Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Re-usable (1) Spiriva® Respimat® 2.5 µg inhalation solution; (2) Striverdi® Respimat® 2.5 µg inhalation solution; and (3) Spiolto® Respimat® 2.5 µg/2.5 µg inhalation solution			
Name of active ingredient: (1) Tiotropium; (2) Olodaterol; and (3) Tiotropium/Olodaterol			
Report date: 22 June 2020	**Study number:** 1237-0097	**Version/Revision:** 2.0	**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. Dr. [redacted]		
Keywords:	Real-world, Chronic obstructive pulmonary disease, non-interventional study, re-usable inhaler, Respimat SMI, PASAPQ		
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.		

Research question and objectives:	The overall aim of this study was to assess patient satisfaction with inhaler attributes of the re-usable Respimat® SMI in adult patients with COPD, including patients who were Respimat SMI-experienced and Respimat SMI-naïve. This study also aimed to examine patient preference for the re-usable Respimat SMI compared to the disposable Respimat SMI in Respimat SMI-experienced patients who switched from a disposable to a re-usable Respimat SMI product at study entry. Primary Objective: The primary objective of the study was 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 who switched 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

Study design:	This was a multi-centre, open-label, prospective, real-world non-interventional study conducted on patients with COPD who received the re-usable Respimat SMI. It included two patient cohorts: (1) Respimat SMI-experienced, defined as patients who had been on maintenance treatment with a Respimat SMI product (Spiriva®, Striverdi® or Spiolto®) and had received a refill prescription at study entry and (2) Respimat SMI-naïve, defined as patients who had not previously used a Respimat SMI product and had received their first prescription at study entry. The prescription at study entry for both cohorts was for a re-usable Respimat SMI product. The Respimat SMI-experienced patient cohort was further 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 who switched to a re-usable Respimat SMI at study entry. Patients were followed from the time of study entry (enrolment visit) for a period of approximately 4-6 weeks (study period). The minimum pack size for the re-usable Respimat SMI was 30 days (4 weeks), after which the follow-up assessment was conducted. An additional 2-week follow-up window was included to account for scheduling of clinic visits and/or provision of time for the patient to complete the questionnaires. All patients completed the PASAPQ and Ease of handling questionnaire at the follow-up assessment (study end). Additionally, Respimat experienced patients who switched from a disposable to a re-usable Respimat SMI product at study entry completed the PASAPQ at baseline and the single question on patient Preference for the re-usable or disposable Respimat SMI at the follow-up assessment. The PASAPQ, Ease of handling questionnaire and the patient Preference question were 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) were collected for all patients throughout the study period.
Setting:	Planned: approximately 250 patients (Respimat SMI-experienced and Respimat SMI-naïve) Enrolled: 262 patients Number of sites: 20 overall, from 6 countries (Belgium, Denmark, Finland, Germany, Netherlands, and Norway) Site selection was performed to reflect the distribution of routine COPD care in the participating countries in order to secure a representative population of COPD patients. This included public and private hospitals and clinics, university hospitals, specialist medical centres, and community dwelling general practitioners and specialists. Patients were treated by general practitioners or specialist physicians, including pneumologists.

Subjects and study size, including dropouts:	The study population included patients with COPD aged 40 and above, who were residing in one of the target countries and were prescribed a re-usable Respimat SMI product per standard medical practice. Patients had to be able to inhale the medication from the Respimat SMI in a competent manner according to the clinical investigator's judgement. *Inclusion criteria:* Patients fulfilling all the following inclusion criteria were eligible for participation in the study: – Provision of signed informed consent prior to study data collection – Patients with COPD aged 40 years or older – Patients prescribed (naïve or already receiving a Respimat SMI product) one of the following re-usable Respimat SMI products per the standard clinical practice: Spiriva® 2.5 µg inhalation solution, Striverdi® 2.5 µg inhalation solution or Spiolto® 2.5 µg/2.5 µg inhalation solution – Patients 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 were not eligible for participation in the study: – Patients using a disposable Respimat SMI product during the study period, after study entry – Patients who had a severe COPD exacerbation requiring hospitalisation in the immediate 3 months prior to study entry – Patients 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 – Patients not fluent and literate in one of the main languages of the country *Sample size:* The primary objective of this study was to assess patient satisfaction for the re-usable Respimat SMI, measured by the mean Total 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 was considered to 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 would not have evaluable data (i.e. loss to follow-up), a total number of 56 patients was required. Considering the primary and secondary objectives, it was planned to enrol in the study approximately 250 COPD patients (Respimat SMI-experienced and Respimat SMI-naïve). It was anticipated that at least half the patients would be Respimat SMI-experienced. This sample size was considered adequate to meet the primary and the secondary objectives of the study.

Variables and data sources:	*Exposures*: The re-usable Respimat SMI was used with one of the 3 products: Spiriva® 2.5 µg inhalation solution (tiotropium), Striverdi® 2.5 µg inhalation solution (olodaterol) or Spiolto® 2.5 µg / 2.5 µg inhalation solution tiotropium/olodaterol). The Respimat SMI product prescribed to the patient (Spiriva®, Striverdi® or Spiolto®) and the inhaler version (disposable or re-usable) used during the study period was recorded. *Outcomes:* Primary outcome The primary outcome of the study was 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 who switched 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 who switched from a disposable to a re-usable Respimat SMI product at study entry The following covariates, where available, were collected and assessed at study enrolment (baseline visit) and/or study end (follow-up assessment): – Patient's year of birth, gender, height, weight, and highest level of education – 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 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) score or modified Medical Research Council (mMRC) dyspnoea scale score (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 – 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) – Serious and non-serious ADRs, AEs with a fatal outcome, pregnancies and other reportable safety events during the study period – Smoking status/history (current smokers, former smokers, and never smokers) and number of cigarettes per day (for former and current smokers) – Details of discontinuation of the re-usable Respimat SMI during the study period (if applicable)

Results:	Overall, 262 patients were enrolled in this study, and 259 patients were considered eligible to participate and included in the full analysis set (FAS). In the FAS, 133 patients belonged to the cohort receiving maintenance treatment with re-usable Respimat SMI at study entry, 70 patients to the cohort who had switched to a re-usable Respimat SMI at study entry (one additional patient from this cohort was excluded from the FAS as he did not use the re-usable Respimat inhaler), and 56 patients to the Respimat SMI-naïve cohort. The mean age was 68.9 years (SD: 7.86), with the highest proportion of patients (n=122; 47.1%) belonging to the ≥65 to <75 years age category. The overall sex ratio was close to 1/1 (51% of patients were male), and most (98.5%) patients were white. More than 90% of patients had reached either a high school or elementary school education level. The majority of patients reported being former smokers (n=162; 64.8%). Most patients had not experienced any previous COPD exacerbations in the 12 months prior to study entry. GOLD grades were available from medical records for 179 patients; most of these patients were either GOLD grade 2 (n=73; 40.8%) or grade 3 (n=74; 41.3%). With regards to GOLD groups, data was available for 133 patients; the highest proportion of patients belonged to group B (n=56; 42.1%). The mean number of previous COPD exacerbations was 0.6 (SD: 0.91). Overall, 158 (61.0%) patients received Spiriva® and 101 (39.0%) patients received Spiolto® at study entry. No patient received Striverdi®. The majority of patients (n= 185; 71.4%) reported having received at least one concomitant COPD related medication, and 24 (9.3%) patients had received at least one previous non-Respimat COPD related medication. Out of the 259 patients included in the FAS, 255 patients completed the PASAPQ at follow-up and reported a mean Total score of 83.3 (SD: 12.79; 95% CI 82.0, 84.6). Patients reported a mean Performance score of 83.7 (SD: 14.11; 95% CI 82.3, 85.1), and a mean Convenience score of 82.9 (SD: 12.95; 95% CI 81.5, 84.2). The mean Total, Performance and Convenience scores were of comparable magnitude across the cohorts (patients on Maintenance re-usable Respimat SMI treatment, patients switching from disposable to re-usable Respimat SMI, and patients naïve to Respimat SMI treatment). The majority of the patients (85-90%), overall and within each cohort, were Satisfied or Very satisfied with the re-usable Respimat SMI. Similarly, the vast majority of patients were willing to continue using the re-usable Respimat SMI (mean score of 87.8 out of a possible 100). Regarding the re-usable Respimat SMI attributes that were related to Ease of handling and Preference, the majority of patients (>75%) were Satisfied or Very satisfied with all the assessed attributes. In particular, the majority of patients (overall, and within each cohort) were Satisfied or Very satisfied with the overall Ease of handling the inhaler (87-95%), the

	Sustainability (eco-friendly) concept of the inhaler due to re-usability (86-89%) and Recognising when to replace the cartridge (86-87%). Among the 68 Switching patients, mean Total, Performance and Convenience PASAPQ scores increased at follow-up (from the baseline visit) but changes were below the minimal important difference (MID) of 8-10 points established for the Total score. The majority (83.8%; n=57) of the patients who had switched at study entry, reported a preference for using the re-usable inhaler over the disposable inhaler, 11.8% (n=8) patients preferred the disposable inhaler, and 4.4% (n=3) patients did not report any preference. All findings remained stable across subgroup analyses. Thirteen (5%) patients experienced an AE of COPD exacerbation, sore throat, or exacerbation of bronchiectasis (all non-serious). One patient discontinued the study treatment due to a non-serious ADR of sore throat. No serious adverse events (SAEs; fatal or non-fatal), serious ADRs or reportable safety events associated with an AE were observed in the study.
Discussion:	• Patients reported being satisfied with the re-usable Respimat SMI, as confirmed by the Total score, and the Performance and the Convenience domain scores of the PASAPQ. • The median exposure to the re-usable inhaler was 56 days for patients who were on re-usable Respimat SMI treatment and 36 days for switching or naïve patients. Slightly higher scores were observed among patients who had been on Maintenance re-usable Respimat SMI treatment for > 3 months (n=90), versus those who were on re-useable Respimat up to 3 months, switching from disposable Respimat SMI or were naïve to any Respimat SMI. • The majority (89%) of the patients were Satisfied or Very satisfied with the re-usable Respimat SMI, and most were willing to continue using it, with median and mean scores for this PASAPQ item reported as 97.5 and 87.8, out of 100. More than 90% of patients reported being Satisfied or Very satisfied with the overall Ease of handling of the re-usable Respimat SMI, showing satisfaction with the Readability of the dose indicator, the Sustainability concept, and Recognising when to replace the cartridge. • Among patients switching from disposable to re-usable Respimat SMI, 83.8% of patients reported a preference for re-usable Respimat SMI at study end. • No safety concern was identified.
Marketing Authorisation Holder(s):	[redacted]

Names and affiliations of principal investigators:	Principal Investigator: Professor [redacted] [redacted] [redacted] Germany