

Statistical Analysis Plan

1237-0097

A real-world non-interventional study to assess satisfaction with and preference for re-usable Respimat® Soft Mist™ Inhaler in patients with chronic obstructive pulmonary disease.

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1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
BMI	Body Mass Index
CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DBL	Database Lock
DBP	Diastolic Blood Pressure
DPI	Dry Powder Inhaler
DRM	Data Review Meeting
eCRF	electronic-Case Report Form
ECSC	European Coal and Steel Community
FAS	Full Analysis Set
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICF	Informed Consent Form
ICS	Inhaled Corticosteroids
LABA	Long-Acting Beta ₂ -Agonists
LAMA	Long-Acting Muscarinic Antagonists
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
Non-SAE	Non-Serious Adverse Event
PASAPQ	Patient Satisfaction and Preference Questionnaire
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RWS	Real-World Solutions
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

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SBP	Systolic Blood Pressure
SD	Standard Deviation
SMI	Soft Mist™ Inhaler
SOC	System Organ Class
TLFs	Tables, Listings and Figures
WHO-DD	World Health Organization Drug Dictionary

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2. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a comprehensive and detailed description of the strategy and statistical methodology to be employed in the analysis of this non-interventional study assessing patient satisfaction with and preference for re-usable Respimat® Soft Mist™ Inhaler (SMI) in patients with chronic obstructive pulmonary disease (COPD).

This version of the SAP is created based on the current study protocol version 1.0, dated 11 June 2019 and electronic-Case Report Forms (eCRFs) version 2.0, dated 23 July 2019. Results of the analyses described in this SAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this SAP may be included in regulatory submissions and/or manuscripts. Any unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective SAP will be clearly identified in the CSR.

The study aims to assess patient satisfaction with the inhaler attributes of the re-usable Respimat® SMI (Spiriva® 2.5 µg inhalation solution, Striverdi® 2.5 µg inhalation solution or Spiolto® 2.5 µg / 2.5 µg inhalation solution) in adult patients (aged 40 years and above) with COPD, including patients who are Respimat® SMI-experienced and Respimat® SMI-naïve. In addition, 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 will also be analysed.

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3. STUDY OBJECTIVES

3.1 Primary Objectives

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

3.2 Secondary Objectives

The secondary objectives of the study are as follows:

For all *Respimat® SMI 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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4. STUDY DESIGN

4.1 General Description

This is a multicentre, open-label, prospective, real-world non-interventional study of patients with COPD, prescribed with re-usable Respimat® SMI. Patient enrolment will commence in September 2019 and is expected to end in December 2019. The last patient last assessment is expected in February 2020 (see Section 6 of the Clinical Study Protocol [CSP] for details of study milestones).

For this study, two patient cohorts will be defined according to the prescription of a Respimat® SMI product:

- 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. This patient cohort will further be divided into two subgroups:
 - 1a) Patients on maintenance treatment with a re-usable Respimat® SMI at study entry.
 - 1b) Patients on maintenance treatment with a disposable Respimat® SMI and switching to a re-usable Respimat® SMI at study entry.
- 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 patient cohorts should be for a re-usable Respimat® SMI product.

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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) 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 switched from a disposable Respimat® SMI (Respimat® SMI-experienced patients).

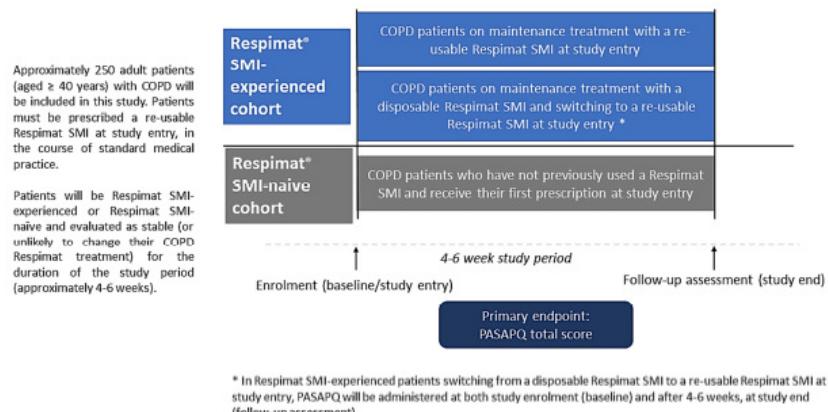
Eligible patients will be asked to provide written informed consent prior to the inclusion in the study. Each patient will be followed prospectively from the time of enrolment until the earliest of: death, loss to follow-up or end of the study period (i.e. approximately 4-6 weeks after the enrolment 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](#)). 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.

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**Figure 1 Study design**

4.2 Schedule of Events

Patients will have two assessments for data collection: one at study enrolment (baseline visit) corresponding to their routine clinic visits for treatment of COPD, and one at the 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 a 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.

All patients will have the PASAPQ administered at study end (follow-up assessment). 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). Patients unable to complete the PASAPQ

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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).

The pack size for the re-usable Respimat® SMI 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).

The study timepoints throughout the study are outlined in the visit flow chart below ([Table 1](#)).

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, highest level of educational attainment)	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

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	Study entry (Baseline)	Follow-up assessment (4-6 weeks after baseline)
COPD-related 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 patient group (A, B, C or D) will be appraised based on available exacerbation history, assessment of symptoms based on CAT, and GOLD grade (1-4) spirometry classification of airflow limitation based on post-bronchodilator spirometry results, if available (GOLD 2019 [1]).

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 disposable to re-usable Respimat® SMI at the time of study entry.

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.

4.3 Changes to Analysis from Protocol

This section summarises changes in analysis or definitions from those planned in the protocol.

The protocol history table below ([Table 2](#)) gives the timing, rationale, and key details of major changes to the statistical methods described in the protocol statistical section.

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Table 2 Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Significant Changes from Previous Authorised Version
No Changes			

5. PLANNED ANALYSES

The following analysis will be performed for this study:

- Final Analysis.

5.1 Interim Analysis

No interim analysis is currently planned for the study.

5.2 Final Analysis

The final analysis outlined in this SAP will be performed by Real-World Solutions (RWS) Biostatistics following the Database Lock (DBL). A dry-run analysis and a Data Review Meeting (DRM) will be held prior to partial DBL. The main purpose of the dry-run is the initial production of the dry-run Tables, Listings and Figures (TLFs) shells contained in the finalized SAP using whatever data presented in the current database (data that has not been cleaned). In addition, the database cannot be locked until this SAP has been approved.

6. SAMPLE SIZE CALCULATION

The primary objective of this study is to assess patient satisfaction with the re-usable Respimat® SMI, measured by the total mean score of PASAPQ. Assuming a population standard deviation

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(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 [2]. 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 the 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 3](#).

Table 3 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

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	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6
Power (%)	80	90	80	90	80	90
Sample size, n	73	97	42	56	28	37

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.

7. ANALYSIS SETS

One analysis set will be defined for this study as outlined below.

7.1 Full Analysis Set

The Full Analysis Set (FAS) will contain all enrolled subjects who met all the eligibility criteria of this study and who have received at least one dose of their re-usable Respimat® SMI product during the study period. The FAS will be the analysis set for descriptive, primary and secondary outcome analyses.

8. GENERAL CONSIDERATIONS

8.1 Enrolled Patients

All patients who provided signed Informed Consent Form (ICF) for this study.

8.2 Eligible Patients

All patients who met all the eligibility criteria of this study.

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8.3 Study Discontinuation

Patients may be discontinued from the study at any time. The following events will be considered as early termination from the study:

- Adverse Event.
- Death.
- Lost to follow-up.
- Poor compliance to protocol.
- Study terminated by sponsor.
- Withdrawal by patient.
- Other.

All data collected from patients who discontinue from the study before completion will be included in all analyses.

8.4 Baseline Visit

The routine visit, at which a patient is enrolled in the study (time of ICF signature), will be treated as the baseline (study entry) visit.

8.5 End of Study Date

End of study date will be defined as the date of the earliest of the following events:

- Discontinuation (see [Section 8.3](#)).

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- End of study period/Follow-up assessment (i.e. approximately 4-6 weeks after the baseline visit).

8.6 Study Observation Period

The study observation period will start on the date of signed ICF (study enrolment date) until the end of study date (see [Section 8.5](#)). The study duration (days) will be calculated as follows:

$$\text{Study duration (days)} = [(End \text{ of study date} - date \text{ of signed ICF}) + 1]$$

8.7 Pooling of Sites

For all analyses, all data across study sites will be pooled. The “site” factor will not be considered for subgroup analyses.

8.8 Unscheduled Visits

No unscheduled visits are defined for this study.

8.9 Software Version

All statistical analyses will be conducted using SAS® (SAS Institute, North Carolina), version 9.4.

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9. STATISTICAL CONSIDERATIONS

9.1 Statistical Tests and Confidence Intervals

Unless otherwise specified in the description of the analyses, all statistical tests will be two-sided and performed considering a significance level of 0.05. All statistical tests are exploratory due to the nature of the study, therefore no adjustment for multiplicity is considered in this SAP.

Whenever applicable, two-sided 95% CIs for proportions calculated using the exact Binomial (Clopper-Pearson) method [3] and 95% CIs of a normal distribution for means will be provided.

The normality assumption of the distributions of continuous variables will be tested using the Kolmogorov-Smirnov test (if $n \geq 50$) or Shapiro Wilk test (if $n < 50$). In addition, the visualisation of data distribution (skewness and kurtosis) may be performed using histograms/box-plot. Non-parametric tests will be used whenever the normality assumption is not accepted.

9.2 Rules for Reporting Statistics

Continuous variables will be summarised using descriptive statistics, i.e., number of non-missing and missing observations, mean, SD, first quartile (Q1), median, third quartile (Q3), minimum and maximum. Whenever applicable, two-sided 95% CIs will be calculated for the difference of means.

For reporting conventions:

- The number of non-missing and missing observations will be presented as whole numbers.

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- The minimum and maximum will be presented with the same number of decimal places as in the raw data.
- The mean, median, Q1 and Q3 will generally be displayed with one more decimal place than the raw data.
- The SD will generally be displayed with two more decimal places than the raw data. If there is only one observation (n=1), the SD will be displayed as a hyphen ("--"). If there is no observation, summary statistics will be displayed with a hyphen ("--").

Qualitative variables will be summarised by frequency counts (n) and percentages (%). Percentages will not include the missing category and are calculated over the number of patients with available (non-missing) data. Counts of missing data will be provided in the tables for information only. Wherever applicable, 95% CIs will also be presented.

For reporting conventions, percentages will be reported to one decimal place unless greater precision is deemed appropriate, except for cases when 100% is presented. In cases of a count of 0, the percentage will not be presented.

P-values will be rounded to three decimal places. P-values rounded to less than 0.001 will be reported as <0.001 in tables. P-values greater than 0.999 will be reported as >0.999.

9.3 Missing Data

Due to the nature of the study, there will likely be missing data (data that are not collected or documented in the patient medical record).

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Unless otherwise specified in this SAP, all data will be evaluated as reported and no imputation for missing values will be done, except for dates and PASAPQ data. Handling of partial dates and PASAPQ data is described in [Appendix 2](#) and [Section 20.1.2](#), respectively.

Missingness for all variables will be indicated in descriptive tables. In all listings, imputed values will not be presented, however, all variables derived based on imputed values will be flagged.

9.4 Examination of Subgroups

Subgroup analyses (in case of more than 20% of patients included in the FAS) will be conducted on primary and secondary outcomes based on the subgroups as defined below (some categories may be grouped when needed). The subgroup analyses will not be performed on any subgroup category “Missing”, “Unknown”, “None” or “Not Assessed”. All the subgroup analyses will be exploratory.

The following subgroups will be defined:

- Age:
 - ≥ 40 to < 65 years.
 - ≥ 65 to < 75 years.
 - ≥ 75 years.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD) patient group:
 - A (less symptoms / low risk).
 - B (more symptoms / low risk).
 - C (less symptoms / higher risk).
 - D (more symptoms / higher risk).

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- GOLD grade:
 - 1 (Mild).
 - 2 (Moderate).
 - 3 (Severe).
 - 4 (Very Severe).
- Smoking status:
 - Current.
 - Former.
 - Never.
- Type of re-usable Respimat® SMI product prescribed at study entry:
 - Spiriva® 2.5 µg inhalation solution.
 - Striverdi® 2.5 µg inhalation solution.
 - Spiolto® 2.5 µg / 2.5 µg inhalation solution.
- For Respimat® SMI-naïve patients, last non-Respimat® SMI maintenance product prescribed prior to study entry: refer to “Medication” column in [Table 4](#).
- For Respimat® SMI-naïve patients, last inhaler device used prior to study entry:
 - Dry powder inhaler (DPI).
 - Metered dose inhaler (MDI).

10. OUTPUT PRESENTATIONS

A separate document displays the format, layout and content of the TLFs shells to be provided by RWS Biostatistics.

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11. PATIENT DISPOSITION

The following data related to patient disposition will be summarised by patient cohort and overall:

- Number of enrolled patients.
- Number (%) of eligible patients.
 - Study duration (days) - calculated relative to date of signed ICF.
- Number (%) of non-eligible patients.
 - Reason for ineligibility: inclusion criteria not met, exclusion criteria not met.
- Number (%) of patients included in FAS.
 - By visit: Baseline visit, Follow-up assessment.
 - Re-usable Respimat® SMI product prescribed at study entry: Spiriva® 2.5 µg inhalation solution, Striverdi® 2.5 µg inhalation solution, Spiolto® 2.5 µg / 2.5 µg inhalation solution.
 - For Respimat® SMI-experienced patients, Respimat® SMI product prescribed prior to study entry: Disposable/Re-usable Spiriva® 2.5 µg inhalation solution, Disposable/Re-usable Striverdi® 2.5 µg inhalation solution, Disposable/Re-usable Spiolto® 2.5 µg / 2.5 µg inhalation solution.
 - Number (%) of patients with any non-Respimat® SMI maintenance product prescribed prior to study entry.
- Number (%) of patients who completed the study.
 - Study duration (days) - calculated relative to date of signed ICF.
- Number (%) of patients who discontinued the study.

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- Reason for study discontinuation: Adverse event, Death, Lost to follow-up, Compliance, Study terminated by sponsor, Withdrawal by patient, Other.
- Study duration (days) - calculated relative to date of signed ICF.

Derivations:

- *Study duration (days) = (End of study date – date of signed ICF + 1).*

Supportive listings for patient disposition will be provided.

12. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

12.1 Demographics

Analysis Set: FAS

Demographic characteristics will be summarised with descriptive statistics by patient cohort and overall using the information collected from the “Demographics” eCRF page. Demographic characteristics will include:

- Age (years) - calculated relative to year of signed ICF.
 - Age categories: ≥ 40 to < 65 years, ≥ 65 to < 75 years, ≥ 75 years.
- Gender: Male, Female.
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown.

- Race: American Indian or Alaska Native, Black or African American, Asian, Native Hawaiian or other Pacific Islander, White, Unknown, Not reported, Not applicable – not collected per local regulations, Other.
Note: An additional category “Mixed” will be created for patients with more than one race reported.
- Education level: Elementary school, High school, University degree.
- Years of education: No formal education, 1-9 years, 10-12 years, 13-15 years, 16 years or more.

Derivations:

- $Age \text{ (years)} = (year \text{ of signed ICF} - year \text{ of birth})$.

12.2 Disease History

Analysis Set: FAS

Disease history will be summarised with descriptive statistics by patient cohort and overall.

The date of COPD diagnosis will be collected from the “Previous COPD History and Exacerbations” eCRF page and will be used to derive age at COPD diagnosis (years) and COPD duration (years):

- Age at COPD diagnosis (years) - calculated relative to year of COPD diagnosis.
- COPD duration (years) - calculated relative to signed ICF date.

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Derivations:

- *Age at COPD diagnosis (years) = (year of COPD diagnosis – year of birth).*
- *COPD duration (years) = Integer part of [(date of signed ICF – date of COPD diagnosis) + 1] / 365.25.*

Details on conversion factors used for dates and handling of partial date of COPD diagnosis are described in [Appendix 1](#) and [Appendix 2](#), respectively.

12.3 Vital Signs

Analysis Set: FAS

Vital signs will be summarised with descriptive statistics by patient cohort and overall using the information collected from the “Vital Signs” eCRF page. Vital signs data will include the following:

- Weight (kg).
- Height (cm).
- Body mass index (BMI) [kg/m²] - calculated relative to baseline weight and height.
 - BMI categories: Underweight (<18.5 kg/m²), Normal (≥18.5 to <25.0 kg/m²), Overweight (≥25.0 to <30.0 kg/m²), Obese (≥30.0 kg/m²).
- Systolic blood pressure (SBP) [mmHg].
 - SBP categories: <120 mmHg, ≥120 to <140 mmHg, ≥140 to <160 mmHg, ≥160 mmHg.
- Diastolic blood pressure (DBP) [mmHg].

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- DBP categories: <80 mmHg, ≥ 80 to <90 mmHg, ≥ 90 to <100 mmHg, ≥ 100 mmHg.

Derivations:

- $BMI \text{ (kg/m}^2\text{)} = \text{Weight (kg)} / [\text{Height (cm)} / 100]^2$.

Height and weight measurements will be converted according to the conversion factors described in [Appendix 1](#).

12.4 COPD Symptom Severity Assessments

Analysis Set: FAS

The COPD Assessment Test (CAT), the Modified Medical Research Council Scale (mMRC) and the GOLD Classifications will be used to assess the presence and magnitude of respiratory symptoms. Data on respiratory symptoms severity will be summarised with descriptive statistics using the information collected from the “COPD Symptom Severity Assessment” eCRF page.

- CAT score.
 - CAT score categories: Low impact (≥ 0 to <10), Medium impact (≥ 10 to <20), High impact (≥ 20 to <30), and Very high impact (≥ 30 to ≤ 40).
- mMRC score: Grade 0, Grade 1, Grade 2, Grade 3, Grade 4, Unknown.
- GOLD grade: 1 (Mild), 2 (Moderate), 3 (Severe), 4 (Very Severe), Not assessed.
- Patient group: A (less symptoms / low risk), B (more symptoms / low risk), C (less symptoms / higher risk), D (more symptoms / higher risk), Not assessed.

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12.5 Spirometry

Last pre-bronchodilator and post-bronchodilator spirometry measurements available in the 12-month period prior to study entry will be summarised with descriptive statistics using the information collected from the “Post-Bronchodilator Spirometry Measurement” eCRF page. Spirometry data will include:

- Time since last available spirometry assessment (months) - calculated relative to signed ICF date.
- Forced vital capacity (FVC) (L).
- Forced expiratory volume (FEV₁) (L).
- FEV₁/FVC ratio (%).
 - FEV₁/FVC ratio (%) categories: <70%, ≥70%.
- FVC predicted (L) – calculated based on European Coal and Steel Community (ECSC) equations [\[4\]](#).
- FEV₁ predicted (L) – calculated based on ECSC equations [\[4\]](#).
- FVC predicted (%).
- FEV₁ predicted (%).

Derivations:

- *Time since last available spirometry assessment (months) = [(date of signed ICF – date of last available spirometry assessment) + 1] / 30.4375.*
- *FVC predicted (L):*

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- *Males: $FVC_{predicted}(L) = 0.0576 * (Height [cm]) - 0.026 * Age (years) - 4.34$, where $Age (years) = (year of last available spirometry assessment - year of birth)$ and $Height (cm) = Height (cm)$ collected from the “Vital Signs” eCRF page.*
- *Females: $FVC_{predicted}(L) = 0.0443 * (Height [cm]) - 0.026 * Age (years) - 2.89$, where $Age (years) = (year of last available spirometry assessment - year of birth)$ and $Height (cm) = Height (cm)$ collected from the “Vital Signs” eCRF page.*
- $FEV_1_{predicted}(L)$:
 - *Males: $FEV_1_{predicted}(L) = 0.043 * (Height [cm]) - 0.029 * Age (years) - 2.49$, where $Age (years) = (year of last available spirometry assessment - year of birth)$ and $Height (cm) = Height (cm)$ collected from the “Vital Signs” eCRF page.*
 - *Females: $FEV_1_{predicted}(L) = 0.0395 * (Height [cm]) - 0.025 * Age (years) - 2.60$, where $Age (years) = (year of last available spirometry assessment - year of birth)$ and $Height (cm) = Height (cm)$ collected from the “Vital Signs” eCRF page.*
- $FVC_{predicted} (\%) = [FVC(L) / FVC_{predicted}(L)] * 100$.
- $FEV_1_{predicted} (\%) = [FEV_1(L) / FEV_1_{predicted}(L)] * 100$.

Details on conversion factors used for dates and handling of partial date of last available spirometry assessment prior to study entry are described in [Appendix 1](#) and [Appendix 2](#), respectively.

Supportive listings for demographic and other baseline characteristics will be provided.

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13. SMOKING STATUS

Analysis Set: FAS

Smoking status at baseline and at follow-up assessment will be summarised with descriptive statistics by patient cohort and overall using the following information collected from the correspondent “Smoking Status” eCRF pages.

At Baseline Visit:

- Smoking status: Current smoker, Former smoker, Never smoked.
- Number of pack-years (one pack-year = one pack of 20 cigarettes per day for a year).
 - Number of pack-years categories: <10 pack-years, ≥ 10 pack-years.

At Follow-up Assessment:

- Any change in smoking status?: Yes, No.
- Change status: Started, Stopped.

Derivations:

- *Number of packs = (Number of cigarettes/20).*

Details on conversion factors used for number of cigarettes are described in [Appendix 1](#).

Supportive listings for smoking status at baseline and at follow-up assessment will be provided.

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14. PREVIOUS AND CONCURRENT COPD EXACERBATIONS

Analysis Set: FAS

Previous (in the 12 months prior to study entry) and concurrent COPD exacerbations (after the study entry, during the study period) will be summarised by patient cohort and overall from the “Previous/Concurrent COPD Exacerbations” and “Previous/Concurrent COPD Exacerbations Details” eCRF pages. Summaries of previous and concurrent COPD exacerbations will include:

- Any COPD exacerbation?: Yes, No.
- Number of COPD exacerbations (per patient).
 - Number of COPD exacerbations (per patient) categories: 0, 1, ≥ 2 .

Supportive listing for previous and concurrent exacerbations will be provided.

15. COMORBIDITIES

Analysis Set: FAS

Comorbidities other than COPD reported during the study period will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of DBL and will be analysed overall and by patient cohort from the “Comorbidities”/“Comorbidities Details” eCRF pages.

Comorbidities will be summarised as the number and percentage of patients by MedDRA preferred term (PT) as an event category and MedDRA primary system organ class (SOC) as a summary category. Each patient will be counted only once within a given SOC and PT.

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Comorbidities will be displayed in terms of frequency tables sorted on alphabetical order of SOC and decreasing frequency of PT within a given SOC. In case of equal frequency regarding PT, alphabetical order will be used. In case any specific comorbidity does not have MedDRA SOC coded term, it will be summarised under the “Unavailable MedDRA SOC classification” category.

A supportive listing for comorbidities will be provided.

16. PREVIOUS AND CONCOMITANT MEDICATIONS

Analysis Set: FAS

Concomitant medications are medications which started prior to the study entry (date of signed ICF) and continued during the study period, as well as those that started during the study period. Any medication without the start and end date will also be considered as concomitant. Previous medications are those medications which were started and stopped in the 6 months prior to study entry.

Previous and concomitant medications will be coded using the most current available version of World Health Organization Drug Dictionary (WHO-DD) B3 Format at the time of DBL and will be analysed overall and by patient cohort regarding COPD-related status from the “Prior & Current COPD & Non-COPD Medications”/“Prior & Current COPD & Non-COPD Medications Details” eCRF pages.

Previous and concomitant medications will be summarised as the number and percentage of patients by PT. Each patient will be counted only once within a given PT. Previous and Document: \\ .net\Enterprise\Sites\USCBG\Depts\BioStat\Boehringer\Documentation\SAP\Final

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concomitant medications will be displayed in terms of frequency tables sorted on decreasing frequency of PT. In case of equal frequency regarding PT, alphabetical order will be used.

A supportive listing for previous and concomitant medications taken previously and during the study period will be provided.

17. PREVIOUS RESPIMAT® SMI USE

Analysis Set: FAS

Information on previous Respimat® use collected on the “Prior Respimat® Use” eCRF page will be summarised for Respimat® SMI-experienced patients cohort subgroups.

For *Respimat® SMI-experienced patients on maintenance treatment with a re-usable Respimat® SMI at study entry* the following will be described:

- Re-usable Respimat® SMI product prescribed prior to study entry: Spiriva®, Striverdi®, Spiolto®.
- By overall and type of re-usable Respimat® SMI product prescribed prior to study entry:
 - Duration of re-usable Respimat® SMI product prescribed prior to study entry (days) - calculated relative to signed ICF date.

For *Respimat® SMI-experienced patients on maintenance treatment with a disposable Respimat and switching to a re-usable Respimat® SMI at study entry* the following will be described:

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- Disposable Respimat® SMI product prescribed prior to study entry: Spiriva®, Striverdi®, Spiolto®.
- By overall and type of disposable Respimat® SMI product prescribed prior to study entry:
 - Duration of disposable Respimat® SMI product prescribed prior to study entry (days) - calculated relative to date of last use of disposable Respimat® SMI product.

Derivations:

- For *Respimat® SMI-experienced patients on maintenance treatment with a re-usable Respimat® SMI at study entry:*
 - *Duration of re-usable Respimat® SMI product prescribed prior to study entry (days) = [(date of signed ICF – date of first use of re-usable Respimat® SMI) + 1].*
- For *Respimat® SMI-experienced patients on maintenance treatment with a disposable Respimat and switching to a re-usable Respimat® SMI at study entry:*
 - *Duration of disposable Respimat® SMI product prescribed prior to study entry (days) = [(date of last use of disposable Respimat® SMI – date of first use of disposable Respimat® SMI) + 1].*

Details on conversion factors used for dates and on handling of partial dates of first and last use of re-usable Respimat® SMI are described in [Appendix 1](#) and [Appendix 2](#), respectively.

Supportive listing for previous Respimat® SMI use will be provided.

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18. PREVIOUS NON-RESPIMAT® SMI MAINTENANCE PRODUCT USE

Analysis Set: FAS

Information on previous non-Respimat® maintenance product use in the 6 months prior to study entry will be collected on the “Prior & Current COPD & Non-COPD Medications”/“Prior & Current COPD & Non-COPD Medications Details” eCRF pages.

Non-Respimat® SMI maintenance product is defined as a related COPD inhaler other than Respimat® SMI products which was given for maintenance treatment. Some of non-Respimat® SMI maintenance products that will be considered in this study and the correspondent type of inhaler devices are described in [Table 4](#). Other non-Respimat® SMI maintenance products identified prior to the DBL that are not presented in [Table 4](#) will also be considered in the final analysis.

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Table 4 Non-Respimat® SMI maintenance products and type of inhaler devices

Medication	Pharmacological class	Inhaler type
Oxeze®/Oxis® Turbuhaler (formoterol)	LABA	DPI
Foradil® Aerolizer (formoterol)	LABA	DPI
Hirobriz®/Onbrez®/Oslif® Breezhaler (indacaterol)	LABA	DPI
Serevent®/Dilamax®/Ultrabeta® Diskus (salmeterol)	LABA	DPI
Atimos® (formoterol)	LABA	MDI
Serevent®/Dilamax®/Salmeterol Neolab®/Ultrabeta® (salmeterol)	LABA	MDI
Seebri®/Tovanor® Breezhaler (glycopyrronium)	LAMA	DPI
Spiriva®/Braltus®/Grgal® Handihaler (tiotropium)	LAMA	DPI
Bretaris®/Eklira® Genuair (aclidinium)	LAMA	DPI
Incruse® Ellipta (umeclidinium)	LAMA	DPI
Anoro®/Laventair® Ellipta (umeclidinium plus vilanterol)	LAMA + LABA	DPI
Brimica®/Duaklir® Genuair (aclidinium plus formoterol)	LAMA + LABA	DPI
Ultibro®/Xoterna® Breezhaler (glycopyrronium plus indacaterol)	LAMA + LABA	DPI
Bevespi® Aerosphere (glycopyrronium plus formoterol)	LAMA + LABA	MDI
Symbicort®/Assieme® Turbuhaler (budesonide plus formoterol)	ICS + LABA	DPI
DuoResp®/BiResp® Spiromax (budesonide plus formoterol)	ICS + LABA	DPI
Bufomix®/Gibiter® Easyhaler (budesonide plus formoterol)	ICS + LABA	DPI
Seretide®/Brisomax®/Maizar®/Veraspir® Diskus (fluticasone propionate plus salmeterol)	ICS + LABA	DPI
Aerivio®/Airexar® Spiromax (fluticasone propionate plus salmeterol)	ICS + LABA	DPI
AirFluSal® ForSpiro (fluticasone propionate plus salmeterol)	ICS + LABA	DPI
Breo®/Relvar®/Revinty® Ellipta (fluticasone furoate plus vilanterol)	ICS + LABA	DPI
Symbicort® Rapihaler (budesonide plus formoterol)	ICS + LABA	MDI
Flutiform® MDI (fluticasone propionate plus formoterol)	ICS + LABA	MDI
Seretide®/Serkep® MDI (fluticasone propionate plus salmeterol)	ICS + LABA	MDI
Trelegy® Ellipta (fluticasone furoate plus umeclidinium bromide plus vilanterol trifenate)	ICS+LAMA+LABA	DPI
Trimbow® (Beclometasone plus formoterol plus glycopyrronium)	ICS+LAMA+LABA	MDI

DPI: Dry powder inhaler; ICS: Inhaled corticosteroids; LABA: Long-acting beta₂-agonists; LAMA: Long-acting muscarinic antagonists; MDI: Metered dose inhaler.

The following will be summarised:

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- Non-Respimat® SMI maintenance products prescribed prior to study entry:
 - Long-acting beta₂-agonists (LABA): refer to “Medication” column in [Table 4](#) for LABA Pharmacological class.
 - Long-acting muscarinic antagonists (LAMA): refer to “Medication” column in [Table 4](#) for LAMA Pharmacological class.
 - LAMA + LABA: refer to “Medication” column in [Table 4](#) for LAMA+LABA Pharmacological class.
 - Inhaled corticosteroids (ICS) + LABA: refer to “Medication” column in [Table 4](#) for ICS+LABA Pharmacological class.
 - ICS+LAMA+LABA: refer to “Medication” column in [Table 4](#) for ICS+LAMA+LABA Pharmacological class.
- By non-Respimat® SMI maintenance products prescribed prior to study entry:
 - Duration of non-Respimat® SMI maintenance product prescribed prior to study entry (days) - calculated relative to end date.

In case of a patient reports more than one period of treatment exposure for a given maintenance product, the duration will be the sum of all the periods (excluding the time without treatment between periods).

- Inhaler device used prior to study entry (by pharmacological class and medication): DPI, MDI, Both (DPI+MDI), None.
- Last non-Respimat® SMI maintenance product prescribed prior to study entry: refer to “Medication” column in [Table 4](#), None.
- Last inhaler device used prior to study entry: DPI, MDI, None.

Derivations:

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- *Duration of non-Respimat® SMI maintenance product prescribed prior to study entry (days) = [(End date – Start date) + 1].*
- *Last non-Respimat® SMI maintenance product prescribed prior to study entry = non-Respimat® maintenance product prescribed prior to study entry where max (Start date) < date of signed ICF and End date < date of signed ICF.*
- *Last inhaler device used prior to study entry = inhaler device associated with the last non-Respimat® SMI maintenance product prescribed prior to study entry.*

Details on conversion factors used for dates and on handling of partial dates of start and end date of medications are described in [Appendix 1](#) and [Appendix 2](#), respectively.

19. RE-USABLE RESPIMAT® SMI PRESCRIPTION

Analysis Set: FAS

Re-usable Respimat® prescription data will be collected under the “Respimat® Exposure” eCRF page. The prescription at study entry of each type of re-usable Respimat® SMI product will be analysed overall and by patient cohort. The following will be described overall and for each type of re-usable Respimat® SMI product prescribed at study entry:

- Duration of use of re-usable Respimat® SMI product during the study period (days) - calculated relative to prescribed date.
- Pack type: Cartridges only, Inhaler and cartridges.
- Pack size: 30 days (1 month), 90 days (3 months).

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Additionally, at the time of the follow-up assessment, a single question will be asked to all patients to confirm the use of a re-usable version of Respimat® SMI during the study period as follows:

- What type of inhaler have you been using since commencing the study?: Re-usable inhaler, Disposable inhaler.

Derivations:

- Duration of re-usable Respimat® SMI product prescribed at study entry (days) = $[(\text{End of study date} - \text{Prescribed date}) + 1]$.

Details on conversion factors used for dates and on handling of partial dispensed date of reusable Respimat® SMI are described in [Appendix 1](#) and [Appendix 2](#), respectively.

20. OUTCOMES

20.1 Primary Outcome

The primary outcome of the study is the total PASAPQ score with re-usable Respimat® SMI at study end (follow-up assessment, 4-6 weeks after study entry). Total PASAPQ score is a measure of patient's satisfaction regarding the handling of the re-usable Respimat® SMI and will be analysed using the relevant components of the self-administered 15-item PASAPQ (see [Appendix 3](#)).

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Derivations:

Total score will be the sum of the 13 items related to performance and convenience PASAPQ domains (7 items for performance domain: Q1-5 and Q10-11 and 6 items for convenience domain: Q6-9 and Q12-13).

Each PASAPQ item has Likert-type response options ranging from 1 to 7 (1 = very dissatisfied, 2 = dissatisfied, 3 = somewhat dissatisfied, 4 = neither dissatisfied nor satisfied, 5 = somewhat satisfied, 6 = satisfied, 7 = very satisfied).

To calculate the total and domain scores, the items within each domain are first summed and then transformed to a 0 (least) to 100 (most) point scale, with higher scores indicating greater satisfaction:

- $Performance\ score = 100 * [(Q1+Q2+Q3+Q4+Q5+Q10+Q11)-7] / (49-7)$.
- $Convenience\ score = 100 * [(Q6+Q7+Q8+Q9+Q12+Q13)-6] / (42-6)$.
- $Total\ score = 100 * [(Q1+Q2+Q3+Q4+Q5+Q6+Q7+Q8+Q9+Q10+Q11+Q12+Q13)-13] / (91-13)$.

20.1.1 Analysis of Primary Outcome

Analysis Set: FAS

The primary objective of this study is to assess patient satisfaction with the re-usable Respimat® SMI measured by the total PASAPO score at study end.

The primary outcome analysis of total PASAPQ score will be performed overall and by patient cohort. All data required for the analysis of the primary outcome will be collected from the “PASAPO (ePRO)” or “PASAPO (Paper)” eCRF pages.

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Total PASAPQ score will be summarised using descriptive statistics for continuous variables. The mean total PASAPQ score will be presented together with the corresponding 95% CI.

In addition, total PASAPQ score will be categorised as follows: 0 to ≤ 20 , > 20 to ≤ 40 , > 40 to ≤ 60 , > 60 to ≤ 80 , > 80 to ≤ 100 .

20.1.2 Missing Data Methods for Primary Outcome

A patient must answer at least half of the items in the performance and convenience domains in order to calculate a score for that domain. The total score will be calculated only when both domains have computable scores and is calculated as the sum of the 13 items after substitution for missing items at the domain level has taken place.

Missing data in the PASAPQ will be handled as follows [\[5\]](#):

- If half or more than half of the items in the individual domains (performance and convenience) of the PASAPQ are missing for a patient, no score is calculated for that domain, and the PASAPQ domain score is marked as missing.
- If a patient answers at least half of the items in the domain, values for missing items will be imputed using the mean of the remaining, non-missing items in that domain. Total and domain scores will be calculated as described in [Section 20.1](#).

20.2 Secondary Outcomes

The secondary outcomes of the study are as follows:

For all *Respimat® SMI patients*, the following will be described at study end:

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- Total performance PASAPQ score (see [Appendix 3](#)).
- Total convenience PASAPQ score (see [Appendix 3](#)).
- Overall satisfaction item score (see [Appendix 3](#)).
- Question on willingness to continue with re-usable Respimat® SMI (see [Appendix 3](#)).
- Questions on ease of handling of re-usable Respimat® SMI (see [Appendix 4](#)).

For *Respimat® SMI*-experienced patients switching from a disposable to a re-usable *Respimat® SMI* at study entry the following will be assessed/described at study end:

- Difference in the mean total PASAPQ score between study entry (baseline visit) and study end (follow-up assessment).
- Question on preference for re-usable or disposable Respimat® SMI (see [Appendix 4](#)).

20.2.1 Analysis of Secondary Outcomes

20.2.1.1 Domain PASAPQ Scores and Overall Satisfaction Score

Analysis Set: FAS

One of the secondary objectives of the study is to examine the performance domain score of the PASAPQ, the convenience domain score of the PASAPQ, and the overall satisfaction score of the PASAPQ at study end.

The secondary analysis of these outcomes will be performed overall and by patient cohort. All data required for this analysis will be collected from the “PASAPQ (ePRO)” or “PASAPQ (Paper)” eCRF pages. The first 13 items will generate the performance domain (7 items: Q1-5

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and Q10-11) and the convenience domain (6 items: Q6-9 and Q12-13). Question 14 will ask for the overall satisfaction with the device used in the study.

Performance PASAPQ score and convenience PASAPQ score will be summarised using descriptive statistics for continuous variables, while the overall satisfaction score will be summarised using descriptive statistics for categorical variables.

Derivations:

For performance and convenience PASAPQ domain scores, derivations will be handled in the same way as for the primary analysis, which are described in [Section 20.1.1](#). No scoring derivation will be performed for overall satisfaction score.

20.2.1.2 Re-usable Respimat® SMI Willingness

Analysis Set: FAS

The secondary analysis to evaluate the willingness to continue with the re-usable Respimat® SMI used in the study will be performed overall and by patient cohort. It will be evaluated through Question 15 of the PASAPQ collected under the “PASAPQ (ePRO)” or “PASAPQ (Paper)” eCRF pages. This score ranges from 0 to 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 using this inhaler

Willingness to continue with the re-usable Respimat® SMI Inhaler will be summarised using descriptive statistics for continuous variables.

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20.2.1.3 Re-usable Respimat® SMI Ease of Handling

Analysis Set: FAS

The secondary analysis to evaluate the ease of handling of re-usable Respimat® SMI used in the study will be performed overall and by patient cohort.

Ease of handling will be accessed using a set of individual items with answers ranging from 1 (very dissatisfied) to 7 (very satisfied) and will be collected from the “Ease of Handling (ePRO)” or “Ease of Handling (Paper)” eCRF pages.

The following ease of handling of re-usable Respimat® SMI items will be summarised using descriptive statistics for categorical variables:

- Q1: How satisfied are you with the ease of removing the clear base?
- 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?

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- Q10: How satisfied are you with recognising when to replace the inhaler?

20.2.1.4 Total PASAPQ Score

Analysis Set: FAS

The total PASAPQ score at study entry (baseline visit) and study end (follow-up assessment) will be summarised using descriptive statistics for continuous variables for the subgroup of Respimat® SMI-experienced patients switching from a disposable to a re-usable Respimat® SMI at study entry.

The absolute change from baseline in total PASAPQ score will also be summarised at study end and will be examined using a two-tailed t-test for paired samples or an appropriate non-parametric test (e.g. Wilcoxon signed ranks test), depending on the distributions of the count/score data. The 95% CI for the difference of the means of the total PASAPQ score will also be presented.

Same analysis will be performed for performance and convenience PASAPQ scores.

Derivations:

- *Absolute change of total PASAPQ score = (Total PASAPQ score at follow-up assessment – Total PASAPQ score at baseline visit).*
- *Absolute change of performance score = (Performance score at follow-up assessment – Performance score at baseline visit).*

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- *Absolute change of convenience score = (Convenience score at follow-up assessment – Convenience score at baseline visit).*

20.2.1.5 *Respimat® SMI Preference*

Analysis Set: FAS

The secondary analysis to determine the preference for re-usable or disposable Respimat® SMI will be performed for Respimat® SMI-experienced patients switching from a disposable to a re-usable Respimat® SMI at study entry.

The preference for the disposable or re-usable Respimat® SMI will be collected by a single question collected in the “Patient Preference (ePRO)” or “Patient Preference (Paper)” eCRF pages. The following will be summarised using descriptive statistics for categorical variables:

- Q1: Comparing the re-usable with disposable inhaler, please indicate which inhaler do you prefer to use?: Re-usable inhaler, Disposable inhaler, No preference.

20.2.2 Missing Data Methods for Secondary Outcomes

For performance and convenience PASAPQ domain scores, missing data will be handled in the same way as for the primary analysis, which are described in [Section 20.1.2](#).

21. SAFETY OUTCOMES

21.1 Adverse Events

Analysis Set: FAS

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Adverse Events (AEs) reported during the study period will be coded using the latest version of MedDRA at the time of DBL and will be analysed overall and by patient cohort using the information collected under the “Adverse Event”/ “Adverse Event Details” eCRF pages.

21.1.1 All Adverse Events

An overall summary of AEs table will include the following:

- Number (%) of patients having at least one AE.
- Number (%) of patients having at least one non-serious AE (Non-SAE).
- Number (%) of patients having at least one serious adverse event (SAE).
- Number (%) of patients having at least one fatal SAE.
- Number (%) of patients having at least one non-fatal SAE.
- Number (%) of patients having at least one AE requiring treatment discontinuation.
- Number (%) of patients having at least one adverse drug reaction (ADR).
- Number (%) of patients having at least one non-serious ADR.
- Number (%) of patients having at least one serious ADR.
- Number (%) of patients having at least one ADR requiring treatment discontinuation.
- Number (%) of patients having at least one other reportable safety event associated with an AE.

In addition, all the AEs reported during the study period will be summarised as the number and percentage of patients experiencing an AE by MedDRA primary SOC as body system category and PT as an event category. If a patient has more than one occurrence of the same AE, the patient will be counted only once within each PT or SOC. Adverse events will be displayed in

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terms of frequency tables sorted on alphabetical order of SOC and decreasing frequency of PT within a given SOC. In case of equal frequency regarding PT, alphabetical order will be used. The number of AEs will also be presented. In case any AE does not have MedDRA SOC coded term, it will be summarised under the “Unavailable MedDRA SOC classification” category.

Similar tables will be created as stated above for: non-SAEs, SAEs, fatal SAEs, non-fatal SAEs, AEs requiring treatment discontinuation, ADRs, non-serious ADRs, serious ADRs and ADRs requiring treatment discontinuation.

Supportive listings will be provided.

21.1.2 Adverse Drug Reactions

An ADR is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

Adverse drug reactions are those events recorded as “Relationship to Study Treatment = Yes” on the “Adverse Events Details” eCRF page.

21.1.3 Serious Adverse Events

An SAE is any untoward medical occurrence which:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.

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- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.

SAEs are those events recorded as “Serious = Yes” on the “Adverse Events Details” eCRF page.

21.1.4 Fatal Serious Adverse Events

Fatal SAEs are those events recorded as “Outcome = Fatal” on the “Adverse Events Details” eCRF page. Otherwise, SAEs will be classified as non-fatal SAEs.

21.1.5 Non-Serious Adverse Events

Non-SAEs are those events recorded as “Serious = No” on the “Adverse Events Details” eCRF page.

21.1.6 Adverse Events Requiring Treatment Discontinuation

Adverse events requiring treatment discontinuation are those events recorded as “Action Taken with Study Treatment = Drug Withdrawn” on the “Adverse Events Details” eCRF page.

21.1.7 Other Reportable Safety Events

Analysis Set: FAS

Other Reportable Safety Events during the study period will be collected if they occur in conjunction with an AE, such as:

- Overdose/under dose.

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- Drug interaction.
- Exposure.
- Medication error.
- Product confusion.
- Use of product outside of product label/authorised product information.
- Lack (or loss) of effect.
- Unexpected therapeutic benefit/effect.

Other Reportable Safety Events associated with an AE will be documented in the “Adverse Event Details” eCRF page as additional information regarding an AE and will be analysed overall and by patient cohort.

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23. APPENDICES

23.1 APPENDIX 1. Conversion Factors

The following conversion factors will be used:

- Height:

1 in = 2.54 cm.

- Weight:

1 lb = 0.4536 kg.

- Dates:

1 week = 7 days.

1 month = 30.4375 days.

1 year = 365.25 days.

1 year = 52.18 weeks.

1 year = 12 months.

- Smoking:

20 cigarettes = 1 pack.

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23.2 APPENDIX 2. Partial Date Conventions

Partial dates will be imputed as follows:

Previous and Concomitant Medications:

Incomplete dates for previous/concomitant medications will be imputed as follows:

- If the medication start date is missing completely, then the medication date will be replaced by the signed ICF date.
- If the day of medication start date is missing, but the month and year are equal to the signed ICF date, then the medication date will be replaced by the signed ICF date.
- If both the day and month of the medication start date are missing but the year is equal to the signed ICF year, then the medication start date will be replaced by the signed ICF date.
- In all other cases, the missing medication day or missing medication month will be replaced by 1.
- Incomplete medication stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of the subject's death. In the latter case, the date of death will be used to impute the incomplete stop date.
- In all other cases, the incomplete medication stop date will not be imputed.

Disease History and Spirometry:

Incomplete dates for date of COPD diagnosis and date of last available spirometry assessment prior to study entry will be imputed as follows:

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- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the signed ICF date, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is the same as the year of the signed ICF date, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

Exposure:

Incomplete and partial dates for date of first use of re-usable Respimat® SMI prior to study entry will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the signed ICF date, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is the same as the year of the signed ICF date, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

Incomplete and partial dates for date of first use and date of last use of disposable Respimat® SMI prior to study entry will be imputed as follows:

- If the day of first use of disposable Respimat® SMI date is missing, it will be imputed to the 15th day of the month.

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- If both day and month of first use of disposable Respimat® SMI date are missing but the first use year is prior to the year of the signed ICF date, the month and day will be imputed as July 1st.
- If both day and month of first use of disposable Respimat® SMI date are missing but the first use year is equal to the year of the signed ICF date, the month and day will be imputed as January 1st.
- If the disposable Respimat® SMI first use date is completely missing, no imputation will be performed.
- Incomplete disposable Respimat® SMI last use date will be replaced by the last day of the month (if day is missing only).
- If the disposable Respimat® SMI last use date is completely missing, it will be imputed by the signed ICF date.

Incomplete and partial dates for prescribed date of re-usable Respimat® SMI at study entry will be imputed as follows:

- If the day of prescribed date of re-usable Respimat® SMI at study entry is missing, but the month and year are equal to the dispensed date, then the prescribed date will be replaced by the dispensed date.
- If both day and month of prescribed date of re-usable Respimat® SMI at study entry are missing but the prescribed year is equal to the year of the dispensed date, then the prescribed date will be replaced by the dispensed date.
- In all other cases, the missing day of the prescribed date of re-usable Respimat® SMI at study entry will be replaced by 1.

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- If the prescribed date is missing, it will be imputed by the dispensed date. If the dispensed date is missing, prescribed date will be imputed by the signed ICF date.

23.3 APPENDIX 3. PASAPQ

The patients' satisfaction with regards to 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 ([Table 5](#)). Questions 1-14 are answered using a 7-point ordinal scale with divisions from 1 = very dissatisfied to 7 = 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 [\[6\]](#). The PASAPQ has been translated and validated for use in all the main languages of the study countries.

Table 5 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	

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Domain	Question	Scoring
	Q8: Durability of inhaler Q9: Ease of cleaning inhaler Q12: Ease of holding during use Q13: Convenience of carrying	
Overall satisfaction question	Q14: Overall satisfaction with the inhaler	
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 will not be willing to continue using this inhaler and 100 indicating that the patient will definitely be willing to continue

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23.5 APPENDIX 4. Ease of Handling Questions and Patient Preference

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 1 = very dissatisfied to 7 = very satisfied.

A single question will be asked only to the Respimat® SMI-experienced patients switching from a disposable to a re-usable Respimat® SMI product at study entry, to determine their preference for the type of Respimat® SMI: re-usable vs the disposable Respimat® SMI ([Table 6](#)).

Table 6 Ease of handling questions and patient preference

For all patients		Scoring
Ease of handling	Q1: How satisfied are you with the ease of removing the clear base?	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?	

Only for Respimat® SMI-Experienced patients switching from disposable to re-usable Respimat® SMI at the

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Rating of inhaler preference	For all patients	Scoring
	time of study entry	
	Q1: Comparing the re-usable with disposable inhaler, please indicate which inhaler do you prefer to use?	<ul style="list-style-type: none"> - Re-usable inhaler - Disposable inhaler - No preference

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