significance level (α)	0.05	0.05	0.05	0.05	0.05	0.05
Mean difference of total PASAPQ score	6	6	8	8	10	10
SD of differences	18	18	18	18	18	18
Power (%)	80	90	80	90	80	90
Sample size, n	**73**	**97**	**42**	**56**	**28**	**37**

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In this study, a total of 250 patients will be enrolled, which is adequate to meet the primary and the secondary outcomes of the study. Further, subgroup analyses will be performed only if the subgroups of interest include more than 20% of all patients.

9.6 DATA MANAGEMENT

A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning and validation. All data will be collected and entered directly into the electronic data capture (EDC) system.

All participating sites will have access to the data entered regarding the individual site of its own enrolled patients. All sites will be fully trained on using the online data capture system, including the eCRF completion guidelines and help files. Sites will be responsible for entering extracted patient data into a secure internet-based EDC registry database via the eCRF. For electronic patient reported outcomes (ePROs), the data entered by the patients will be directly captured into the EDC.

The 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.

High data quality standards will be maintained, and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data.

9.7 DATA ANALYSIS

A comprehensive statistical analysis plan (SAP) will be prepared before database lock. The SAP will detail the most appropriate statistical methodology and analyses to be performed in accordance with the study design and objectives.

All patients who have received at least one dose of their re-usable Respimat SMI product will be included in the analysis; this is the full analysis set (FAS). All analyses will be performed on the FAS. If a patient withdraws consent, the patient's data collected before the consent withdrawal will remain in the dataset.

Results for both primary and secondary outcomes will be presented as the total study population, Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry, Respimat SMI-experienced patients on maintenance

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therapy with a re-usable Respimat SMI product at study entry and Respimat SMI-naïve patients (where applicable and if the sufficient number of patients are available). Further details will be provided in the SAP.

Qualitative variables will be summarised by frequency counts (n) and percentages (%) of patients in each category (unless otherwise specified) and 95% CIs, when applicable. Counts of missing data will be provided in all tables for information only. Percentages will not include the missing category and are calculated over the number of patients with available (non-missing) data. Continuous variables will be summarised by descriptive statistics (mean and SD, first quartile [Q1], median, third quartile [Q3], minimum and maximum). The number of non-missing and missing observations for each variable will also be reported. Whenever applicable, two-sided 95% CIs will be calculated for the difference of means.

9.7.1 Main analysis

9.7.1.1 Primary outcome

The primary outcome is the mean total PASAPQ score at study end (follow-up assessment, 4-6 weeks after study entry), which will be summarised using descriptive statistics for continuous variables. The mean will be estimated together with a corresponding 95% CI.

9.7.1.2 Secondary outcomes

The total performance PASAPQ score, the total convenience PASAPQ score, the overall patient satisfaction score and the rating of willingness to continue with the inhaler at the follow-up assessment will be summarised using descriptive statistics for continuous variables.

Responses to the questions on the ease of handling of the re-usable Respimat SMI for all patients and patient preference for the re-usable or disposable Respimat SMI in Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry will be summarised using descriptive statistics for categorical or continuous variables, as appropriate.

The change in total PASAPQ score from baseline to the end of the study period in the Respimat SMI-experienced patients switching from a disposable to a re-usable Respimat SMI product at study entry will be analysed. The difference in the means of the total score and the performance and convenience domain scores between study entry and the follow-up assessment will be calculated along with the 95% CIs and compared using a two-tailed paired t-test or an appropriate non-parametric test (e.g. Wilcoxon signed ranks test), depending on the distributions of the count / score data.

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9.7.3 Handling of missing data

Due to the nature of the study, missing data (i.e. data that are not collected or documented in the patient medical record) may be observed for some variables. In general, missing data will not be imputed (except for dates). Partial dates will be imputed using the rules described in the SAP.

Missing data in the PASAPQ will be handled as per the rules outlined in **Section 9.4.2.1**.

9.8 QUALITY CONTROL

A study monitoring plan (Clinical Operations Plan), including for-cause monitoring, that is appropriate for the study design will be developed and implemented.

During the remote site initiation visit, the monitor will provide training on the conduct of the study to the investigator, co-investigator(s), and all site staff involved in the study. Remote Site monitoring will be performed to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study.

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

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9.9 LIMITATIONS OF THE RESEARCH METHODS

The intention of this non-interventional study (NIS) is to collect data on patient satisfaction and preference for the re-usable Respimat SMI in a real life setting in patients with COPD. However, heterogeneities in health-seeking behaviour, treatment and reporting practices between countries and sites within countries may introduce selection and information bias. Moreover, due to the real-world nature of the study and due to variabilities in efficiency and completeness of records, missing data are likely to be present and this may vary by country and/or site.

The sites selected will be a convenience sample and may not be representative of the geographic distribution or the clinic/hospital type or size in each of the participating countries. The enrolment will be competitive, although there may be capping at the country level to ensure that all countries are represented.

At the patient level, consecutive enrolment will be employed to minimise selection bias. Potential selection bias arising from the lack of complete enrolment of potentially eligible patients will be reduced by maintaining screening logs at sites. The eligibility criteria are largely non-restrictive, which will permit the enrolment of a broad COPD-patient population. The choice of treatment is at the discretion of the investigator, reflective of real-world clinical practice.

Information bias will be minimised by using standard eCRF, questionnaires and physicians' training on the study protocol. The patients' interpretation and understanding of the questionnaires and different educational backgrounds may also influence the results. Further, while the PASAPQ questionnaire has been validated (Kozma et al. 2005), the additional questions on the ease of handling of the re-usable Respimat SMI is a self-designed BI questionnaire.

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 the 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.

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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 (or reported) 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.

9.10.2.2 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/eCRFs and all source documents, including progress notes and copies of medical test results must be available at all times for review by the Sponsor's clinical study monitor, auditor and inspection by health authorities. The Clinical Research Associate/Clinical Monitor Local and the auditor may review all CRFs/eCRFs and written informed consents.

9.10.3 Completion of study

The IRB/IEC/competent authority (CA) in each participating European Union (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.

9.11 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.

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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 AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction

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

Serious adverse event (SAE)

A SAE is defined as any AE which

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

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

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for

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allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a SAE.

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.

Other Reportable Safety Events

If occurring in conjunction with an AE, other reportable safety events (defined in Table 6) should be captured in the CRF/eCRF.

Table 6: Definitions for other reportable safety events

Safety Event	**Definition**
Overdose/Under dose	The patient has taken (accidentally or intentionally) above the maximal / below the minimal recommended dose as stated in the product label / authorised product information
Drug Interaction	Includes an interaction with another drug, device, disease, food or alcohol
Exposure	Accidental exposure to BI product
Medication Error	Inappropriate use of BI product that was not intended. This may be an actual error that occurred, an error that was intercepted (near miss) or an error that could occur (potential)
Product Confusion	Type of medication error involving confusion between BI products or confusion between BI product with another manufacturer's product
Use of Product outside of Product Label / Authorised Product Information	May be intentional (e.g. off-label use, misuse or abuse), unintentional (e.g. medication error) or the intention is not known
Lack (or Loss) of Effect	BI drug was ineffective (did not work) or the expected effect was not achieved
Unexpected Therapeutic Benefit / Effect	Beneficial effect of a product aside from the use for which it has been given

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Technical Product Complaints

The term technical product complaints (TPC) refers to any indication of a product defect involving the possible failure of a product to meet any of its specifications or functionalities. TPC may have their origin in the design, materials and substances used, production, packaging, storage, or distribution of a product

10.2 COLLECTION AND REPORTING OF ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY-RELEVANT INFORMATION

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

Collection of AEs

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

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

- All serious and non-serious ADRs related to the re-usable Respimat SMI products (Spiriva, Striverdi, Spiolto)
- All AEs with a fatal outcome
- All AEs occurring in conjunction with other reportable safety events (cf **Table 6**)
- Pregnancy

All ADRs, including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterised, 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 AE. An adverse reaction, in contrast to an AE, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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Medical judgement 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 aetiologies** that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

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

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

  Of note, this criterion may not be applicable to those events where the 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

<u>Intensity of adverse event</u>

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

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Moderate: Enough discomfort to cause interference with usual activity
Severe: Incapacitating or causing inability to work or to perform usual activities

Pregnancy

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

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

Expedited reporting of AEs and drug exposure during pregnancy

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

Type of Report	Timeline
All **serious ADRs** associated with Spiriva® Respimat®, Striverdi® Respimat or Spiolto® Respimat	Immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to Spiriva Respimat, Striverdi Respimat or Spiolto Respimat	Immediately within 24 hours
All **non-serious ADRs** associated with Spiriva Respimat, Striverdi Respimat or Spiolto Respimat	7 calendar days
All **pregnancy monitoring** forms	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 AE, the investigator should provide the information requested on the appropriate eCRF pages and the NIS AE form.

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Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all AEs related to any BI drug other than the Spiriva Respimat, Striverdi Respimat or 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.

Reporting of other events

Other reportable safety events (for definitions see **Table 6**) are to be captured only if they occur in conjunction with an AE, and are documented in the eCRF as additional information regarding that AE.

Reporting of Technical Product Complaints (TPC)

In case of a potential Technical Product Complaint (TPC), please inform the Local Pharmaceutical Complaint Officer (LPCO) of the Marketing Site where the complaint was received within 24 hours and provide the necessary information. If the potential TPC also involves a reportable AE, including lack of efficacy, off-label use or if the wrong dosage was taken, the investigator must ensure that the relevant information is provided on the appropriate eCRF pages and the NIS AE form is completed and forwarded as well within the respective timelines outlined under expedited reporting.

Overview on Collection and Reporting of Safety-relevant Information

Figure 3 provides an overview of the requirements and processes described above.

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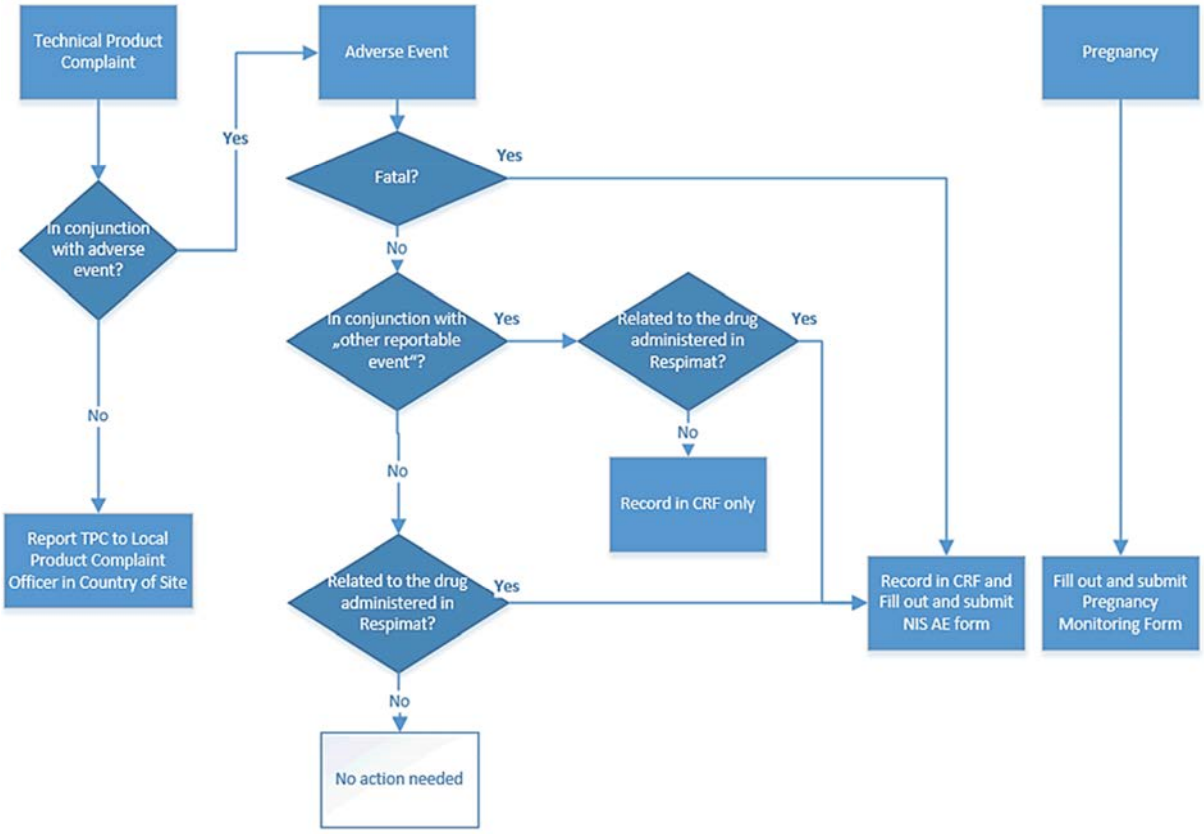


Figure 3. Collection and Reporting of Safety-Relevant Information

10.3 REPORTING TO HEALTH AUTHORITIES

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

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11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

A study specific publication plan will be developed to describe planned publications.

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12. REFERENCES

12.1 PUBLISHED REFERENCES

[1] Caillaud D, Le Merre C, Martinat Y, Aguilaniu B and Pavia D (2007). "A dose-ranging study of tiotropium delivered via Respimat Soft Mist inhaler or HandiHaler in COPD patients." Int J Chron Obstruct Pulmon Dis 2(4): 559-565.

[2] Chrystyn H, Small M, Milligan G, Higgins V, Gil EG and Estruch J (2014). "Impact of patients' satisfaction with their inhalers on treatment compliance and health status in COPD." Respir Med 108(2): 358-365.

[3] Dalby RN, Eicher J and Zierenberg B (2011). "Development of Respimat(®) Soft Mist™ inhaler and its clinical utility in respiratory disorders." Med Devices 4: 145-155.

[4] Dhand R, Cavanaugh T and Skolnik N (2018). "COPD in Primary Care: Key Considerations for Optimized Management: Considerations for Optimal Inhaler Device Selection in Chronic Obstructive Pulmonary Disease." J Fam Pract. 67(2 Suppl): S19-s27.

[5] Dhand R, Eicher J, Hansel M, Jost I, Meisenheimer M and Wachtel H (2019). "Improving usability and maintaining performance: human-factor and aerosol-performance studies evaluating the new reusable Respimat inhaler." Int J Chron Obstruct Pulmon Dis. 14: 509-523.

[6] Dias Barbosa C, Balp M-M, Kulich K, Germain N and Rofail D (2012). "Literature review to explore the link between treatment satisfaction and adherence, compliance, and persistence." Patient Prefer Adherence 6: 39-48.

[7] Fletcher CM (1960). "Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score)." Br Med J 2: 1665.

[8] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators (2018). "Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017." Lancet 392(10159): 1789-1858.

[9] GOLD (2019). "Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Pulmonary Disease (GOLD) (2019 Report)." (https://goldcoped.org/. Accessed April 10, 2019).

[10] Hodder R and Price D (2009). "Patient preferences for inhaler devices in chronic obstructive pulmonary disease: experience with Respimat Soft Mist inhaler." Int J Chron Obstruct Pulmon Dis. 4: 381-90.

[11] Jones PW, Harding G, Berry P, Wiklund I, Chen WH and Kline Leidy N (2009). "Development and first validation of the COPD Assessment Test." Eur Respir J 34(3): 648-654.

[12] Kozma CM, Slaton TL, Monz BU, Hodder R and Reese PR (2005). "Development and validation of a patient satisfaction and preference questionnaire for inhalation devices." Treat Respir Med 4(1): 41-52.

[13] Miravitlles M, Montero-Caballero J, Richard F, Santos S, Garcia-Rivero JL, Ortega F and Ribera X (2016). " A cross-sectional study to assess inhalation device handling and patient satisfaction in COPD." Int J Chron Obstruct Pulmon Dis 11: 407-415.

[14] Mirza, S., R. D. Clay, M. A. Koslow and P. D. Scanlon (2018). "COPD Guidelines: A Review of the 2018 GOLD Report." Mayo Clin Proc 93(10): 1488-1502.

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[15] Rabe KF and Watz H (2017). "Chronic obstructive pulmonary disease." Lancet 389: 1931-1940.

[16] Schürmann W, Schmidtmann S, Moroni P, Massey D and Qidan M (2005). "Respimat Soft Mist inhaler versus hydrofluoroalkane metered dose inhaler: patient preference and satisfaction." Treat Respir Med 4(1): 53-61.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

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

- Informed Consent Form
- Patient Satisfaction and Preference Questionnaire (PASAPQ)
- Statistical Analysis Plan (SAP)
- Serious Adverse Event Report in Non-Interventional Studies - (S)AE NIS Form
- Pregnancy Monitoring Form

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

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ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

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ANNEX 3. PATIENT SATISFACTION AND PREFERENCE QUESTIONNAIRE (PASAPQ) DIRECT VERSION

PART 1: RATING OF SATISFACTION WITH INHALER ATTRIBUTES

Instructions: For the following questions, please check the response that best describes how satisfied you are with each of the following items. Please take as much time as you need to answer each question.

	How satisfied are you…		Very Dissatisfied	Dissatisfied	Somewhat Dissatisfied	Neither Satisfied nor Dissatisfied	Somewhat Satisfied	Satisfied	Very Satisfied
1.	With the overall feeling of inhaling your medicine?	Inhaler	☐	☐	☐	☐	☐	☐	☐
2.	With the feeling that the inhaled dose goes to your lungs?	Inhaler	☐	☐	☐	☐	☐	☐	☐
3.	That you can tell the amount of medication left in your inhaler?	Inhaler	☐	☐	☐	☐	☐	☐	☐
4.	That the inhaler works reliably?	Inhaler	☐	☐	☐	☐	☐	☐	☐
5.	With the ease of inhaling a dose from the inhaler?	Inhaler	☐	☐	☐	☐	☐	☐	☐
6.	With the instructions for use?	Inhaler	☐	☐	☐	☐	☐	☐	☐
7.	With the size of your inhaler?	Inhaler	☐	☐	☐	☐	☐	☐	☐
8.	That the inhaler is durable (hard wearing)?	Inhaler	☐	☐	☐	☐	☐	☐	☐

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			Very Dissatisfied	Dissatisfied	Somewhat Dissatisfied	Neither Satisfied nor Dissatisfied	Somewhat Satisfied	Satisfied	Very Satisfied
9.	With the ease of cleaning your inhaler?	Inhaler	☐	☐	☐	☐	☐	☐	☐
10.	With using the inhaler?	Inhaler	☐	☐	☐	☐	☐	☐	☐
11.	With the speed at which medicine comes out of the inhaler?	Inhaler	☐	☐	☐	☐	☐	☐	☐
12.	With the ease of holding the inhaler during use?	Inhaler	☐	☐	☐	☐	☐	☐	☐
13.	With the overall convenience of carrying the inhaler with you?	Inhaler	☐	☐	☐	☐	☐	☐	☐
14.	Overall, how satisfied are you with your inhaler?	Inhaler	☐	☐	☐	☐	☐	☐	☐

▼ ***Please go to the next page***

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PART 2: RATING OF WILLINGNESS TO CONTINUE WITH INHALER

15. How would you feel about continuing to use the inhaler?

Please indicate your willingness to continue using the inhaler that you used during the study by providing a value between 0 and 100.

0 indicates that you would not be willing to continue using this inhaler and 100 indicates that you would definitely be willing to continue.

Please write in a number in the box that is between 0 and 100.

Inhaler ☐

The box should contain a number between 0 and 100.