STATISTICAL ANALYSIS PLAN

Final Version 2.0

18/02/2019

OTIVACTO (1237.58)	Assessment of physical functioning and handling of Spiolto® Respimat® in patients with chronic obstructive pulmonary disease (COPD) requiring long-acting dual bronchodilation in routine clinical practice

Sponsor

Boehringer Ingelheim

Document:

OTIVACTO - SAP_v 2 0_20190218

SIGNATURE SHEET

	Person responsible	Signature	Date (dd/mm/yyyy)
Prepared by:	Statistician		
Reviewed by:	Statistician 2		
	Project		
Approved by:	Global Statistician		
	Sponsor Project		

1. GENERAL INFORMATION ABOUT THE STUDY

1.1. SPONSOR IDENTIFICATION

Boehringer Ingelheim España, S.A.

C/ Prat de la Riba, 50

08174 Sant Cugat del Vallès (Barcelona)

1.2. STUDY TITLE

Assessment of physical functioning and handling of Spiolto® Respimat® in patients with chronic obstructive pulmonary disease (COPD) requiring long-acting dual bronchodilation in routine clinical practice

1.3. PROTOCOL CODE

BI study number: 1237.58

1.4. COORDINATING INVESTIGATOR/S

1.5. TYPES OF SITE WHERE THE STUDY WILL BE CONDUCTED

It is expected that data will be collected from approximately 200 sites (primary care centres) in Spain. Sites will be selected in a way that reflects routine clinical practice for COPD in order to ensure the representativeness of the population with COPD. The inclusion of 5 patients per investigator has been planned.

1.6. IEC EVALUATING THE STUDY

Badajoz IEC, in Spain

1.7. PRIMARY OBJECTIVE

The primary objective of the study is to measure changes in physical functioning - serving as a surrogate for physical activity and exercise capacity - in COPD patients being treated with Spiolto® Respimat® after approximately 6 weeks.

1.8. STUDY DESIGN

This is an observational study, since the pharmaceutical product is prescribed in accordance with routine clinical practice. The allocation of the patient to a particular therapeutic strategy is not decided in advance in the study protocol, but it will be determined by routine clinical practice and the decision to prescribe a specific medicinal product will be clearly disassociated from the decision to include the patient in the study. No other clinical intervention (or diagnosis, or clinical follow-up) which is different from routine clinical practice will be applicable in the study.

This is a self-controlled study design which will include patients with COPD who have given their consent and who will be treated with Spiolto® Respimat® in accordance with the product's authorised summary of product characteristics.

Patients will be included consecutively and follow-up will be carried out over an observation period of approximately 6 weeks.

The decision to treat with Spiolto® Respimat® will be taken independently of the participation in this NIS and will be made before participation is considered.

1.9. DISEASE(S) OR DISORDER(S) UNDER STUDY

Chronic obstructive pulmonary disease (COPD)

1.10. INFORMATION ON THE STUDY MEDICINAL PRODUCTS

Spiolto® Respimat® 2.5 micrograms/2.5 micrograms solution for inhalation; tiotropium/olodaterol

1.11. STUDY POPULATION AND TOTAL NUMBER OF SUBJECTS

COPD patients requiring a fixed combination therapy of two long-acting bronchodilators (LAMA + LABA) according to approved SmPC and GOLD guidelines. Approximately 1000 patients will be included.

1.12. STUDY SCHEDULE

The planned schedule is as follows:

Milestone	Planned date
Start of data collection (FPFV)	24/04/2017
End of data collection (LPLV)	18/09/2018 (estimated)
Final report of study results	June 2019 (estimated)

FPFV: First Patient First Visit; LPLV: Last Patient Last Visit

1.13. SOURCE OF FUNDING

Boehringer Ingelheim España, S.A.

C/ Prat de la Riba, 50

08174 Sant Cugat del Vallès (Barcelona)

1.14. DETAILS OF THE COORDINATING SITE

Tel.:

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2. GLOSSARY OF ABBREVIATIONS

The meanings of the abbreviations used in this document are explained below:

95% CI	95% confidence interval
AE	Adverse event
AR	Adverse reaction to the drug
COPD	Chronic obstructive pulmonary disease
CRA	Clinical Research Associate
CRF	Case report form
DMP	Data management plan
eCRF	Electronic case report form
FEV1	Forced expiratory volume in one second
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICH	International Conference on Harmonisation
ICF	Informed consent form
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
LABA	Long-acting $beta_2$ adrenoceptor agonist
LAMA	Long-acting muscarinic antagonist
LCM	Local Clinical Monitor
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mMRC	Modified Medical Research Council Scale
p	p-value associated with the statistical test used
P25-P75	25th percentile - 75th percentile
PASS	Power Analysis & Sample Size
PF-10	Physical Functioning patient questionnaire
PGE	Physician's Global Evaluation
SAE	Serious adverse event
SAMA	Short-acting muscarinic antagonist
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
SF-36	36-Item Short Form Health Survey

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of the study is to measure changes in physical functioning - serving as a surrogate for physical activity and exercise capacity - in COPD patients being treated with Spiolto® Respimat® after approximately 6 weeks.

3.2. SECONDARY OBJECTIVES

The secondary objectives are to assess the changes in PF-10 score from visit 1 (baseline visit at start of the study) to visit 2 (final visit, approximately 6 weeks after visit 1), the patient's general condition (physician's assessment – PGE score) at visit 1 and at visit 2, as well as patient satisfaction with Spiolto® Respimat® at visit 2.

4. STUDY POPULATION

It is expected that data will be collected from approximately 1000 patients at approximately 200 sites (primary care centres) in Spain. Sites will be selected in a way that reflects routine clinical practice for COPD in order to ensure the representativeness of the population with COPD. The inclusion of 5 patients per investigator has been planned.

A record will be kept of all patients included in the study (i.e., who have given their informed consent) in the investigating site's file, irrespective of whether they have been treated or not.

4.1. SELECTION CRITERIA

Patients who meet all the criteria listed below may be included:

4.1.1. Inclusion criteria

1. Written informed consent prior to participation
2. Female and male patients ≥ 40 years of age
3. Patients diagnosed with COPD and requiring long-acting dual bronchodilation (LAMA + LABA) treatment according to approved Spiolto® Respimat® SmPC and COPD GOLD guideline recommendation

4.1.2. Exclusion criteria

1. Patients with contraindications according to Spiolto® Respimat® SmPC
2. Patients who have been treated with a LABA/LAMA combination (free and fixed dose) in the previous 6 months
3. Patients continuing LABA-iCS treatment should not be additionally treated with Spiolto® Respimat® in order to avoid a double dosing of long-acting beta-agonists
4. Patients for whom further follow-up is not possible at the enrolling site during the planned study period of approx. 6 weeks
5. Pregnancy and lactation
6. Patients currently listed for lung transplantation
7. Current participation in any clinical trial or any other non-interventional study of a

drug or device

4.2. RATIONALE FOR SAMPLE SIZE

In a previous study, 205.426 (clinicaltrials.gov NCT 00699699: *"Assessment of Physical Activity (PF10 Sub Domain of SF-36 Activity Score) and Tolerability in COPD Patients During Treatment With Spiriva® Respimat®*)", with more than 1000 patients treated with Spiriva® Respimat®, therapeutic success (i.e., 10-point increase in the PF-10 score between visit 1 and visit 2) was achieved in 61% of patients.

In this study, a lower therapeutic success rate is expected, as patients may already be on maintenance treatment at the start. Assuming a therapeutic success rate of 50% and 900 patients, the 95% confidence interval for the therapeutic success rate would be between 46.7% (lower limit) and 53.3% (upper limit) (level of accuracy of ± 3.3%), basing the calculations on a normal approximation to the binomial distribution.

Taking into account a possible drop-out rate of 10%, the sample size is adjusted to 1000 patients.

Calculations were made using the PASS software package, version 2011.

5. METHODS

5.1. DATA PROCESSING

The data management process detailed in the Data Management Plan (DMP) for studies conducted only in electronic format, includes the coding and the definition of the filters for the validation of data during the tabulation of the data or once in tabulated form.

5.2. DATA ANALYSIS AND STATISTICAL TESTS

5.2.1. Important protocol violations

The next table defines the different categories of important protocol violations (PVs). The final column describes which PVs will be used to exclude subjects from the different patient analysis sets:

Description	Requirements	Excluded from
Entrance criteria not met		
Inclusion criterion 1 (Written informed consent prior to participation)	not met as specified in the protocol	None
Inclusion criterion 2 (Female and male patients ≥ 40 years of age)	not met as specified in the protocol	None
Inclusion criterion 3 (Patients diagnosed with COPD and requiring long-acting dual bronchodilation (LAMA + LABA) treatment according to approved Spiolto® Respimat® SmPC and COPD GOLD guideline recommendation)	not met as specified in the protocol	None
Exclusion criterion 1 (Patients with contraindications according to Spiolto® Respimat® SmPC)	met as specified in the protocol	None
Exclusion criterion 2 (Patients who have been treated with a LABA/LAMA combination (free and fixed dose) in the previous 6 months)	met as specified in the protocol	None
Exclusion criterion 3 (Patients continuing LABA-ICS treatment should not be additionally treated with Spiolto® Respimat® in order to avoid a double dosing of long-acting beta-agonists)	met as specified in the protocol	None
Exclusion criterion 4 (Patients for whom further follow-up is not possible at the enrolling site during the planned study period of approx. 6 weeks)	met as specified in the protocol	None
Exclusion criterion 5 (Pregnancy and lactation)	met as specified in the protocol	None
Exclusion criterion 6 (Patients currently listed for lung transplantation)	met as specified in the protocol	None
Exclusion criterion 7 (Current participation in any clinical trial or any other non-interventional study of a drug or device)	met as specified in the protocol	None
Informed consent		
Informed consent not available/not done	Inclusion criterion not met as specified in the protocol or informed consent date missing	All

5.2.2. Population for analysis

Three populations will be used for the analysis:

1. **All screened patients:** defined as all recruited patients with informed consent and date of registration.
2. **Treated Set (TS):** All screened patients with at least one documented administration of Spiolto® Respimat®. This population will be used in the safety endpoints, demographics/baseline, and other summary tables.
3. **Full Analysis Set (FAS):** All screened patients with at least one documented administration of Spiolto® Respimat® and available PF-10 score at visit 1 and visit 2. This population will be used in the primary and secondary tables,

5.2.3. Analysis of primary endpoint

For the primary endpoint, the proportion of patients with therapeutic success at visit 2 i.e., approximately 6 weeks (define as 10-point increase in the PF-10 score between visit 1 and visit 2) together with the 95% confidence interval will be presented.

*__PF-10__ is a sub-domain of SF-36 and consists of 10 items evaluating the scope of the restrictions experienced when carrying out routine activities. Each PF-10 item may be answered with “yes, limited a lot”, “yes, limited a little”, or “no, not limited at all”, with a score of 1, 2 or 3. The scores of the 10 items are added up, resulting in a value between 10 (a patient who answers all questions with “yes, limited a lot”) and 30 (a patient who answers all questions with “no, not limited at all”). The final sum of the individual scores will be standardised to a range of 0 to 100 using the following formula: 100x(sum-10)/20.[1]

5.2.4. Analysis of secondary endpoints

The secondary endpoints are listed below:

- Changes in PF-10 score from visit 1 to visit 2
- Patient’s general condition assessed by the physician (PGE score) at visit 1 and visit 2.
- Patient satisfaction with Spiolto® Respimat® at visit 2.

The head physician will use the Physician’s Global Evaluation (**PGE**) to assess the patient’s general condition on an 8-point ordinal scale from 1 (very poor) to 8 (excellent). The PGE will be completed before and approximately 6 weeks after the start of treatment.

A patient **satisfaction** questionnaire will also be completed during visit 2, using a 7-point ordinal scale, from 1 (very unsatisfied) to 7 (very satisfied).

5.2.5. Analysis of other endpoints

In addition, at visit 1 and/or visit 2 the following parameters will be analysed:

- Patient demographic data (age, gender, height and weight)
- Smoking history
- Reported exacerbations
- Dyspnoea based on the mMRC score at visit 1
- GOLD spirometric classification (1, 2, 3, 4)
- GOLD group of patients (A, B, C, D)
- Comorbidities
- Medication related to COPD and other concomitant medication
- Details of treatment with inhaled drugs for the airways prior to the study
- Details of treatment with inhaled drugs for the airways during the study
- Reasons for ending treatment during the observation period
- Details of treatment continuation/discontinuation
- Adverse reactions to the drug (AR and SAR), fatal AEs, pregnancies

Medical history collected during routine clinical care will be used to evaluate patient inclusion/exclusion criteria. These medical histories will be used to collect patient demographic data, smoking history, prior medications for COPD, concomitant diseases and concomitant medication.

The mMRC scale will be used to assess the status of the patient's dyspnoea before and after treatment.

GOLD group (A, B, C, D) of patients will be analyzed according:

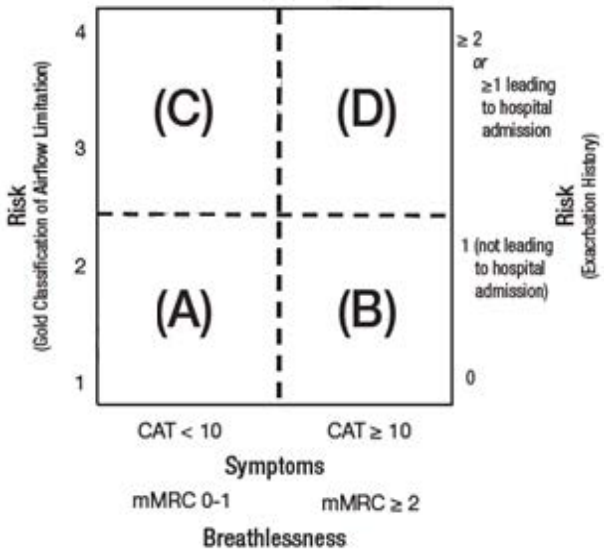
1. GOLD version 2014 – COPD degree of severity (GOLD group)[2]:

As detailed above, the CAT is recommended as a comprehensive measure of symptoms, with a CAT score ≥ 10 indicating a high level of symptoms. Comprehensive assessment of the

symptomatic impact of the disease is preferred, but in its absence mMRC scores provide an assessment of the impact of dyspnoea. It is unnecessary and possible confusing to use more than one scale.

There are three methods of assessing exacerbation risk. One is the population-base method using the GOLD spirometric classification, with GOLD 3 or GOLD 4 categories indicating high risk. The second based on the individual patient's history of exacerbations, with two or more exacerbations in the preceding year indicating high risk. The third is a history of hospitalization due to an exacerbation in the preceding year. If there is a discrepancy between these criteria, the assessment pointing to the highest risk should be used.

Figure 1. GOLD version 2014



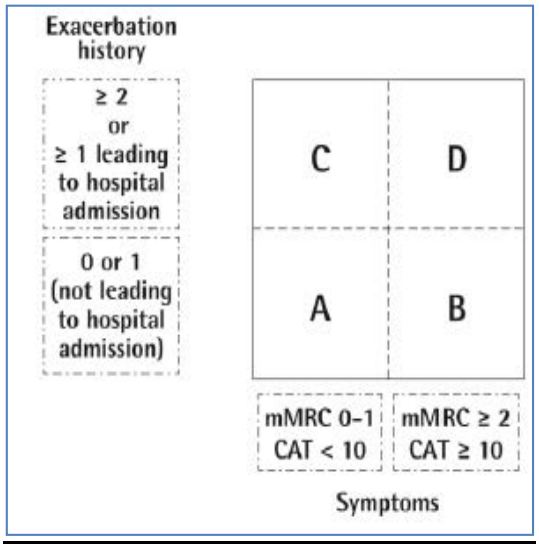
2. GOLD version 2017 – COPD degree of severity (GOLD group)[3]- Based on symptoms and exacerbations only

A refinement of the ABCD assessment tool is proposed in the 2017 GOLD Report that separates spirometric grades from the ABCD groups. ABCD groups and their associated for pharmacotherapy recommendations will be derived exclusively from patients symptoms and their history of exacerbations.

In the refined assessment scheme, patients should undergo spirometry to determine the severity of airflow limitations (i.e. spirometric grade). They should also undergo assessment of their dyspnoea using mMRC or symptoms using CAT. Finally, their history of exacerbations

(including prior hospitalizations) should be recorded. The number provides information regarding severity of airflow limitation (spirometric grade 1 to 4) while the letter (groups A to D) provides information regarding symptom burden and the risk of exacerbation which can be used to guide therapy.

Figure 2. GOLD version 2017



5.2.7. Statistical methodology

In this observational study, cross-sectional data will be collected at the start of the study and longitudinal follow-up data will be collected in the 6-week period for patients with COPD disease requiring dual bronchodilator therapy in routine clinical practice.

Baseline data will be described using a cross-sectional approach. Longitudinal follow-up data will be summarised descriptively. Due to the observational nature of this study, it is not planned to carry out (confirmatory) hypothesis testing in a strict statistical sense. Analyses are descriptive in nature and confidence intervals and p-values from statistical models will be used for exploratory purposes. No adjustments for multiple testing will be carried out in the statistical significance evaluation. Consequently, significant differences may be observed by chance along and p-values should be interpreted as exploratory and treated with caution. No formal hypothesis testing will be performed as this is a self-controlled study.

The statistical characteristics presented in the results tables will include: N (total number of valid values), mean, standard deviation (SD), 95% confidence interval of the mean (95% CI), median, 25th and 75th percentiles (P25 and P75, respectively), minimum and maximum (min and max, respectively) for continuous endpoints. The categorical endpoints will be described by their absolute and relative frequencies. The proportion rates and the 95%CIs will be provided when appropriate.

For the primary endpoint, the proportion of patients with therapeutic success at visit 2 (a 10-point increase in the PF-10 score between visit 1 and visit 2) together with the 95% confidence interval will be presented.

For the secondary endpoints:

- Changes in PF-10 score from visit 1 to visit 2
- Patient's general condition assessed by the physician (PGE score) at visit 1 and visit 2.
- Patient satisfaction with Spiolto® Respimat® at visit 2.

The patient's general condition (PGE score) at visit 1 and visit 2, the mMRC at visit 1 and patient satisfaction at visit 2 are categorical endpoints, so they will be analysed in frequency tables. The change from visit 1 to visit 2 in the PF-10 score is a continuous assessment criterion, so it will be analysed by: n (total number of valid values), mean, standard deviation (SD), 95% confidence interval of the mean (95% CI), median, 25th and 75th percentiles (P25 and P75, respectively), minimum and maximum (min and max, respectively).

Changes in the PF-10 between visit 1 and visit 2 will be analysed using a paired t-test or the non-parametric Wilcoxon Rank-Sum Test for data with non-normal distribution). Changes in the PGE between visit 1 and visit 2 will be analysed using McNemar test.

Data on safety will be reported according to local requirements. Statistical analyses and reporting of adverse reactions (ARs)/adverse events (AEs) will be descriptive in nature. The incidences of ARs and AEs will be analysed in relation to the number of treated patients.

Every effort will be made to collect complete data at the specified study visits (see DMP). Any data removed from the analysis will be documented, recording the site and the patient number, as well as the reason for the removal (see the ANNEX 1. DB DEBUGGING).

A statistical significance level of 0.05 will be applied in all the statistical tests. The evaluation will be carried out using SAS® software, version 9.4 or later.

5.2.8. Handling of missing data

In context of PF-10 questionnaire, if less than half of the items on the PF-10 for a patient are missing, the missing values will be replaced with the mean of the other values and the PF-10 score will be calculated. If half or more of the items on the PF-10 are missing, no score will be calculated and the PF-10 score will be marked as not available.

No other missing data will be imputed. If patients have missing values for any other endpoints, these patients will be excluded from the analysis of that endpoint.

6. PLANNED ANALYSIS

6.1. STUDY POPULATION

6.1.1. Recruited and assessable patients

According to the section 5.2.2, three populations will be used for the analysis: All screened patients, Treated Set (TS) and Full Analysis Set (FAS). Details of patients excluded from the TS and patients excluded from the FAS will be included in Annex 2, section 8.2.

The important protocol violations will be described in the following table:

Table 1. Important protocol violations-All screened patients

	n	%
Total patients		**100.0**
Total with violation of informed consent (IC-1) Total with violation of any other inclusion criterion Total with violation of any exclusion criterion Total with violation of any inclusion or exclusion criterion		

The inclusion criteria and exclusion criteria based on all screened patients according to CRFs:

Table 2. Inclusion and Exclusion criteria-All screened patients

	n	%
Total patients at screen		
Inclusion criteria not fulfilled		
IC1. Written informed consent prior to participation		
IC2. Female and male patients ≥ 40 years of age		
IC3. Patients diagnosed with COPD and requiring dual bronchodilator (LAMA + LABA) treatment according to approved Spiolto® Respimat® SmPC and GOLD guideline recommendation		
Exclusion criteria fulfilled		
EC1. Patients with contraindications according to Spiolto® Respimat® SmPC		
EC2. Patients who have been treated with a LABA/LAMA combination (free and fixed dose) in the previous 6 months		
EC3. Patients continuing LABA/ICS treatment should not be additionally treated with Spiolto® Respimat® in order to avoid a double dosing of long-acting beta-agonists		
EC4. Patients for whom further follow-up is not possible at the enrolling site during the planned study period of approx. 6 weeks		
EC5. Pregnancy and lactation		
EC6. Patients currently listing for lung transplantation		

Table 2. Inclusion and Exclusion criteria-All screened patients		
	n	%
EC7. Current participation in any clinical trial or any other non-interventional study of a drug or device		

The disposition of patient will be described in the following table:

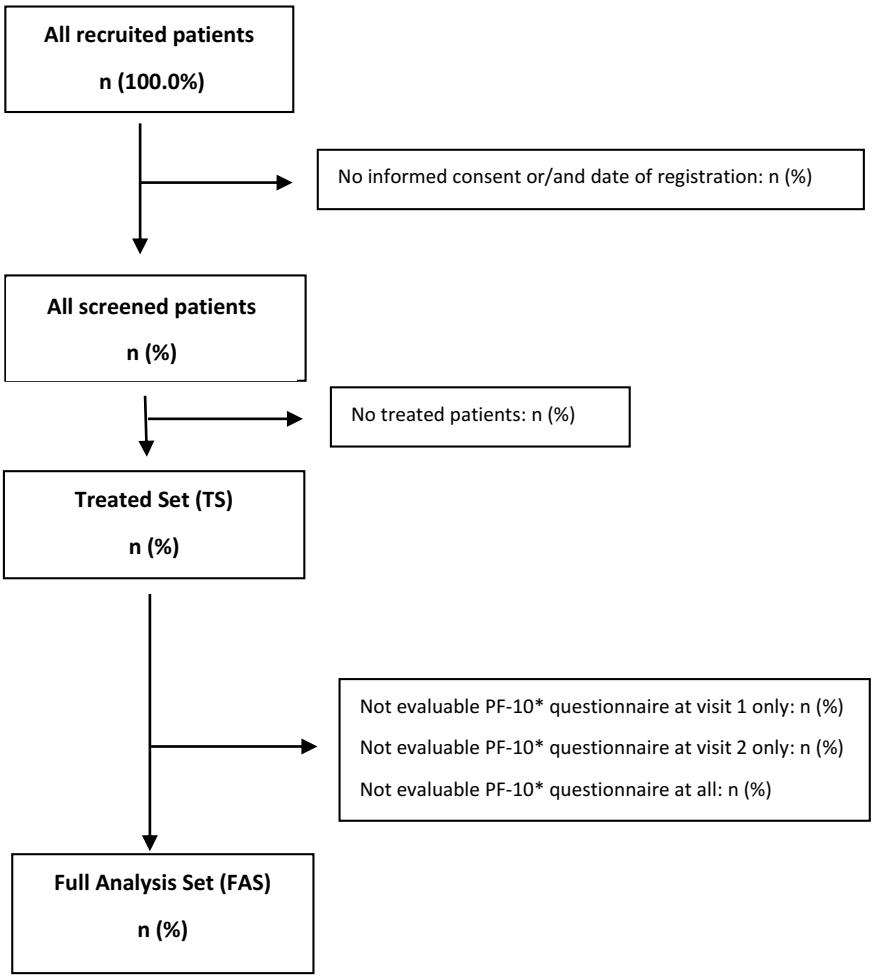
Table 3. Disposition of patients-All screened patients		
	n	%
Total patients at screen		
Total patients at visit 1		
Total patients at visit 2		
Total patients on Reason for not performing visit 2		
Adverse event		
Serious adverse event		
Patient's wish		
Withdrawn consent		
Lost to follow-up		
Patient died		
Other		
Total patients for discontinuation		
Lost to follow-up		
Not meet inclusion/exclusion criteria		
Adverse event		
Protocol deviation		
Patient's wish		
Investigator's wish		
Other		

The following table describes the number of assessable patients with data in visit 1 and visit 2 according the sample sets (screened patients, TS, FAS):

Table 4. Assessable patients by visit and sample set				
	Recruited patients n (%)	All screened patients n (%)	Assessable patients in TS n (%)	Assessable patients in FAS n (%)
Visit 1				
Visit 2				

All screened patients: All recruited patients with informed consent and date of registration.
Treated Set (TS): All screened patients with at least one documented administration of Spiolto® Respimat®.
Full Analysis Set (FAS): All screened patients with at least one documented administration of Spiolto® Respimat® and available PF-10 score at visit 1 and visit 2.

Figure 3. Flow chart of patients recruited onto the study



*In context of PF-10 questionnaire, if less than half of the items on the PF-10 for a patient are missing, the missing values will be replaced with the mean of the other values and the PF-10 score will be calculated. If half or more of the items on the PF-10 are missing, no score will be calculated and the PF-10 score will be marked as not available.

In the ANNEX 2. DETAILS OF THE NON-ASSESSABLE PATIENTS , the lists of the non-assessable patients in TS and FAS will be specified.

Table 5. Summary of analysis population and endpoints

n %	Baseline characteristics	Characteristics after 6 weeks	Primary endpoint	Secondary endpoints	Safety endpoints
Treated Set (TS)	X	X			X
Full Analysis Set (FAS)			X	X	

All screened patients: All recruited patients with informed consent and date of registration.
Treated Set (TS): All screened patients with at least one documented administration of Spiolto® Respimat®.
Full Analysis Set (FAS): All screened patients with at least one documented administration of Spiolto® Respimat® and available PF-10 score at visit 1 and visit 2.

6.2. DESCRIPTION OF THE SAMPLE AT BASELINE VISIT (VISIT 1, TS)

This section will describe the socio-demographic characteristics, anthropometric data, smoking history and baseline characteristics in terms of the COPD diagnosis, exacerbations, lung function, concomitant diseases, concomitant medication, and previous and current treatment for COPD of the **Treated Set (TS)** (n=xxx) (*see Table 4)*.

6.2.1. Bio-demographic characteristics

This section will describe the socio-demographic data and anthropometric data of the treated patients being studied.

Table 6. Socio-demographic data - Treated Set (TS)

	Total
Age (years)	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
Pooled age n (%)	
< 65 years	
≥ 65 years	
Gender n (%)	
Male	
Female	
Employment status n (%)	
Working	
Unemployed	
Temporarily unable to work	
Permanently unable to work	
Retired	
Other[1]	

[1] Specify 'other':

Table 7. Anthropometric data - Treated Set (TS)

	n	mean	SD	(95% CI)	Median [P25 ; P75]	Min	Max	p[1]
Weight (kg)								
Male								
Female								
Height (cm)								
Male								
Female								
BMI (kg/m^2)								

Table 7. Anthropometric data - Treated Set (TS)								
	n	mean	SD	(95% CI)	Median [P25 ; P75]	Min	Max	p[1]
Male								
Female								

[1] *Student's t-test/Mann-Whitney U test*

6.2.2. Smoking history

This section will describe the smoking history of the assessable patients being studied.

Table 8. Smoking history - Treated Set (TS)	
	Total
Smoking n (%)	
Non-smoker	
Ex-smoker	
Smoker	
Number of pack-years - Ex-smoker	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
Number of pack-years - Smoker	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
Number of pack-years[1]	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	

[1] Sample of ex-smokers and smokers (n=xx)

Pack-years = (number of cigarettes smoked per day x number of smoking years) / 20

6.2.3. Start of COPD

This section will describe the time from the diagnosis of COPD to the baseline visit (visit 1).

Table 9. Medical history - Treated Set (TS)	
	Total
Time from COPD diagnosis to date of baseline visit (years)	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	

6.2.4. Exacerbations

This section will describe the exacerbation episodes, attendance at the emergency department and hospital admission which have occurred in the last 12 months relative to the baseline visit (visit 1).

Table 10. Exacerbations in the last 12 months - Treated Set (TS)	
	Total
Has the patient experienced any moderate COPD exacerbation episodes (which required corticosteroids and/or systemic antibiotics)? n (%)	
Yes	
No	
Unknown	
Number of moderate exacerbation episodes[1]	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
Frequency of moderate exacerbation episodes[1] n (%)	
0	
1	
2	
…	
Frequency of moderate exacerbation episodes[1] n (%)	
≤ 1 exacerbation episode	
≥ 2 exacerbation episodes	
Time from the last episode until visit 1 (months)[1]	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	

Table 10. Exacerbations in the last 12 months - Treated Set (TS)	
	Total
Did the patient come to the emergency department because of COPD (exacerbation)? n (%)	
Yes	
No	
Unknown	
He/she came to the emergency department in the Primary setting[2] n (%)	
He/she came to the emergency department in the Hospital setting[2] n (%)	
Number of times he/she came to the emergency department in the Primary setting[3]	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
Number of times he/she came to the emergency department in the Hospital setting[4]	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
Did he/she require hospital admission because of his/her COPD (severe exacerbation)? n (%)	
Yes	
No	
Unknown	
Number of hospitalisations that he/she has had[5]	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
Total number of days admitted[5]	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
Time from the last hospitalisation until visit 1 (months)[5]	
Mean (SD)	
95% CI	

Table 10. Exacerbations in the last 12 months - Treated Set (TS)	
	Total
Median (P25; P75)	
(Min; Max)	
N	

[1] If the patient has experienced any moderate exacerbation episodes (n=xx)

[2] If the patient came to the emergency department because of his/her COPD (n=xx)

[3] If the patient came to the emergency department in the Primary setting (n=xx)

[4] If the patient came to the emergency department in the hospital setting (n=xx)

[5] If the patient required hospital admission because of his/her COPD (n=xx)

6.2.5. Lung function

This section will describe the lung function of the patient at the baseline visit (visit 1).

Table 11. Baseline lung function (visit 1) - Treated Set (TS)	
	Total
Time from spirometry to visit 1 (months)	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
FVC (ml)	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
FVC (%)	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
FEV_1 (ml)	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
FEV_1 (%)	
Mean (SD)	
95% CI	
Median (P25; P75)	

Table 11. Baseline lung function (visit 1) - Treated Set (TS)	
	Total
(Min; Max)	
N	
FEV_1/FVC	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
mMRC Dyspnoea Scale n (%)	
Grade 0	
Grade I	
Grade II	
Grade III	
Grade IV	
GOLD classification of severity[1] n (%)	
GOLD 1 (Mild)	
GOLD 2 (Moderate)	
GOLD 3 (Severe)	
GOLD 4 (Very severe)	
GOLD version 2014[2] n (%)	
GOLD A	
GOLD B	
GOLD C	
GOLD D	
GOLD version 2017[3] n (%)	
GOLD A	
GOLD B	
GOLD C	
GOLD D	

[1]GOLD classification of COPD severity (based on post-bronchodilator FEV1): Mild: $FEV_1 \geq 80\%$ of predicted value, Moderate: $50\% \leq FEV_1 < 80\%$ of predicted value; Severe: $30\% \leq FEV_1 < 50\%$ of predicted value; Very severe: $FEV_1 < 30\%$ of predicted value

[2] GOLD version 2014 group of patients: See **¡Error! No se encuentra el origen de la referencia.**

[3] GOLD version 2017 group of patients: See Figure 2

6.2.6. Concomitant diseases

This section will describe the concomitant diseases (CDs) of treated patients, and it will give details on whether they still have them on the date of the baseline visit (visit 1).

Table 12. Concomitant diseases at baseline visit (visit 1) - Treated Set (TS)			
	Total[1]	**Total with CDs[2]**	**Ongoing[2]**
Does the patient present with any COPD-related concomitant diseases? n (%)			
Yes			
No			
Type of concomitant disease - Yes n (%)			
Cardiovascular disease			
Diabetes mellitus			
Musculoskeletal disorders			
Kidney diseases			
Liver diseases			
Osteoporosis			
Gastro-oesophageal reflux (GOR)			
Lung cancer			
Other[3]			

Note: Concomitant disease (CD). A patient could have more than one CD

[1] Of the total number of treated patients (n=xx)

[2] Of the total number of patients with CDs (n=xx)

[3] Other: AAA (n=x); BBB (n=xx); ...

In the ANNEX 3. RECORDED CONCOMITANT DISEASES, the diagnoses of the concomitant diseases, as well as their duration, will be specified.

6.2.7. Concomitant medication

This section will describe the indication of concomitant medication (CM) of treated patients, as well as the active substance and whether they continue with treatment after the baseline visit (visit 1).

Table 13. Concomitant medication at baseline visit (visit 1) - Treated Set (TS)			
	Total[1]	**Total with CM[2]**	**Ongoing[2]**
Is the patient receiving any concomitant medication? n (%)			
Yes			
No			
Indication of the concomitant medication - Yes n (%)			
Indication 1			
Indication 2			
Indication 3			
…			

Note: Concomitant medication (CM). The same patient could have more than one CM

[1] Of the total number of treated patients (n=xx)

[2] Of the total number of patients with CM (n=xx)

Table 13. Concomitant medication at baseline visit (visit 1) - Treated Set (TS)			
	Total[1]	**Total with CM[2]**	**Ongoing[2]**

The medication for each of the indications, as well as its duration, will be specified in the ANNEX 4. CONCOMITANT MEDICATION.

6.2.8. Previous treatment for COPD

This section will describe previous treatments for COPD in the 6 months prior to the baseline visit (visit 1).

Table 14. Treatment for COPD in the 6 months prior to the baseline visit (visit 1) - Treated Set (TS)			
	Total[1]	**Total COPD[2]**	**Ongoing[2]**
Has the patient received treatment for COPD in the previous 6 months? n (%)			
Yes			
No			
SAMA			
Yes			
No			
SABA			
Yes			
No			
LAMA			
Yes			
No			
LABA			
Yes			
No			
ICS			
Yes			
No			
LAMA/LABA n (%)			
Yes			
No			
LABA/ICS n (%)			
Yes			
No			
Other[3]			
Yes			
No			

NOTE: Patients treated with a LABA/LAMA combination (free and/or fixed combination) within the 6 previous months should not be selected for the study; the same applies to patients who continue with

Table 14. Treatment for COPD in the 6 months prior to the baseline visit (visit 1) - Treated Set (TS)			
	Total[1]	**Total COPD[2]**	**Ongoing[2]**

LABA/ICS treatment, who should not be treated in addition with Spiolto® Respimat® to prevent double-dosing of long-acting beta agonists (see section 4.1.2).

[1] Of the total number of treated patients (x = xx)

[2] Of the total number of patients who have received treatment for COPD in the previous 6 months (n=xx)

[3] Other: AAA (n=x); BBB (n=x); ...

The drugs (active substance) for each one of the drug classes, as well as their duration, will be specified in the ANNEX 5. PREVIOUS TREATMENT FOR COPD.

6.2.9. Current treatment for COPD

This section will describe the current treatment for COPD that the patients will receive.

Table 15. Current treatment for COPD - Treated Set (TS)		
	Total[1]	**Total[2]**
Is the patient going to be treated with Spiolto® Respimat®? n (%)		---
Yes		
No		
Has the patient been trained properly on how to use Respimat®? n (%)		---
Yes		
No		
Is the patient going to receive other inhaled treatments for COPD? n (%)		---
Yes		
No		
Other inhaled treatments for COPD[1] n (%)		
SABA		
ICS		

NOTE: All treated patients must have received a dose of the study treatment

[1] Of the total number of patients (n=xxx)

[2] If the patient has received another treatment for COPD (n=xx)

The ANNEX 6. CURRENT TREATMENT FOR COPD will specify the concomitant medication prescribed for COPD and its duration.

6.3. DESCRIPTION OF THE SAMPLE AFTER 6 WEEKS (VISIT 2, TS)

This section will describe the follow-up of patients after 6 weeks of the study and the changes which occurred after 6 weeks of treatment with Spiolto® Respimat® (treatment for COPD, concomitant diseases and medication, smoking habit, etc.) of the **Treated Set (TS)** and those with data at the visit after 6 weeks (*see Table 4)*.

6.3.1. Data after 6 weeks

This section will describe the number of patients who have completed their visit after 6 weeks (visit 2), the reason for discontinuation if they have not attended the visit and the time between visits (approx. 6 weeks).

Table 16. Continuation of the patient in the study after 6 weeks (visit 2) - Treated Set (TS)

	Total
Is the patient continuing in the study n (%)	
Yes	
No	
Lost to follow-up	
Does not meet inclusion/exclusion criteria	
Adverse event	
Protocol deviation	
Patient's decision	
Investigator's decision	
Other[1]	
Time between visits (weeks)[2]	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
Time to early termination (weeks)[3]	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	

[1] Specify others: other 1 (n=x); other 2 (n=x); …

[2] If the patient continues in the study (n=xx)

[3] If the patient does not continue in the study (n=xx)

6.3.2. Treatment for COPD

This section will describe the continuity of the treatment received for COPD started at the baseline visit and the change in concomitant medication for COPD.

Table 17. Continuation of treatment with Spiolto® Respimat® after 6 weeks (visit 2) - Treated Set (TS)	
	Total n (%)
Is the patient continuing to receive the treatment with Spiolto® Respimat® started at the baseline visit?	
Yes	
No	
Reason why the patient is no longer receiving Spiolto® Respimat®[1]	
Reason 1	
Reason ...	
Has the concomitant medication for COPD changed with respect to the last visit or is the patient receiving a new medication?	
Yes	
SABA	
ICS	
No	

[1] If the patient is no longer receiving the treatment with Spiolto® Respimat® started at the baseline visit (n=xx)

The ANNEX 6. CURRENT TREATMENT FOR COPD 6 will specify the new concomitant medication prescribed for COPD and its duration.

6.3.3. Concomitant diseases

This section will describe the presence of any new concomitant diseases with respect to those of the last visit.

Table 18. New concomitant diseases after 6 weeks (visit 2) - Treated Set (TS)			
	Total[1]	**Total with new CD[2]**	**Ongoing[2]**
Does the patient have any new concomitant diseases with respect to those of the last visit? n (%)			
Yes			
No			

Table 18. New concomitant diseases after 6 weeks (visit 2) - Treated Set (TS)			
	Total[1]	**Total with new CD[2]**	**Ongoing[2]**
Type of new concomitant disease - Yes n (%)			
Cardiovascular disease			
Diabetes mellitus			
Musculoskeletal disorders			
Kidney diseases			
Liver diseases			
Osteoporosis			
Gastro-oesophageal reflux (GOR)			
Lung cancer			
Other[3]			

Note: Concomitant disease (CD). A patient could have more than one CD

[1] Of the total number of treated patients (n=xx)

[2] Of the total number of patients with new CD (n=xx)

[3] Other: AAA (n=x); BBB (n=x); ...

The ANNEX 3. RECORDED CONCOMITANT DISEASES will specify the diagnoses of new concomitant diseases, as well as their duration.

6.3.4. Concomitant medication

The additional intake of concomitant medication will be described in this section.

Table 19. Additional concomitant medication after 6 weeks (visit 2) - Treated Set (TS)			
	Total[1]	**Total with additional CM[2]**	**Ongoing[2]**
Is the patient receiving any additional concomitant medication? n (%)			
Yes			
No			
Indication of the concomitant medication - Yes n (%)			
Indication 1			
Indication 2			
Indication 3			
...			

Note: Concomitant medication (CM)

[1] Of the total number of treated patients (n=xx)

[2] Of the total number of patients with additional CM (n=xx)

The additional medication for each of the indications, as well as its duration, will be specified in the ANNEX 4. CONCOMITANT MEDICATION.

6.3.5. Tobacco consumption

This section will describe whether the patient has changed his/her smoking habits since the last visit.

Table 20. Tobacco consumption after 6 weeks (visit 2) - Treated Set (TS)	
	Total
Has he/she changed his/her smoking habits since the last visit? n (%)	
Yes	
No	
Change of smoking habit[1] n (%)	
He/she has quit smoking	
He/she is smoking less	
He/she is smoking more	
Number of cigarettes/day in patients who are smoking less	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	
Number of cigarettes/day in patients who are smoking more	
Mean (SD)	
95% CI	
Median (P25; P75)	
(Min; Max)	
N	

[1] Of the total number of patients who have changed their smoking habit (n=xx)

[2] Of the sample of patients who are ex-smokers and smokers in the visit after 6 weeks (n=xx). The pack-years value from the baseline visit is taken as the value in patients who have not changed their smoking habit

6.4. ANALYSIS OF EFFICACY (FAS)

This section will describe the results for the study's primary objective as well as for the secondary endpoints in **Full Analysis Set (FAS)**.

6.4.1. Analysis of primary endpoint

This section will describe the frequency and percentage of "Therapeutic success" at visit 2 (defined as: 10-point increase in the PF-10 score between the baseline visit (visit 1) and the visit after 6 weeks (visit 2) will be presented together with the 95% confidence interval.

Table 21. Therapeutic success after 6 weeks (visit 2) – Full Analysis Set (FAS)

	Total n (%)	CI (95%)
Therapeutic success[1] n (%)		
Therapeutically successful		
Not therapeutically successful		

Therapeutic success: 10-point increase in the PF-10 score between visit 1 and visit 2.

[1] Of the total number of patients who have PF-10 data at the baseline visit (visit 1) and at the visit after 6 weeks (visit 2)

Figure 4. Therapeutic success after 6 weeks (visit 2) – Full Analysis Set (FAS)

[pie chart]

6.4.2. Analysis of secondary endpoints

This section will describe the data corresponding to the secondary efficacy endpoints.

Changes in PF-10 score

A descriptive analysis of the PF-10 score from the baseline visit (visit 1) to the visit after 6 weeks (visit 2), as well as the change (difference visit 2 - visit 1), will be conducted in this section.

Table 22. PF-10 score at baseline visit, after 6 weeks and change – Full Analysis Set (FAS)

	n	mean	SD	(95% CI)	Median	[P25-P75]	Min	Max	P[1]
Baseline PF-10 (Visit 1)									-
PF-10 after 6 weeks (Visit 2)									-
Change in PF-10 (v2-v1)									

[1] paired t-test /Wilcoxon Rank-Sum

Figure 5. PF-10 Score – Full Analysis Set (FAS)

[line/bar charts of the mean/median PF-10 at the baseline visit (visit 1) and the visit after 6 weeks (visit 2)]

Table 23. Change in PF-10 score according to therapeutic success – Full Analysis Set (FAS)									
	n	mean	SD	(95% CI)	Median	[P25-P75]	Min	Max	P[1]
Baseline PF-10 (visit 1)									
Therapeutically successful									
Not therapeutically successful									
PF-10 after 6 weeks (visit 2)									
Therapeutically successful									
Not therapeutically successful									
Change in PF-10 (v2-v1)									
Therapeutically successful									
Not therapeutically successful									

[1] independent two-sample t-test/Mann–Whitney U test

Figure 6. PF-10 score according to therapeutic success – Full Analysis Set (FAS)

[line/bar charts of the mean/median PF-10 at the baseline visit (visit 1) and the visit after 6 weeks (visit 2) according to therapeutic success]

Patient's general condition - PGE score

A descriptive analysis of the PGE score at the baseline visit (visit 1) and the visit after 6 weeks (visit 2) will be conducted in this section, to assess the patient's general condition according to the investigator, using an 8-point ordinal scale from 1 (very poor) to 8 (excellent).

Table 24. General condition of the patient – PGE score as assessed by the physician at the baseline visit and after 6 weeks in completed patients – Full Analysis Set (FAS)			
	Baseline (Visit 1)	6 weeks (Visit 2)	P[1]
PGE score n (%)			
1			
2			

Table 24. General condition of the patient – PGE score as assessed by the physician at the baseline visit and after 6 weeks in completed patients – Full Analysis Set (FAS)

	Baseline (Visit 1)	6 weeks (Visit 2)	P[1]
3			
4			
5			
6			
7			
8			
Pooled PGE Score n (%)			
Poor (1-2)			
Satisfactory (3-4)			
Good (5-6)			
Excellent (7-8)			

[1] McNemar test

Figure 7. Patient's general condition –PGE score as assessed by the physician – Full Analysis Set (FAS)

[bar chart of PGE score at the baseline visit (visit 1) and the visit after 6 weeks (visit 2)]

[bar chart of pooled PGE score at the baseline visit (visit 1) and the visit after 6 weeks (visit 2)]

Patient satisfaction with Spiolto® Respimat®

A descriptive analysis of patient satisfaction with Spiolto® Respimat® after 6 weeks of treatment (visit 2) will be conducted in this section, using a 7-point ordinal scale, from 1 (very satisfied) to 7 (very dissatisfied).

Table 25. Patient satisfaction with Spiolto® Respimat® after 6 weeks of treatment (visit 2) in completed patients - Full Analysis Set (FAS)

	Total n (%)
Patient overall satisfaction with inhalation with the Spiolto® Respimat® treatment	
Very unsatisfied	
Unsatisfied	
Rather unsatisfied	
Neither satisfied, nor unsatisfied	
Rather satisfied	
Satisfied	
Very satisfied	

Table 25. Patient satisfaction with Spiolto® Respimat® after 6 weeks of treatment (visit 2) in completed patients - Full Analysis Set (FAS)	
	Total n (%)
Patients satisfaction with inhaling from Respimat® device?	
Very unsatisfied	
Unsatisfied	
Rather unsatisfied	
Neither satisfied, nor unsatisfied	
Rather satisfied	
Satisfied	
Very satisfied	
Patients satisfaction with haling of the Respimat® inhalation device?	
Very unsatisfied	
Unsatisfied	
Rather unsatisfied	
Neither satisfied, nor unsatisfied	
Rather satisfied	
Satisfied	
Very satisfied	

[1] Chi-square test/Fisher's exact test

Figure 8. Patient satisfaction with Spiolto® Respimat® – Full Analysis Set (FAS)

[cumulative bar charts for the three items]

6.5. SAFETY ANALYSIS (TS)

This section will describe the data related to suspected adverse reactions linked to Spiolto® Respimat® (serious or non-serious) and/or adverse events not related to Spiolto® Respimat®, but with a fatal outcome, reported by patients during the course of the study.

Pregnancies will also be indicated, at the start and at the end of the study. The sample analysed will be the **Treated Set** (n=xxx, *see Table 4*).

Table 26. Adverse events (AE) overall summary - Treated Set (TS)

	Total n (%)
Number of patients	
Patients with investigator defined drug-related AE	
Patients with investigator defined drug-related AE leading to discontinuation of trial drug	
Patients with serious AE	
Mortal	
Life-threatening	
Incapacity	
Hospitalisation	
Prolongation of hospitalisation	
Congenital anomaly	
Patients with serious AE leading to discontinuation	
Patients with serious drug-related AE	

6.5.1. Adverse events

Table 27. AE according to MedDRA-SOC and PT - Treated Set (TS)

	Patients n (%)	**Events n (%)**
Presence of AE during the study n (%)		
SOC 1		
PT1		
PT2		
…		
SOC 2		
PT1		

Table 27. AE according to MedDRA-SOC and PT - Treated Set (TS)		
	Patients n (%)	**Events n (%)**
PT2 …		
…		

6.5.2. Drug-related adverse events

Table 28. Summary Drug-related adverse events - Treated Set (TS)	
	Events n (%)
Total drug-related adverse events	
Serious Drug-related adverse event	
Non-Serious drug-related adverse event	

Table 29. Serious Drug-related adverse events - Treated Set (TS)	
	Events n (%)
Total Serious drug-related adverse events	
Description	
SOC 1	
PT1	
PT2	
…	
SOC 2	
PT1	
PT2	
…	
…	

Table 30. Non-Serious Drug-related adverse events - Treated Set (TS)	
	Events n (%)
Total Non-Serious drug-related adverse events	
Description	
SOC 1	
PT1	

Table 30. Non-Serious Drug-related adverse events - Treated Set (TS)	
	Events n (%)
PT2	
…	
SOC 2	
PT1	
PT2	
…	

Table 31. Outcome Drug-related adverse events - Treated Set (TS)	
	Events n (%)
Total drug-related adverse events	
Outcome	
Recovered/resolved	
Not recovered/resolved	
Recovered/resolved with sequelae	
Exitus	
Unknown	

6.5.3. Serious Adverse Events

Table 32. Characteristics of Serious adverse events - Treated Set (TS)	
	Total n (%)
Total Serious adverse events	
Description	
SOC 1	
PT 1	
…	
SOC 2	
…	

6.5.4. Pregnancy

Table 33. Patient pregnant at AE - Treated Set (TS)	
	n (%)
Total Patient at AE	
Yes	
No	
Not applicable	

All AEs reported in the study, together with the provided characteristics of intensity, severity, treatment administered to treat the AR, action taken, causal relationship with study treatment and outcome will be listed in the ANNEX 7. REPORTED ADVERSE EVENTS.

7. REFERENCES

1 Vilagut G, et al. El Cuestionario de Salud SF-36 español: una década de experiencia y nuevos desarrollos [The Spanish version of the Short Form 36 Health Survey: a decade of experience and new developments]. Gac Sanit. 2005;19(2):135-50

2 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2014). http://www.goldcopd.org/uploads/users/files/GOLD_Report_2014.pdf (access date: 22 January 2014); Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2014)

3 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2017). https://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/(access date: 15 May 2017) Global Initiative for Chronic Obstructive Lung Disease (GOLD) (2017)

8. ANNEX

8.1. ANNEX 1. DB DEBUGGING

The DB debugging process, which is established in the Data Management Plan (DMP) will be described in this annex.

The description of debugging and/or variables generated during the data analysis process will also be described.

Table 48. Validation during data entry: Selection criteria

	Variables	Visit	Data block	Inconsistency in CRF	Message / Warning	Can be validated
						No
						No

[Note, if applicable]

Table 49. Debugging performed during the statistical analysis

Patient	Visit	Variable	Data block	Inconsistency in DB	Action taken

[Note, if applicable]

Table 50. New variables created for the preparation of the results report

New variable	Data block	Description

8.2. ANNEX 2. DETAILS OF THE NON-ASSESSABLE PATIENTS

This section will include the list of non-assessable patients for this study:

Table 51. Description of the TS non-assessable patients

Patient No.	Inclusion criterion 1	Informed consent date	Patient with no data on treatment with Spiolto® Respimat®

Table 52. Description of the FAS non-assessable patients

Patient No.	Inclusion criterion 1	Informed consent date	Patient with no data on treatment with Spiolto® Respimat®	Patients with PF-10 assessable at baseline visit only	Patients with PF-10 assessable at visit after 6 weeks only	Patients without PF-10 assessable at baseline visit and at visit after 6 weeks

8.3. ANNEX 3. RECORDED CONCOMITANT DISEASES

Concomitant diseases recorded throughout the study, according to Table 12 (concomitant diseases at the baseline visit); and Table 18 (new concomitant diseases after 6 weeks) will be listed in the following tables.

Table 53. Concomitant diseases at baseline visit (visit 1) – Treated Set (TS)

	Total[1]	Total with CDs[2]	Ongoing[2]
Does the patient present with any COPD-related concomitant diseases? n (%)			
Yes			
No			
Cardiovascular disease n (%)			
Yes			
No			
Type of cardiovascular disease (diagnosis)[3]			
Diagnosis 1			
Diagnosis ...			
Diabetes mellitus n (%)			
Yes			
No			
Musculoskeletal disorders n (%)			
Yes			
No			
Type of musculoskeletal disorder (diagnosis)[4]			
Diagnosis 1			
Diagnosis ...			
Kidney diseases n (%)			
Yes			
No			
Type of kidney disease (diagnosis)[5]			
Diagnosis 1			
Diagnosis ...			
Liver diseases n (%)			
Yes			
No			
Type of liver disease (diagnosis)[6]			
Diagnosis 1			
Diagnosis ...			

Table 53. Concomitant diseases at baseline visit (visit 1) – Treated Set (TS)			
	Total[1]	**Total with CDs[2]**	**Ongoing[2]**
Osteoporosis n (%)			
Yes			
No			
Gastro-oesophageal reflux (GOR) n (%)			
Yes			
No			
Lung cancer n (%)			
Yes			
No			
Other n (%)			
Yes			
No			
Type of liver disease (diagnosis)[7]			
Diagnosis 1			
Diagnosis ...			

Note: Concomitant disease (CD). A patient could have more than one CD

[1] Of the total number of treated patients (n=xx)

[2] Of the total number of patients with CDs (n=xx)

[3] In the event of cardiovascular disease (n=xx)

[4] In the event of osteoporosis (n=xx)

[5] In the event of kidney diseases (n=xx)

[6] In the event of liver diseases (n=xx)

[7] In the event of other concomitant diseases (n=xx)

Table 54. Duration of concomitant diseases at baseline visit (months)) – Treated Set (TS)								
	n	**mean**	**SD**	**(95% CI)**	**Median**	**[P25-P75]**	**Min**	**Max**
Cardiovascular disease								
Diagnosis 1								
Diagnosis ...								
Diabetes mellitus								
Musculoskeletal disorders								
Diagnosis 1								
Diagnosis ...								
Kidney diseases								
Diagnosis 1								
Diagnosis ...								
Liver diseases								

Diagnosis 1 *Diagnosis ...*
Osteoporosis
Gastro-oesophageal reflux (GOR)
Lung cancer
Other
Diagnosis 1 *Diagnosis ...*

Note: n according to each of the concomitant diseases

Table 55. New concomitant diseases after 6 weeks (visit 2)) – Treated Set (TS)

	Total[1]	Total with new CD[2]	Ongoing[2]
Does the patient have any new concomitant diseases with respect to those of the last visit? n (%)			
Yes			
No			
Cardiovascular disease n (%)			
Yes			
No			
Type of cardiovascular disease (diagnosis)[3] *Diagnosis 1* *Diagnosis ...*			
Diabetes mellitus n (%)			
Yes			
No			
Musculoskeletal disorders n (%)			
Yes			
No			
Type of musculoskeletal disorder (diagnosis)[4] *Diagnosis 1* *Diagnosis ...*			
Kidney diseases n (%)			
Yes			
No			
Type of kidney disease (diagnosis)[5] *Diagnosis 1* *Diagnosis ...*			

Table 55. New concomitant diseases after 6 weeks (visit 2)) – Treated Set (TS)			
	Total[1]	**Total with new CD[2]**	**Ongoing[2]**
Liver diseases n (%)			
Yes			
No			
Type of liver disease (diagnosis)[6]			
Diagnosis 1			
Diagnosis ...			
Osteoporosis n (%)			
Yes			
No			
Gastro-oesophageal reflux (GOR) n (%)			
Yes			
No			
Lung cancer n (%)			
Yes			
No			
Other n (%)			
Yes			
No			
Type of liver disease (diagnosis)[7]			
Diagnosis 1			
Diagnosis ...			

Note: Concomitant disease (CD). A patient could have more than one CD

[1] Of the total number of treated patients (n=xx)

[2] Of the total number of patients with new CD (n=xx)

[3] In the event of cardiovascular disease (n=xx)

[4] In the event of osteoporosis (n=xx)

[5] In the event of kidney diseases (n=xx)

[6] In the event of liver diseases (n=xx)

[7] In the event of other concomitant diseases (n=xx)

Table 56. Duration of new concomitant diseases after 6 weeks (months) – Treated Set (TS)								
	n	**mean**	**SD**	**(95% CI)**	**Median**	**[P25-P75]**	**Min**	**Max**
Cardiovascular disease								
Diagnosis 1								
Diagnosis ...								
Diabetes mellitus								
Musculoskeletal disorders								
Diagnosis 1								

Table 56. Duration of new concomitant diseases after 6 weeks (months) – Treated Set (TS)								
	n	**mean**	**SD**	**(95% CI)**	**Median**	**[P25-P75]**	**Min**	**Max**
Diagnosis ...								
Kidney diseases								
Diagnosis 1								
Diagnosis ...								
Liver diseases								
Diagnosis 1								
Diagnosis ...								
Osteoporosis								
Gastro-oesophageal reflux (GOR)								
Lung cancer								
Other								
Diagnosis 1								
Diagnosis ...								

Note: n according to each of the concomitant diseases

8.4. ANNEX 4. CONCOMITANT MEDICATION

Concomitant medications administered throughout the study, according to Table 13 (concomitant medication at the baseline visit) and Table 19 (additional concomitant medication after 6 weeks) will be listed in the following tables.

Table 57. Concomitant medication at baseline visit (visit 1) – Treated Set (TS)

	Total[1]	Total with CM[2]	Ongoing[2]
Is the patient receiving any concomitant medication? n (%)			
Yes			
No			
Indication of the concomitant medication - Yes n (%)			
Indication 1			
xxxxx			
xxxxx			
Indication 2			
xxxxx			
xxxxx			
Indication 3			
xxxxx			
xxxxx			
…..			

Note: Concomitant medication (CM). The same patient could have more than one CM

[1] Of the total number of treated patients (n=xx)

[2] Of the total number of patients with CM (n=xx)

Table 58. Duration of concomitant medication at baseline visit (months) – Treated Set (TS)

	n	mean	SD	(95% CI)	Median	[P25-P75]	Min	Max
Indication 1								
xxxx								
xxxx								
Indication 2								
xxxx								
xxxx								
Indication 3								
xxxx								
xxxx								

Table 58. Duration of concomitant medication at baseline visit (months) – Treated Set (TS)							
	n	mean	SD	(95% CI)	Median	[P25-P75]	Min	Max
…							

Note: n according to each of the concomitant medications

Table 59. Additional concomitant medication after 6 weeks (visit 2) – Treated Set (TS)			
	Total[1]	Total with CM[2]	Ongoing[2]
Is the patient receiving any additional concomitant medication? n (%)			
Yes			
No			
Indication of the additional concomitant medication - Yes n (%)			
Indication 1			
xxxxx			
xxxxx			
Indication 2			
xxxxx			
xxxxx			
Indication 3			
xxxxx			
xxxxx			
…..			

Note: Concomitant medication (CM). The same patient could have more than one CM

[1] Of the total number of treated patients (n=xx)

[2] Of the total number of patients with CM (n=xx)

Table 60. Duration (months) of the additional concomitant medication after 6 weeks (visit 2) – Treated Set (TS)								
	n	mean	SD	(95% CI)	Median	[P25-P75]	Min	Max
Indication 1								
xxxx								
xxxx								
Indication 2								
xxxx								
xxxx								
Indication 3								

Table 60. Duration (months) of the additional concomitant medication after 6 weeks (visit 2) – Treated Set (TS)								
	n	mean	SD	(95% CI)	Median	[P25-P75]	Min	Max
xxxx								
xxxx								
…								

Note: n according to each of the concomitant medications

8.5. ANNEX 5. PREVIOUS TREATMENT FOR COPD

Previous treatments for COPD (in the 6 months prior to the baseline visit), as well as the duration, according to Table 14 (medication) will be specified in the following tables.

Table 61. Treatment for COPD in the 6 months prior to the baseline visit (visit 1) - Active Substance – Treated Set (TS)

	Total[1]	Total COPD[2]	Ongoing[2]
Has the patient received treatment for COPD in the previous 6 months? n (%)			
Yes			
No			
Specify treatment for COPD - Yes n (%)			
SAMA			
Active substance 1 (units)			
Active substance … (units)			
SABA			
Active substance 1 (units)			
Active substance … (units)			
LAMA			
Active substance 1 (units)			
Active substance … (units)			
LABA			
Active substance 1 (units)			
Active substance … (units)			
ICS			
Active substance 1 (units)			
Active substance … (units)			
LAMA/LABA n (%)			
Active substance 1 (units)			
Active substance … (units)			
LABA/ICS n (%)			
Active substance 1 (units)			
Active substance … (units)			
Other			
Active substance 1 (units)			
Active substance … (units)			

Table 62. Duration of treatment for COPD in the 6 months prior to the baseline visit (visit 1) - Active substance – Treated Set (TS)								
	n	mean	SD	(95% CI)	Median	[P25-P75]	Min	Max
SAMA								
Active substance 1 (units)								
Active substance … (units)								
SABA								
Active substance 1 (units)								
Active substance … (units)								
LAMA								
Active substance 1 (units)								
Active substance … (units)								
LABA								
Active substance 1 (units)								
Active substance … (units)								
ICS								
Active substance 1 (units)								
Active substance … (units)								
LAMA/LABA								
Active substance 1 (units)								
Active substance … (units)								
LABA/ICS								
Active substance 1 (units)								
Active substance … (units)								
Other								
Active substance 1 (units)								
Active substance … (units)								

Note: n according to each of the treatments for COPD

8.6. ANNEX 6. CURRENT TREATMENT FOR COPD

This annex will specify the current concomitant treatment (active substance) for COPD (SABA, ICS-Table 15), as well as the treatment dose.

Table 63. Current treatment for COPD (visit 1) – Treated Set (TS)

	Total
Is the patient going to receive other inhaled treatments for COPD? n (%)	
Yes	
No	
Other inhaled treatments for COPD[1] n (%)	
SABA	
Active substance 1 (units)	
Active substance … (units)	
ICS	
Active substance 1 (units)	
Active substance … (units)	

[1] If the patient has received any other treatment for COPD (n=xx)

Table 64. Current treatment for COPD (visit 2) – Treated Set (TS)

	Total
Other inhaled treatments for COPD[1] n (%)	
SABA	
Active substance 1 (units)	
Active substance … (units)	
ICS	
Active substance 1 (units)	
Active substance … (units)	

[1] If the patient has changed his/her concomitant medication for COPD (n=xx)

8.7. ANNEX 7. REPORTED ADVERSE EVENTS

This section will include the list of patients with reported AEs, , detailing the characteristics provided in terms of severity, reasonable causal relationship with the study drug (AR), action taken and outcome. In addition, the patient's gender and age will be specified.

Table 65. Individualised description of the adverse events under study – Treated Set (TS)

Patient code	Gender	Age	System organ class	Preferred term	Reported term	Start date	End date (or ongoing)	Intensity	Severity	Type of severity	Reasonable relationship with the study drug (AR)	Action taken	Outcome

System organ class / Preferred term: Description of the adverse reaction according to SOC and PT of the MedDRA; Reported term: Description of the adverse reaction according to the investigator's description

Table 66. Individualised description of the serious adverse events under study – Treated Set (TS)

Patient code	Gender	Age	System organ class	Preferred term	Reported term	Start date	End date (or ongoing)	Intensity	Severity	Type of severity	Reasonable relationship with the study drug (AR)	Action taken	Outcome

System organ class / Preferred term: Description of the adverse reaction according to SOC and PT of the MedDRA; Reported term: Description of the adverse reaction according to the investigator's description