Technical Trial Statistical Analysis Plan- CTR display plan

AERIAL®

Changes in health and functional status in patients with COPD during therapy with Spiolto® Respimat®

Project No:	5312000_AERIAL
Medication:	Spiolto® Respimat®
Dokument ID:	TechnicalSAP_1237-0065_Final_3.0_2019-03-12.docx
Version:	Final 3.0
Date:	12.03.2019
Sponsor:	Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein Germany
Author:	
Protocol (Version, Date):	Version 2.0, 24.04.2017

Tables of contents

The following tables, listings and figures are planned. The checkered fields as well as the terms in brackets {…} show the programmer where the parameter to be analysed may be found and will not appear in the report. In this context, the variable before the point displays the dataset and the variable after the point stands for the field name within the corresponding dataset. Take note, that the variable before the point must be always reported again as first term after the point, e.g. patient.birthyear stands for the field patient.patient_birthyear in the eCRF.

1 Methods for calculation of derived variables

Age at registration: Year of registration {year(registration.registered_at)} - Year of birth {patient.birthyear}

Clinical COPD Questionnaire (CCQ): Each of the 10 CCQ questions is scored by the patient on a 7-point scale between 0 (Never/Not limited at all) and 6 (Almost all the time/Totally limited or unable to do) at baseline and end of the observation after approximately 6 weeks. The (total) CCQ score measures the health and functional status. A higher CCQ score is indicative of worse status and a decrease of 0.4 points is considered to be the minimum clinically important difference (MCID). The total CCQ score and the corresponding subscales are calculated as followed, in case that at least the number of required answers is available:

Scale	Items	Items required	Scoring (For details see www.ccq.nl)	Field names
Symptom	1; 2; 5; 6	3	$\frac{Sum\ of\ answered\ questions}{Number\ of\ answered\ questions}$	ccq.q_ [01;02;05;06]
Functional state (CCQ-4)	7-10	3	$\frac{Sum\ of\ answered\ questions}{Number\ of\ answered\ questions}$	ccq.q_07-ccq.q_10
Mental state	3; 4	2	$\frac{Item\ 3 + 4}{2}$	ccq.q_03; ccq.q_04
Total CCQ score	All subscales must be calculable		$\frac{(Symptom\ + Functional\ state) * 4 + (Mental\ state) * 2}{10}$	ccq.q_01-ccq.q_10

Change of CCQ score: total CCQ score at baseline minus total CCQ score after approximately 6 weeks

Therapeutic success: total CCQ score at baseline minus total CCQ score after approximately 6 weeks is greater or equal to 0.4

Non therapeutic success: total CCQ score at baseline minus total CCQ score after approximately 6 weeks is less than 0.4

Share of patients with therapeutic success: number of patients with therapeutic success divided by total number of patients

mMRC questionnaire {mmrc.activity}:

mMRC Classification	Answer
Grade 0	Breathless with strenuous exercise
Grade 1	Short of breath when hurrying on the level or walking up a slight hill
Grade 2	Walk slower than people of the same age on the level because of breathlessness, or have to stop for breath when walking at own pace on the level
Grade 3	Stop for breath after walking about 100 meters or after a few minutes on level
Grade 4	Too breathless to leave the house or breathless when dressing or undressing

GOLD group

GOLD group	Definition	Exacerbations* per year {anamnesis.exacerbation} and/or hospitalizations due to excerbations {anamnesis_exacerbation_hospital}	mMRC classification {mmrc.activity}
A		0-1 and =0	≤1
B	Low risk, more symptoms	0-1 and =0	≥ 2
C	High risk , less symptoms	≥ 2 or ≥1	0-1
D	High risk , more symptoms	≥ 2 or ≥1	≥ 2

*For unknown number of exacerbations “0” is included in the calculation of the GOLD group

If 0 or 1 excerbation per year is documented along with a mMRC of at least grade 2 at baseline the patient is assigned GOLD group B.

If two and more excerbations per year are documented along with a mMRC of grade 0 or 1 at baseline the patient is assigned GOLD group C.

If two and more excerbations per year are documented along with a mMRC of at least grade 2 at baseline the patient is assigned GOLD group D.

Duration between initial diagnosis of COPD and baseline visit: Year of Visit 1 {year(anamnesis.date)}- Year of initial COPD diagnosis {anamnesis.copd_year}

Time between start of treatment and end of observation/discontinuation [weeks]: (Date of Visit 2 {visit.date}/Date of last treatment within observation period {visit.spiolto_last_date}-Date of start of treatment {anamnesis.spiolto_date})/7

Time between Visit 1 and Visit 2 [weeks]: (Date of Visit 2 {visit.date}-Date of Visit 1 {anamnesis.date})/7

Pack years: (Years of smoking)*(Cigarette parcels per day){anamnesis.smoker_pack_years; visit.smoker_pack_years}

2 DISPLAY TEMPLATES

2.1 Display templates for in - text reports

2.1.1 In-text table templates

Not applicable.

2.1.1 In-text figure examples

Not applicable.

2.2 Display templates for in- or end-of-text reports

2.2.1 End-of-text table templates

2.2.1.1 15.1 Trial subject

2.2.1.1.1 15.1.1 Disposition of subjects

Table 15.1.1 1: Disposition

	N (%)
Patients recruited *{patient.id}*	xx (100.0)
Patients with visit 1 *{anamnesis.done}*	xx (yy.y)
Reason for not performing Visit 1 *{anamnesis.done_reason}*	
Adverse event	xx (yy.y)
Serious adverse event	xx (yy.y)
Patient's wish	xx (yy.y)
Withdrawn consent	xx (yy.y)
Lost to follow-up	xx (yy.y)
Patient died	xx (yy.y)
Other	xx (yy.y)
Study participation not possible *{patient.no_participation}*	xx (yy.y)
Patients with visit 1, but no registration *{anamnesis.done}{registration.registered_by}*	xx (yy.y)
Patients not treated	xx (yy.y)
Patients included in Treated Set	xx (yy.y)
Patients with Visit 2 *{visit.done}*	xx (yy.y)
Reason for not performing Visit 2 *{visit.done_reason}*	
Adverse event	xx (yy.y)
Serious adverse event	xx (yy.y)
Patient's wish	xx (yy.y)
Withdrawn consent	xx (yy.y)
Lost to follow-up	xx (yy.y)
Patient died	xx (yy.y)
Other	xx (yy.y)
Patients with Visit 2- Continuation of medication after end of observation (Spiolto® Respimat®) *{visit.spiolto_continued}*	xx (yy.y)
Patients with Visit 2- Discontinuation of medication after end of observation (Spiolto® Respimat®)	xx (yy.y)
Reason for discontinuation of Spiolto® Respimat® *{visit.spiolto_reason}*	
Adverse event	xx (yy.y)
Serious adverse event	xx (yy.y)
Patient's wish	xx (yy.y)
Withdrawn consent	xx (yy.y)
Lost to follow-up	xx (yy.y)
Patient died	xx (yy.y)
Other	xx (yy.y)

Patients included in FAS	xx (yy.y)
Reason for not included in FAS	
Available total CCQ score at visit 1 only	xx (yy.y)
Available total CCQ score at visit 2 only	xx (yy.y)
No available total CCQ score at all	xx (yy.y)
Not included in TS	xx (yy.y)

15.1.2 Important protocol violations

Table 15.1.2 1: Patients with visit 1- Important protocol violations

	N (%)
Total	xx (100.0)
Total with violation of informed consent *{patient.ic_01}*	xx (yy.y)
Total with violation of any other inclusion criteria *{patient.ic_02-patient.ic_04}*	xx (yy.y)
Total with violation of any exclusion criteria *{patient.ec_01-patient.ec_05}*	xx (yy.y)
Total with violation of any inclusion or exclusion criteria *{ patient.ic_01-patient.ic_04; patient.ec_01-patient.ec_05}*	xx (yy.y)

Table 15.1.2 2 Patients with visit 1- Inclusion criteria

Inclusion criteria not fulfilled	N	%
patient.ic_01		
IC 1- Written informed consent prior to participation		
patient.ic_03		
IC 2- Female and male patients >=40 years of age		
patient.ic_02		
IC 3- Patients diagnosed with COPD and requiring a combination of two long-acting bronchodilators (LAMA+LABA) according to approved SmPC and GOLD COPD guideline recommendation 2017 (GOLD COPD groups B to D)		
patient.ic_04		
IC 4- Treatment with Spiolto® Respimat® acc. to SmPC at the discretion of the physician		
At least one inclusion criteria not fulfilled		
Number of patients	xx	100.00

Table 15.1.2 3: Patients with visit 1- Exclusion criteria

Exclusion criteria fulfilled	N	%
patient.ec_01		
EC 1- Patients with contraindications according to Spiolto® Respimat® SmPC		
patient.ec_02		
EC 2- Patients already on a LABA/LAMA combination (free and fixed dose) in the last 6 weeks before study entry		
patient.ec_03		
EC 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		

Exclusion criteria fulfilled	N	%
patient.ec_05		
EC 4- Pregnancy and lactation		
patient.ec_04		
EC 5- Current participation in any clinical trial or any other non-interventional study of a drug or devise		
At least one exclusion criteria fulfilled		
Number of patients	xx	100.00

2.2.1.1.2 15.1.3 Definition of analysis sets

Table 15.1.3 1: Patients with visit 1 patients- Summary of analysis population

Sample size	N	%
Treated Set (TS)		
Full Analysis Set (FAS)		
Patients with visit 1	xx	100.00

2.2.1.1.3 15.1.4 Demographic data and baseline characteristics

Table 15.1.4 1: Treated Set- Age at registration [years]

patient.birthyear; registration.registered_at	N (Number of non-missing values)	Mean	SD	Min	Median	Max	Nmiss (Number of missing values)
Age at registration							

Table 15.1.4 2: Treated Set- Age at registration, categorical

patient.birthyear; registration.registered_at	N	%
Age, categorical		
<65 years		
≥65 years		
Missing		
Number of patients		

Table 15.1.4 3: Treated Set- Gender

patient.gender	N	%
Gender		
Male		
Female		
Number of patients		

Table 15.1.4 4: Treated Set- Height [cm]

patient.bodysize	N	Mean	SD	Min	Median	Max	Nmiss
Height							

Table 15.1.4 5: Treated Set- Weight [kg]

patient.bodyweight	N	Mean	SD	Min	Median	Max	Nmiss
Weight							

Visit 1- Baseline

Table 15.1.4 6: Treated Set- Duration between initial diagnosis of COPD and baseline visit [years]

anamnesis.date; anamnesis.copd_year	N	Mean	SD	Min	Median	Max	Nmiss
Duration between initial diagnosis and baseline visit							

Table 15.1.4 7: Treated Set- COPD degree of severity (spirometric)

anamnesis.copd_severity COPD degree of severity (spirometric)	N	%
1		
2		
3		
4		
No preliminary examination result		
Missing		
Number of patients in Treated Set		

Table 15.1.4 8: Treated Set- COPD degree of severity (spirometric) [grouped]

anamnesis.copd_severity COPD degree of severity (spirometric) [grouped]	N	%
1/2		
3/4		
No preliminary examination result		
Missing		
Number of patients in Treated Set		

Table 15.1.4 9: mMRC Questionnaire

mmrc.activity mMRC Questionnaire	N	%
Grade 0		
Grade 1		
Grade 2		
Grade 3		
Grade 4		

mmrc.activity mMRC Questionnaire	N	%
Missing		
Number of patients in Treated Set		

Table 15.1.4 10: Treated Set- Exacerbations and hospitalizations due to excerbations in the last 12 months

Exacerbations and hospitalizations due to excerbations in the last 12 months	Number of patients	Number of exa-cerbations	Mean	SD	Min	Median	Max	Nmiss	Patients with events	
									N	%
anamnesis.exacerbation Number of exacerbations										
anamnesis.exacerbation_hospital Number of hospitalizations due to excerbations										

Table 15.1.4 11: Treated Set- Exacerbations and hospitalizations due to excerbations in the last 12 months, categorical

anamnesis.exacerbation; anamnesis.exacerbation_hospital		Hospitalizations due to excerbations in the last 12 months								Number of patients in Treated Set	
Exacerbations- Overview		0		1		2		…			
		N	%	N	%	N	%	N	%	N	%
Exacerbations in the last 12 months	0										
	1										
	2										
	…										
Number of patients in Treated Set											100.0

Table 15.1.4 12: Treated Set- COPD degree of severity (GOLD group)

COPD degree of severity (GOLD group)	N	%
A		
B		
C		
D		
Missing		
Number of patients in Treated Set		

Table 15.1.4 13: Treated Set- COPD degree of severity (GOLD group) [grouped]

COPD degree of severity (GOLD group) [grouped]	N	%
A/B		
C/D		
Missing		
Number of patients in Treated Set		

Table 15.1.4 14: Treated Set- COPD degree of severity (GOLD group) – Distribution

		A		B		C		D		Missing	
GOLD stadium- Distribution		N	%	N	%	N	%	N	%	N	%
Symptoms	Exacerbations										
0-1	0-1										
	>=2										
2-4	0-1										
	>=2										
Number of patients in Treated Set											

Table 15.1.4 15: Treated Set- COPD degree of severity (GOLD group) – Smoking

GOLD stadium- Smoking	A		B		C		D		Missing	
	N	%	N	%	N	%	N	%	N	%
Smoker										
Ex-smoker										
Non-smoker										
Missing										
Number of patients in Treated Set										

Table 15.1.4 16: Treated Set- COPD degree of severity (GOLD group) – ICS at baseline

GOLD stadium- ICS at baseline	A		B		C		D		Missing	
	N	%	N	%	N	%	N	%	N	%
No baseline ICS										
ICS only at baseline										
LABA+ICS at baseline										
Missing										
Number of patients in Treated Set										

Table 15.1.4 17: Treated Set- Patients with concomitant diseases

anamnesis.disease Patients with concomitant diseases	N	%
No		
Yes		
Missing		
Number of patients in Treated Set		

Table 15.1.4 18: Treated Set- Concomitant diseases (multiple answers possible)

Concomitant diseases	N	%
anamnesis.disease_allergic		
Allergic		
anamnesis.disease_gastro		
Gastrointestinal/Hepatobiliary		
anamnesis.disease_pulmo		
Pulmonary (except COPD)		
anamnesis.disease_reproductive		
Reproductive		
anamnesis.disease_renal		
Renal/Urogenital		
anamnesis.disease_psychic		
Psychiatric		
anamnesis.disease_neuro		
Neurologic		
anamnesis.disease_cardiac		
Cardial		
anamnesis.disease_vascular		
Vascular		
anamnesis.disease_metabolic		
Metabolic/Endocrine		
anamnesis.disease_muscular		
Muscular-skeletal/Dermatological		
anamnesis.disease_other		
Other		
Number of patients in Treated Set		

Table 15.1.4 19: Treated Set- Concomitant diseases- Gastrointestinal/Hepatobiliary (multiple answers possible)

Gastrointestinal/Hepatobiliary disease	N	%
anamnesis.disease_gastro_gerd		
Gastro-esophageal reflux disease (GERD)		
anamnesis.disease_gastro_other		
Other		
Patients with gastrointestinal/hepatobiliary diseases		
Number of patients in Treated Set		

Table 15.1.4 20: Treated Set- Concomitant diseases- Pulmonary (except COPD) (multiple answers possible)

Pulmonary (except COPD)	N	%
anamnesis.disease_pulmo_cancer		
Lung cancer		
anamnesis.disease_pulmo_other		
Other		
Patients with pulmonary diseases		
Number of patients in Treated Set		

Table 15.1.4 21: Treated Set- Concomitant diseases- Metabolic/Endocrine (multiple answers possible)

Metabolic/Endocrine	N	%
anamnesis.disease_metabolic_dia		
Diabetes mellitus		
anamnesis.disease_metabolic_oth		
Other		
Patients with metabolic/endocrine diseases		
Number of patients in Treated Set		

Table 15.1.4 22: Treated Set- Concomitant diseases- Muscular-skeletal/ Dermatological (multiple answers possible)

Muscular-skeletal/Dermatological	N	%
anamnesis.disease_muscular_osteo		
Osteoporosis		
anamnesis.disease_muscular_other		
Other		
Patients with muscular-skeletal/ dermatological diseases		
Number of patients in Treated Set		

Table 15.1.4 23: Treated Set- Smoking

anamnesis.smoker Smoking	N	%
Smoker		
Ex-smoker		
Non-smoker		
Missing		
Number of patients in Treated Set		

Table 15.1.4 24: Treated Set- Smoking- Pack-years

anamnesis.smoker_pack_years	N	Mean	SD	Min	Median	Max	Nmiss
Pack-years							

Table 15.1.4 25: Treated Set- Patients with concomitant medication (except respiratory therapeutics)

anamnesis.medication Concomitant medication	N	%
No		
Yes		
Missing		
Number of patients in Treated Set		

Table 15.1.4 26: Treated Set- Diseases treated with concomitant medication (except respiratory therapeutics)- (multiple answers possible)

anamnesis_medication.disease Concomitant medication- Disease treated	N	%
Allergic		
Gastrointestinal/Hepatobiliary- Gastro esophageal reflux disease (GERD)		
Gastrointestinal/Hepatobiliary- Other		
Pulmonary (except COPD)- Lung cancer		
Pulmonary (except COPD)- Other		
Reproductive		
Renal/Urogenital		
Psychiatric		
Neurologic		
Cardial		
Vascular		
Metabolic/Endocrine- Diabetes mellitus		
Metabolic/Endocrine- Other		
Muscular-skeletal/Dermatological- Osteoporosis		
Muscular-skeletal/Dermatological- Other		
Other		
Number of patients in Treated Set		

Table 15.1.4 27: Treated Set- Concomitant medication (except respiratory therapeutics)- Continuation or new prescription (multiple answers possible)

anamnesis_medication.type Concomitant medication- Continuation or new prescription	N	%
Continuation		
New prescription		
Missing		
Number of patients in Treated Set		

Table 15.1.4 28: Treated Set- Spiolto® Respimat® - Patient trained to use inhaler

anamnesis.spiolto_training Patient trained to use inhaler	N	%
No		
Yes		
Missing		
Number of patients in Treated Set		

Table 15.1.4 29: Treated Set- Treatment with past COPD therapies (6 weeks prior to start of study treatment) according to mMRC value

	mMRC value											
anamnesis.respiratory	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4		Total	
Treatment with past COPD therapies	N	%	N	%	N	%	N	%	N	%	N	%
No												
Yes												
Missing												
Number of patients in Treated Set												

Table 15.1.4 30: Treated Set- Treatment with past COPD therapies (6 weeks prior to start of study treatment)- Respiratory therapeutics (multiple answers possible)

anamnesis_resp.therapy/anamnesis_resp_prescribe	Withdrawn		New		Continued		Missing	
Treatment with past COPD therapies- Therapeutics	N	%	N	%	N	%	N	%
Short-acting β_2-Agonist								
Long-acting β_2-Agonist								
Short-acting anticholinergic								
Long-acting anticholinergic								
Long-acting anticholinergic and long-acting β_2-Agonist in a fixed combination								
Short-acting anticholinergic and short-acting β_2-Agonist in a fixed combination								
Long-acting β_2-Agonist and inhaled corticosteroid in a fixed combination								
Inhaled corticosteroid								
Systemic corticosteroid								
Theophylline								
Roflumilast (Daxas®)								
Other								
Missing								
Number of patients in Treated Set								

Visit 2 (after approx. 6 weeks of therapy)

Table 15.1.4 31: Treated Set- Therapy with Spiolto® Respimat® carried out regularly

visit.spiolto_regular Therapy with Spiolto® Respimat® carried out regularly	N	%
No		
Yes		
Missing		
Number of patients in Treated Set with visit 2		

Table 15.1.4 32: Treated Set- Reason for therapy with Spiolto® Respimat® carried out irregularly

visit.spiolto_regular_reason Reason for irregular treatment	N	%
Adverse event		
Serious adverse event		
Patient's wish		
Other		
Missing		
Number of patients with irregular treatment		

Table 15.1.4 33: Treated Set- Changes of treatment with other COPD related therapies besides Spiolto® Respimat® since visit 1 [i.e. new therapy introduced or existing baseline therapy discontinued*]

visit.further_resp Changes of treatment with other COPD related therapies	N	%
No		
Yes		
Missing		
Number of patients in Treated Set with visit 2		

*New therapy: New therapy in addition to already existing baseline therapies besides Spiolto® Respimat®

Table 15.1.4 34: Treated Set- Changes of treatment with other COPD related therapies besides Spiolto® Respimat® since visit 1- Affected respiratory therapeutics (multiple answers possible)

visit_resp.therapeutic Changes of treatment with other COPD related therapies- Affected therapeutics		N	%
New therapy in addition to already existing baseline therapies besides Spiolto® Respimat® introduced after visit 1	Short-acting β_2-Agonist		
	Long-acting β_2-Agonist		
	Short-acting anticholinergic		
	Long-acting anticholinergic		
	Long-acting anticholinergic and long-acting β_2-Agonist in a fixed combination		
	Short-acting anticholinergic and short-acting β_2-Agonist in a fixed combination		
	Long-acting β_2-Agonist and inhaled corticosteroid in a fixed combination		
	Inhaled corticosteroid		
	Systemic corticosteroid		

visit_resp.therapeutic		N	%
Changes of treatment with other COPD related therapies- Affected therapeutics			
	Theophylline		
	Roflumilast (Daxas®)		
	Other		
	Number of patients in Treated Set with visit 2		
Components of existing baseline therapy at visit 1 discontinued since then	Short-acting β_2-Agonist		
	Long-acting β_2-Agonist		
	Short-acting anticholinergic		
	Long-acting anticholinergic		
	Long-acting anticholinergic and long-acting β_2-Agonist in a fixed combination		
	Short-acting anticholinergic and short-acting β_2-Agonist in a fixed combination		
	Long-acting β_2-Agonist and inhaled corticosteroid in a fixed combination		
	Inhaled corticosteroid		
	Systemic corticosteroid		
	Theophylline		
	Roflumilast (Daxas®)		
	Other		
	Number of patients in Treated Set with visit 2		

Table 15.1.4 35: Treated Set- Changes of concomitant diseases since visit 1 [i.e. new diagnosis or now-defunct diagnosis]

visit.disease	N	%
Changes of concomitant diseases		
No		
Yes		
Missing		
Number of patients in Treated Set with visit 2		

Table 15.1.4 36: Treated Set- Changes of concomitant diseases- Diseases (multiple answers possible)

visit_disease.disease		N	%
Changes of concomitant diseases- Diseases			
A new diagnosis after visit 1	Allergic		
	Gastrointestinal/Hepatobiliary- Gastro esophageal reflux disease (GERD)		
	Gastrointestinal/Hepatobiliary- Other		
	Pulmonary (except COPD)- Lung cancer		
	Pulmonary (except COPD)- Other		
	Reproductive		
	Renal/Urogenital		
	Psychiatric		
	Neurologic		

visit_disease.disease		N	%
Changes of concomitant diseases- Diseases			
	Cardial		
	Vascular		
	Metabolic/Endocrine- Diabetes mellitus		
	Metabolic/Endocrine- Other		
	Muscular-skeletal/Dermatological- Osteoporosis		
	Muscular-skeletal/Dermatological- Other		
	Other		
	Number of patients in Treated Set with visit 2		
Existing diagnosis at visit 1 now-defunct	Allergic		
	Gastrointestinal/Hepatobiliary- Gastro esophageal reflux disease (GERD)		
	Gastrointestinal/Hepatobiliary- Other		
	Pulmonary (except COPD)- Lung cancer		
	Pulmonary (except COPD)- Other		
	Reproductive		
	Renal/Urogenital		
	Psychiatric		
	Neurologic		
	Cardial		
	Vascular		
	Metabolic/Endocrine- Diabetes mellitus		
	Metabolic/Endocrine- Other		
	Muscular-skeletal/Dermatological- Osteoporosis		
	Muscular-skeletal/Dermatological- Other		
	Other		
	Number of patients in Treated Set with visit 2		

Table 15.1.4 37: Treated Set- Changes of concomitant medication since visit 1 [i.e. new medication introduced or existing medication discontinued]

visit.medication	N	%
Changes of concomitant medication		
No		
Yes		
Missing		
Number of patients in Treated Set with visit 2		

Table 15.1.4 38: Treated Set- Changes of concomitant medication- Disease treated

visit_medication.disease		N	%
Changes of concomitant medication- Disease treated			
New medication after visit 1	Allergic		
	Gastrointestinal/Hepatobiliary- Gastro esophageal reflux disease (GERD)		
	Gastrointestinal/Hepatobiliary- Other		
	Pulmonary (except COPD)- Lung cancer		
	Pulmonary (except COPD)- Other		
	Reproductive		
	Renal/Urogenital		
	Psychiatric		
	Neurologic		
	Cardial		
	Vascular		
	Metabolic/Endocrine- Diabetes mellitus		
	Metabolic/Endocrine- Other		
	Muscular-skeletal/Dermatological- Osteoporosis		
	Muscular-skeletal/Dermatological- Other		
	Other		
	Number of patients in Treated Set with visit 2		
Existing medication at visit 1 discontinued since then	Allergic		
	Gastrointestinal/Hepatobiliary- Gastro esophageal reflux disease (GERD)		
	Gastrointestinal/Hepatobiliary- Other		
	Pulmonary (except COPD)- Lung cancer		
	Pulmonary (except COPD)- Other		
	Reproductive		
	Renal/Urogenital		
	Psychiatric		
	Neurologic		
	Cardial		
	Vascular		
	Metabolic/Endocrine- Diabetes mellitus		
	Metabolic/Endocrine- Other		
	Muscular-skeletal/Dermatological- Osteoporosis		
	Muscular-skeletal/Dermatological- Other		
	Other		
	Number of patients in Treated Set with visit 2		

Table 15.1.4 39: Treated Set- Smokers at baseline- Current status (smoking status at visit 2)

visit.smoker Smoker at baseline- Current status	N	%
Patient still smokes		
Patient stopped smoking		
Missing		
Number of smokers at baseline in Treated Set with visit 2		

Table 15.1.4 40: Treated Set- Pregnancy during treatment

visit.pregnancy Pregnancy during treatment	N	%
No		
Yes		
Number of female patients in Treated Set with visit 2		

2.2.1.1.4 15.2. Efficacy evaluation

Primary endpoints

Table 15.2.1 1: Full Analysis Set- Total CCQ score- Share of patients with therapeutic success after 6 weeks (approximately), defined as 0.4-point decrease of total CCQ score between baseline and week 6 (approximately)

CCQ Share of patients with therapeutic success	N	%*	CI 95%
Therapy successful			
Therapy not successful			
Missing			
Total			

*percentage is based on the total number of patients, irrespective of the availability of the CCQ score

Table 15.2.1 2: Full Analysis Set- CCQ score

CCQ CCQ score		N	Mean	CI 95%	Std	Min	Median	Max	Nmiss
Baseline (Visit 1)	Symptom								
	Functional state (CCQ-4)								
	Mental state								
	Total CCQ score								
Week 6 (appr.) (Visit 2)	Symptom								
	Functional state (CCQ-4)								
	Mental state								
	Total CCQ score								

Secondary endpoints

Table 15.2.1 3: Full Analysis Set- Absolut change of CCQ score between baseline and week 6 (approximately)

CCQ CCQ score- Change between baseline and Week 6 (approximately)	N	Mean	CI 95%	Std	Min	Median	Max	Nmiss
Symptom								
Functional state (CCQ-4)								
Mental state								
Total CCQ score								

Table 15.2.1 4: Full Analysis Set- General condition of the patient evaluated by the physician (PGE- score)

General condition of patient (PGE score)*		N	%
anamnesis.general_condition	1		
Baseline (Visit 1)	2		
	3		
	4		
	5		
	6		
	7		
	8		
	Missing		
	Number of patients		
visit.general_condition	1		
Week 6 (approximately) (Visit 2)	2		
	3		
	4		
	5		
	6		
	7		
	8		
	Missing/Not applicable		
	Number of patients		

*poor=1-2, satisfactory=3-4, good=5-6, excellent=7-8

Table 15.2.1 5: Full Analysis Set- Patient satisfaction with Spiolto® Respimat®

Patient satisfaction		N	%
visit.satisfaction_spiolto	Very satisfied		
Patient overall satisfaction with Spiolto® Respimat® treatment	Satisfied		
	Rather satisfied		
	Neither satisfied nor dissatisfied		
	Rather dissatisfied		
	Dissatisfied		
	Very dissatisfied		
	Not answered		
	Missing		
	Total		
visit.satisfaction_inhalator	Very satisfied		
Patient satisfaction with inhaling from the Respimat® device	Satisfied		
	Rather satisfied		

Patient satisfaction		N	%
	Neither satisfied nor dissatisfied		
	Rather dissatisfied		
	Dissatisfied		
	Very dissatisfied		
	Not answered		
	Missing		
	Total		
visit.satisfaction_handling	Very satisfied		
Patient satisfaction with handling of the Respimat® inhalation device	Satisfied		
	Rather satisfied		
	Neither satisfied nor dissatisfied		
	Rather dissatisfied		
	Dissatisfied		
	Very dissatisfied		
	Not answered		
	Missing		
	Total		

Table 15.2.1 6: Full Analysis Set- Patient's willingness to continue Spiolto® Respimat®

visit.spiolto_continued Willing to continue treatment	N	%
Yes		
No		
Missing		
Number of patients with visit 2		

Table 15.2.1 7: Full Analysis Set- Reason for discontinuation of Spiolto® Respimat®

visit.spiolto_spiolto_reason Reason for treatment discontinuation	N	%
Adverse event		
Serious adverse event		
Patient's wish		
Withdrawal of informed consent		
Lost to follow-up		
Patient's death		
Other		
Missing		
Number of patients with visit 2		

2.2.1.1.5 15.3. Safety analysis

Extent of exposure

Table 15.3.1 1: Treated Set- Time between start of treatment and end of observation/discontinuation [weeks]

anamnesis.spiolto_date; visit.date; visit.spiolto_last_date	N	Mean	Std	Min	Median	Max	Nmiss
Time between start of treatment and end of observation/discontinuation							

Table 15.3.1 2: Treated Set- Survival status

sae.therapy; visit.done_reason Survival status	N	%
Patient died		
Patient alive		
No. of patients in Treated Set		

Safety

Table 15.3.2 1: Treated Set- Adverse events overall summary

	N (%)
Number of patients	xx (100.0)
Patients with investigator defined drug-related AE *{sae.spiolto_causality}*	xx (yy.y)
Patients with investigator defined drug-related AE leading to discontinuation of trial drug *{sae.spiolto_action_taken}*	xx (yy.y)
Patients with serious AE *{sae.sae}*	xx (yy.y)
Fatal *{sae.criteria_fatal}*	xx (yy.y)
Life threatening *{sae.criteria_life_therating}*	xx (yy.y)
Persistant or significant disability/incapacity *{sae.criteria_disability}*	xx (yy.y)
Hospitalization *{sae.criteria_hospital}*	xx (yy.y)
Prolongation of hospitalization necessary *{sae.criteria_prolonged}*	xx (yy.y)
Congenital anomaly/birth defect *{sae.criteria_congenital}*	xx (yy.y)
Other important medical event *{sae.criteria_other}*	xx (yy.y)
Patients with serious AE leading to discontinuation *{sae.sae} {sae.spiolto_action_taken}*	xx (yy.y)
Patients with serious drug-related AE *{sae.sae} {sae.spiolto_causality}*	xx (yy.y)

Drug-related adverse events (Drug-related AE)

Table 15.3.2 2: Treated Set- Drug-related AE according to MedDRA-SOC and PT (event based)

sae.nci Drug-related AE (event based)		N	%
SOC1	PT1		
	PT2		
	…		
SOC2	PT1		
	PT2		
	…		

sae.nci		N	%
Drug-related AE (event based)			
…	PT1		
	PT2		
	…		
Total			

Table 15.3.2 3: Treated Set- Drug-related AE by MedDRA system organ class and preferred term- Maximum NCI grade per patient

sae.nci		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
Drug-related AE-Maximum grade per patient		N	%	N	%	N	%	N	%	N	%	N	%
Any SOC													
SOC1	PT1												
	PT2												
	…												
SOC2	PT1												
	PT2												
	…												
…	PT1												
	PT2												
	…												
No. of patients in Treated Set													

Table 15.3.2 4: Treated Set- Number of patients with drug-related AE occurring with share in preferred term greater than 5% by primary system organ class and preferred term

	N (%)
Total with drug-related AE occurring with share in preferred term greater than 5%	xx (100.0)
Primary SOC *{sae.nci}*	xx (yy.y)
Preferred term	xx (yy.y)
…	xx (yy.y)

Table 15.3.2 5: Treated Set- Drug-related AE- Worst outcome per patient

sae.outcome	N	%
Drug-related AE- Worst outcome		
Recovered/Resolved		
Not yet recovered/resolved		
Recovered/resolved with sequelae		
Fatal		
Unknown		
No drug-related AE		
No. of patients in Treated Set		

Order: From best to worst: Recovered/resolved; Recovered/resolved with sequelae; Not recovered/Not resolved; Unknown; Fatal

Table 15.3.2 6: Treated Set- Drug-related AE- Patients with at least one drug-related AE for which therapy was required

sae.therapy Drug-related AE- Therapy required	N	%
No		
Yes		
Missing		
No drug-related AE		
No. of patients in Treated Set		

Table 15.3.2 7: Treated Set- Drug-related AE- Patient pregnant at AE

sae.pregnancy Drug-related AE- Pregnant	N	%
No		
Yes		
Not applicable		
Missing		
Total		

Table 15.3.2 8: Treated Set- Drug-related AE- Week of pregnancy

sae.pregnancy_week	N	Mean	SD	Min	Median	Max	Nmiss
Drug-related AE- Week of pregnancy							

Table 15.3.2 9: Treated Set- Drug-related AE- Action taken concerning therapy (patient based; multiple answers possible)

sae.nci; sae.spiolto_action_taken Drug-related AE- Action taken	N	%
Continued		
Reduced		
Stopped		
Increased		
Missing		
No. of patients with drug-related AE		

Table 15.3.2 10: Treated Set- Drug-related AE leading to treatment discontinuation by MedDRA system organ class and preferred term

sae.nci Drug-related AE leading to discontinuation (patient based)		N	%
Any SOC			
SOC1	PT1		
	PT2		
	…		
SOC2	PT1		
	PT2		

sae.nci		N	%
Drug-related AE leading to discontinuation (patient based)			
	…		
…	PT1		
	PT2		
	…		
No. of patients in Treated Set			

Table 15.3.2 11: Treated Set- Drug-related AE- Improvement after stop of therapy (patient based; multiple answers possible)

sae.spiolto_action_taken_stop	N	%
Drug-related AE- Improvement after stop		
No		
Yes		
Missing		
No. of patients with stop of treatment because of drug-related AE		

Table 15.3.2 12: Treated Set- Drug-related AE- Re-exposition done for at least one event

sae.spiolto_action_taken_expo	N	%
Drug-related AE- Re-exposition		
No		
Yes		
Not applicable		
Missing		
No. of patients with stop of treatment because of drug-related AE		

Table 15.3.2 13: Treated Set- Drug-related AE- Recurrence of at least one TEAE after re-exposition

sae.spiolto_action_taken_again	N	%
Drug-related AE- Recurrence after re-exposition		
No		
Yes		
Missing		
No. of patients with re-exposition		

Table 15.3.2 14: Treated Set- Incorrect administration of medication (multiple answers possible)

Incorrect administration of medication	N	%
sae.application_abuse		
Abuse/Incorrect use		
sae.application_medication_error		
Medication error		
sae.application_overdose		

Incorrect administration of medication	N	%
Overdosing		
sae.application_other		
Other		
Patients with incorrect administration		
Number of patients with drug-related AE		

Serious AE

Table 15.3.2 15: Treated Set- Serious AE according to MedDRA-SOC and PT (event based)

sae.nci; sae.sae		N	%
Serious AE (event based)			
SOC1	PT1		
	PT2		
	…		
SOC2	PT1		
	PT2		
	…		
…	PT1		
	PT2		
	…		
Total			

Table 15.3.2 16: Treated Set- Serious AE- Reason for seriousness (patient based; multiple answers possible)

Reason for serious AE	N	%
sae.criteria_fatal		
Fatal		
sae.criteria_life_threatening		
Life threatening		
sae.criteria_disability		
Sustained or significant disability/incapacity		
sae.criteria.hospital		
Hospitalization required		
sae.criteria_prolonged		
Hospitalization extended		
sae.criteria_congenital		
Congenital anomaly		
sae.criteria_other		
Otherwise medically significant		
Number of patients with serious AE		

Table 15.3.2 17: Treated Set- Serious AE by MedDRA system organ class and preferred term- Maximum NCI grade per patient

sae.nci		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
Serious AE- Maximum grade per patient		N	%	N	%	N	%	N	%	N	%	N	%
Any SOC													
SOC1	PT1												
	PT2												
	…												
SOC2	PT1												
	PT2												
	…												
…	PT1												
	PT2												
	…												
No. of patients in Treated Set													

Table 15.3.2 18: Treated Set- Serious AE- Worst outcome per patient

sae.outcome; sae.sae	N	%
Serious AE- Outcome		
Recovered/Resolved		
Not yet recovered/resolved		
Recovered/resolved with sequelae		
Fatal		
Unknown		
No serious AE		
No. of patients in Treated Set		

Order: From best to worst: Recovered/resolved; Recovered/resolved with sequelae; Not recovered/Not resolved; Unknown; Fatal

Table 15.3.2 19: Treated Set- Serious AE- Action taken concerning treatment (patient based; multiple answers possible)

sae.nci; sae.spiolto_action_taken	N	%
Serious AE- Action taken		
Continued		
Reduced		
Stopped		
Increased		
Missing		
No. of patients with serious AE		

Table 15.3.2 20: Treated Set- Serious AE leading to treatment discontinuation by MedDRA system organ class and preferred term

sae.nci Serious AE leading to discontinuation (patient based)		N	%
Any SOC			
SOC1	PT1		
	PT2		
	…		
SOC2	PT1		
	PT2		
	…		
…	PT1		
	PT2		
	…		
No. of patients in Treated Set			

Table 15.3.2 21: Treated Set- Serious AE- Number of patients with at least one serious AE with causal relationship to treatment

sae.causality Serious AE- Relationship	N	%
No		
Yes		
Missing		
Total		

Table 15.3.2 22: Treated Set- Serious AE by relationship with Spiolto® Respimat® by MedDRA system organ class and preferred term

sae.nci; sae.spiolto_causality		Not related		Related		Total	
Serious AE by relationship (patient based)		N	%	N	%	N	%
Any SOC							
SOC1	PT1						
	PT2						
	…						
SOC2	PT1						
	PT2						
	…						
…	PT1						
	PT2						
	…						
No. of patients in Treated Set							

2.3 Sensitivity analysis I- Time between Visit 1 and Visit 2

Sensitivity analysis- Table 1: Full Analysis Set- Time between Visit 1 and Visit 2 [weeks]

Anamnesis.date.; visit.date	N	Mean	Std	Min	Median	Max	Nmiss
Sensitivity analysis I- Time between Visit 1 and Visit 2							

Sensitivity analysis- Table 2: Full Analysis Set- Time between Visit 1 and Visit 2 [categorical]

Anamnesis.date.; visit.date Sensitivity analysis I- Time between Visit 1 and Visit 2 [categorical]	N	%
< 4 weeks		
4-8 weeks		
> 8 weeks		
Patients in FAS		

Sensitivity analysis- Table 3: Analysis stratified by time between Visit 1 and Visit 2- Full Analysis Set- Total CCQ score- Share of patients with therapeutic success after 6 weeks (approximately)- defined as 0.4-point decrease of total CCQ score between baseline and week 6 (approximately)

CCQ Sensitivity analysis I- Share of patients with therapeutic success		N	%	CI 95%
< 4 weeks	Therapy successful			
	Therapy not successful			
	Missing			
	Total			
4-8 weeks	Therapy successful			
	Therapy not successful			
	Missing			
	Total			
> 8 weeks	Therapy successful			
	Therapy not successful			
	Missing			
	Total			
Total	Therapy successful			
	Therapy not successful			
	Missing			
	Total			

Sensitivity analysis- Table 4: Analysis stratified by time between Visit 1 and Visit 2- Full Analysis Set- Total CCQ score- Share of patients with therapeutic success- χ^2-Test (Fisher's Exact test)

Therapy success	p-Value
X^2-Test (Fisher's Exact test)	

Sensitivity analysis- Table 5: Analysis stratified by time between Visit 1 and Visit 2- Full Analysis Set- CCQ score

CCQ Sensitivity analysis I- CCQ score			N	Mean	CI 95%	Std	Min	Median	Max	Nmiss
Baseline (Visit 1)	Symptom	< 4 weeks								
		4-8 weeks								
		> 8 weeks								
		Total								
	Functional state (CCQ-4)	< 4 weeks								
		4-8 weeks								
		> 8 weeks								
		Total								
	Mental state	< 4 weeks								
		4-8 weeks								
		> 8 weeks								
		Total								
	Total CCQ score	< 4 weeks								
		4-8 weeks								
		> 8 weeks								
		Total								
Week 6 (appr.) (Visit 2)	Symptom	< 4 weeks								
		4-8 weeks								
		> 8 weeks								
		Total								
	Functional state (CCQ-4)	< 4 weeks								
		4-8 weeks								
		> 8 weeks								
		Total								
	Mental state	< 4 weeks								
		4-8 weeks								
		> 8 weeks								
		Total								
	Total CCQ score	< 4 weeks								
		4-8 weeks								
		> 8 weeks								
		Total								

*2.4 Sensitivity analysis II- Non-estimated number of exacerbations**

*****If the physician does not know the exact number of exacerbations he is allowed to give an estimate. In this analysis only those documentations are considered in which the physician knew the exact number, i.e. the number is not estimated (non-estimated).

Sensitivity analysis- Table 6: Full Analysis Set- Patients with non-estimated number of exacerbations

anamnesis.estimate Sensitivity analysis II- Non-estimated number of exacerbations	N	%
No		
Yes		
Patients in FAS		

Sensitivity analysis- Table 7: Full Analysis Set- Patients with non-estimated number of exacerbations- Exacerbations in the last 12 months

anamnesis.exacerbation	Number of patients	Number of exa-cerbations	Mean	SD	Min	Median	Max	Nmiss	Patients with event	
									N	%
Sensitivity analysis II- Exacerbations in the last 12 months										

Sensitivity analysis- Table 8: Full Analysis Set- Patients with non-estimated number of exacerbations- Exacerbations in the last 12 months [categorical]

anamnesis.exacerbation; Sensitivity analysis II- Exacerbations in the last 12 months- Overview	N	%
No		
Yes		
Patients in FAS with non-estimated number of exacerbations		

Sensitivity analysis- Table 9: Full Analysis Set- Patients with non-estimated number of exacerbations- COPD degree of severity (GOLD group)

Non-estimated number of exacerbations- COPD degree of severity (GOLD group)	N	%
A		
B		
C		
D		
Missing		
Patients in FAS with non-estimated number of exacerbations		

Sensitivity analysis- Table 10: Full Analysis Set- Patients with non-estimated number of exacerbations- COPD degree of severity (GOLD group) [grouped]

Sensitivity analysis II- COPD degree of severity (GOLD group) [grouped]	N	%
A/B		
C/D		
Missing		
Patients in FAS with non-estimated number of exacerbations		

Sensitivity analysis- Table 11: Full Analysis Set- Patients with non-estimated number of exacerbations- COPD degree of severity (GOLD group) – Distribution

		A		B		C		D		Missing	
Sensitivity analysis II- GOLD stadium- Distribution		N	%	N	%	N	%	N	%	N	%
Symptoms	Exacerbations										
0-1	0-1										
	>=2										
2-4	0-1										
	>=2										
Patients in FAS with non-estimated number of exacerbations											

Sensitivity analysis- Table 12: Full Analysis Set- Patients with non-estimated number of exacerbations- Total CCQ score- Share of patients with therapeutic success after 6 weeks (approximately)- defined as 0.4-point decrease of total CCQ score between baseline and week 6 (approximately)

CCQ		N	%	CI 95%
Sensitivity analysis II- Share of patients with therapeutic success				
Gold A	Therapy successful			
	Therapy not successful			
	Missing			
	Total			
GOLD B	Therapy successful			
	Therapy not successful			
	Missing			
	Total			
GOLD C	Therapy successful			
	Therapy not successful			
	Missing			
	Total			
GOLD D	Therapy successful			
	Therapy not successful			
	Missing			
	Total			
Total	Therapy successful			
	Therapy not successful			

CCQ		N	%	CI 95%
Sensitivity analysis II- Share of patients with therapeutic success				
	Missing			
	Total			

Sensitivity analysis- Table 13: Full Analysis Set- Patients with non-estimated number of exacerbations- CCQ score

CCQ			N	Mean	CI 95%	Std	Min	Median	Max	Nmiss
Sensitivity analysis II- CCQ score										
Baseline (Visit 1)	Symptom	A								
		B								
		C								
		D								
		Total								
	Functional state (CCQ-4)	A								
		B								
		C								
		D								
		Total								
	Mental state	A								
		B								
		C								
		D								
		Total								
	Total CCQ score	A								
		B								
		C								
		D								
		Total								
	Symptom	A								
		B								
		C								
		D								
		Total								
	Functional state (CCQ-4)	A								
		B								
		C								
		D								
		Total								
	Mental state	A								
		B								
		C								

CCQ Sensitivity analysis II- CCQ score			N	Mean	CI 95%	Std	Min	Median	Max	Nmiss
		D								
		Total								
	Total CCQ score	A								
		B								
		C								
		D								
		Total								

2.5 Tables for subgroup analysis

For each of the following subgroups

- Maintenance naïve patients vs. patients already treated at baseline (i.e. before start of therapy with Spiolto® Respimat®) with long-acting bronchodilators (LAMA only or LABA only) or LABA+ICS [Only if both categories include more than 20% of all patients, respectively]
- Maintenance naïve patients vs. patients already treated at baseline with long-acting bronchodilators (LAMA only) vs patients already treated at baseline with long-acting bronchodilators (LABA only) vs patients already treated at baseline with long-acting bronchodilators (LABA+ICS)
- ICS treatment at baseline (Patients with ICS vs. Patients without ICS) [Only if both categories include more than 20% of all patients, respectively]
- GOLD spirometric classifications (Group 1) (1/2 vs. 3/4)
- GOLD spirometric classifications (Group 2) (2 vs. 3 vs. 4)
- GOLD patients group (Group 1) (B vs. C/D)
- GOLD patients group (Group 2) (B vs. C vs. D)
- Age (≤ 65 years vs. >65 years)
- Exacerbations in the last 12 months (≤1 vs. ≥2)
- Hospitalizations due to exacerbations (0 vs. ≥1)
- Smoker (Smoker vs. Ex-Smoker vs. Non-smoker)
- Patients with cardiac comorbidities (No vs. Yes)
- Continuation of Spiolto® Respimat® usage after end of study observation (No vs. Yes)

Table 1 to Table 9 given below will be displayed for each subgroup, respectively, subgroup and group 1, group … are respective placeholders.

Primary endpoints

Subgroup analysis- Table 1: Analysis stratified by subgroup- Full Analysis Set- Total CCQ score- Share of patients with therapeutic success after 6 weeks (approximately), defined as 0.4-point decrease of total CCQ score between baseline and week 6 (approximately)

CCQ Share of patients with therapeutic success		N	%	CI 95%
Group 1	Therapy successful			
	Therapy not successful			
	Missing			
	Total			
Group …	Therapy successful			
	Therapy not successful			
	Missing			
	Total			
Total	Therapy successful			

CCQ		N	%	CI 95%
Share of patients with therapeutic success				
	Therapy not successful			
	Missing			
	Total			

Subgroup analysis- Table 2: Analysis stratified by subgroup- Full Analysis Set- Total CCQ score- Share of patients with therapeutic success- χ^2-Test (Fisher's Exact test)

X^2-Test (Fisher's Exact test) - Therapy success	p-Value
Group 1 vs. Group …	

Subgroup analysis- Table 3: Analysis stratified by subgroup- Full Analysis Set- CCQ score

CCQ			N	Mean	CI 95%	Std	Min	Median	Max	Nmiss
CCQ score										
Baseline (Visit 1)	Symptom	Group 1								
		Group …								
		Total								
	Functional state (CCQ-4)	Group 1								
		Group …								
		Total								
	Mental state	Group 1								
		Group …								
		Total								
	Total CCQ score	Group 1								
		Group …								
		Total								
Week 6 (appr.) (Visit 2)	Symptom	Group 1								
		Group …								
		Total								
	Functional state (CCQ-4)	Group 1								
		Group …								
		Total								
	Mental state	Group 1								
		Group …								
		Total								
	Total CCQ score	Group 1								
		Group …								
		Total								

Secondary endpoints

Subgroup analysis- Table 4: Analysis stratified by subgroup- Full Analysis Set- Absolut change of CCQ score between visit 1 and visit 2

CCQ CCQ score- Change between baseline and Week 6 (approximately)		N	Mean	CI 95%	Std	Min	Median	Max	Nmiss
Symptom	Group 1								
	Group …								
	Total								
Functional state (CCQ-4)	Group 1								
	Group …								
	Total								
Mental state	Group 1								
	Group …								
	Total								
Total CCQ score	Group 1								
	Group …								
	Total								

Subgroup analysis- Table 5: Analysis stratified by subgroup- Full Analysis Set- Absolut change of CCQ- Wilcoxon Rank-Sum Test (Mann-Whitney-U-Test)/Kruskal-Wallis Test

Change from baseline- Wilcoxon Rank-Sum Test (Mann-Whitney-U-Test)/Kruskal-Wallis Test	p-Value
CCQ-4 score- Group 1 vs. Group …	
Total CCQ score- Group 1 vs. Group …	

Subgroup analysis- Table 6: Analysis stratified by subgroup- Full Analysis Set- General condition of patient (PGE score)

General condition of patient (PGE score)		Group 1		Group …		Total	
		N	%	N	%	N	%
anamnesis.general_condition	1						
Baseline (Visit 1)	2						
	3						
	4						
	5						
	6						
	7						
	8						
	Missing						
	Number of patients						
visit.general_condition	1						
Week 6 (approximately) (Visit 2)	2						
	3						
	4						

General condition of patient (PGE score)		Group 1		Group …		Total	
		N	%	N	%	N	%
	5						
	6						
	7						
	8						
	Missing						
	Number of patients						

*bad=1-2, satisfactory=3-4, good=5-6, excellent=7-8

Subgroup analysis- Table 7: Analysis stratified by subgroup- Full Analysis Set- General condition of patient (PGE score)- χ^2-Test

PGE- X^2-Test*	p-Value
Baseline- Group 1 vs. Group …	
Week 6 (approximately) - Group 1 vs. Group …	

*If χ^2-Test is not valid, Fisher's Exact test will be done or PGE will be treated as continuous variable and compared by Wilcoxon Rank-Sum Test (Mann-Whitney-U-Test)/Kruskal-Wallis Test.

Subgroup analysis- Table 8: Analysis stratified by subgroup- Full Analysis Set- Patient satisfaction with Spiolto® Respimat®

Patient satisfaction		Group 1		Group …		Total	
		N	%	N	%	N	%
visit.satisfaction_spiolto	Very satisfied						
Patient overall satisfaction with Spiolto® Respimat® treatment	Satisfied						
	Rather satisfied						
	Neither satisfied nor dissatisfied						
	Rather dissatisfied						
	Dissatisfied						
	Very dissatisfied						
	Not answered						
	Missing						
	Total						
visit.satisfaction_inhalator	Very satisfied						
Patient satisfaction with inhaling from the Respimat® device	Satisfied						
	Rather satisfied						
	Neither satisfied nor dissatisfied						
	Rather dissatisfied						
	Dissatisfied						
	Very dissatisfied						
	Not answered						
	Missing						
	Total						
visit.satisfaction_handling	Very satisfied						
Patient satisfaction with	Satisfied						

Patient satisfaction		Group 1		Group …		Total	
		N	%	N	%	N	%
handling of the Respimat® inhalation device	Rather satisfied						
	Neither satisfied nor dissatisfied						
	Rather dissatisfied						
	Dissatisfied						
	Very dissatisfied						
	Not answered						
	Missing						
	Total						

Subgroup analysis- Table 9: Analysis stratified by subgroup- Full Analysis Set- Patient satisfaction with Spiolto® Respimat®- χ^2-Test

Satisfaction assessment- X^2-Test*	p-Value
Patient overall satisfaction with Spiolto® Respimat® therapy- Group 1 vs. Group …	
Patient satisfaction with inhalation device Respimat®- Group 1 vs. Group …	
Patient satisfaction with handling of the inhalation device- Group 1 vs. Group …	

*If χ^2-Test is not valid, Fisher's Exact test will be done or satisfaction will be treated as continuous variable and compared by Wilcoxon Rank-Sum Test (Mann-Whitney-U-Test)/Kruskal-Wallis Test.

2.6 Appendix

Appendix 1: Other reason for not performing corresponding visit (free text)

[anamnesis,visit].done_reason_spec	Baseline		Visit 2	
Other reason for not performing corresponding visit	N	%	N	%
Reason 1				
Reason 2				
…				
Total				

Appendix 2: Other concomitant diseases during observation (free text)

[anamnesis,visit].disease_other_spec	Baseline		Visit 2	
Other concomitant diseases	N	%	N	%
Disease 1				
Disease 2				
…				
Total				

Appendix 3: Concomitant medication during observation (free text)

[anamnesis,visit]_medication.drug	N	%
Concomitant medication		
Medication 1		
Medication 2		
…		
Total		

Appendix 4: Concomitant medication during observation- Other diseases treated

[anamnesis,visit]_medication.disease_spc	N	%
Concomitant medication- Other diseases treated		
Disease 1		
Disease 2		
…		
Total		

Appendix 5: Other respiratory therapeutics prior/during observation (free text)

[anamnesis;visit]_resp.therapy_spec	Baseline		Visit 2	
Other respiratory therapeutics	N	%	N	%
Therapeutic 1				
Therapeutic 2				
…				
Total				

Appendix 6: Respiratory therapeutics prior/during observation- Trade name (free text)

[anamnesis,visit]_resp.therapy_spec	Baseline		Visit 2	
Trade name of therapeutic	N	%	N	%
Name 1				
Name 2				
…				
Total				

Appendix 7: Other reasons for irregular treatment with Spiolto® Respimat® (free text)

visit.spiolto_regular_reason_spc	N	%
Other reason for irregular treatment with Spiolto® Respimat®		
Reason 1		
Reason 2		
…		
Total		

Appendix 8: Other reasons for no continuation of Spiolto® Respimat® treatment (free text)

visit.spiolto_reason_spec	N	%
Other reason for no continuation of Spiolto® Respimat® treatment		
Reason 1		
Reason 2		
…		
Total		

Appendix 9: Adverse events- No causality with Spiolto®- Suspected context (free text)

sae.spiolto_causality_spec	N	%
No causality with Spiolto®- Suspected context		
Context 1		
Context 2		
…		
Total		

Appendix 10: Adverse events- Other reason for seriousness (free text)

sae.criteria_other_spec	N	%
Adverse events- Other reason for seriousness		
Criteria 1		
Criteria 2		
…		
Total		

Appendix 11: Cause of death (free text)

sae.criteria_other_spec Cause of death	N	%
Cause 1		
Cause 2		
…		
Total		

2.7 Listings

Listing 1: Patients with visit 1- Violation of inclusion or exclusion criteria (Patients with violations only)

org. name; org.city	patient.no				
Site	Patient-No.	Violation of inclusion criteria	Which criteria	Violation of exclusion criteria	Which criteria

Listing 2: Patients with visit 1- Disposition

org. name; org.city	patient.no				
Site	Patient-No.	Included in Treated Set	Reason, why not	Included in FAS	Reason, why not

Listing 3: Treated Set- GOLD group

org. name; org.city	patient.no	mmrc.activity	anamnesis.exacerbation	anamnesis.estimate	anamnesis.exacerbation_hospital	anamnesis.estimate_hospital	
Site	Patient-No.	mMRC classification	Exacerbations within the last 12 months before initial visit	Number of exacerbations estimated?	Hospitalizations due to exacerbations	Number of hospitalizations due to exacerbations estimated?	GOLD group

Listing 4: Treated Set- Patient characteristics

org. name; org.city	patient.no	Age	patient. gender	anamnesis.copd_year	anamnesis.spiolto_training
Site	Patient-No.	Age	Gender	Year of initial COPD diagnosis	Training with Spiolto® Respimat®

Listing 5: Treated Set- Subgroup classification

org. name; org.city	patient. no	Age	anamnesis_respiratory; anamnesis_resp.therapy		anamnesis .copd_ severity		anamn esis. exacer bation	anamnesis. exacerbation_ hospital	anam- nesis. smoker	anamnesis. disease_ cardiac	anamnesis. spiolto_ reason
Site	Patient-No.	Age	Maintenance naïve/ Pretreated	ICS treatment at baseline	COPD degree of severity	GOLD group	Within the last 12 months before initial visit		Smoker	Cardiac comorbidities	Continuation of medication after end of observation
							Exacer-bations	Hospitalizations due to excerbations			

Listing 6: Treated Set- Study course (Visit 2)

org. name; org.city	patient. no	visit. done	visit.done_ reason	visit.spiolto_regular	visit.spiolto_ regular_reason	visit.smoker_ change	visit.spiolto_ pregnancy	visit.spiolto_ continued	visit.spiolto_ reason
Site	Patient-No.	Visit 2 done	Reason why not	Therapy with Spiolto® Respimat® carried out regularly	Reason for irregular treatment	Smoker-Changes in smoking since visit 1	Pregnancy during treatment	Continuation of medication after end of observation	Reason for discontinuation

Listing 7: Treated Set- Concomitant diseases at baseline

org. name; org.city	patient.no	anamnesis.disease	anamnesis.disease_allergic;…; anamnesis.disease_other
Site	Patient-No.	Concomitant diseases	Which disease

Listing 8: Treated Set- Concomitant diseases during study course

org. name; org.city	patient.no	visit.disease	visit_disease.type ; visit_disease.disease	
Site	Patient-No.	Change of concomitant diseases	Existing diagnosis at visit 1 now-defunct	New diagnosis after visit 1

Listing 9: Treated Set- Concomitant medication at baseline

org. name; org.city	patient.no	anamnesis.medication	anamnesis_medication.drug	anamnesis_medication.disease
Site	Patient-No.	Concomitant medication	Which medication	Disease treated

Listing 10: Treated Set- Concomitant medication during study course

org. name; org.city	patient.no	visit.disease	visit_medication.type ; visit_medication.disease; visit_medication.drug			
Site	Patient-No.	Change of concomitant medciation	Existing medication at visit 1 discontinued since then- Medication	Existing medication at visit 1 discontinued since then- Disease treated	New medication after visit 1- Medication	New medication after visit 1- Disease treated

Listing 11: Treated Set- Treatment with past COPD therapies (Patients with past COPD therapies only)

org. name; org.city	patient.no	anamnesis.respiratory	anamnesis_resp.therapy	anamnesis_resp.name	anamnesis_resp.prescribe
Site	Patient-No.	Treatment with past COPD therapies	Therapeutics	Trade name	Prescription

Listing 12: Treated Set- Treatment with other COPD related therapies besides Spiolto® Respimat® during study course

org. name; org.city	patient.no	visit.disease	visit_resp.type ; visit_resp.therapeutic	
Site	Patient-No.	Change of other COPD related therapies besides Spiolto®	Components of existing baseline therapy at visit 1 discontinued since then	New therapy in addition to already existing baseline therapies besides Spiolto® Respimat® introduced after visit 1

Listing 13: Full Analysis Set- CCQ – Primary endpoint

org. name; org.city	patient.no	ccq.q_01-ccq.q_10																			
Site	Patient-No.	Baseline- Questions										Visit 2- Questions									
		1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10

Listing 14: Full Analysis Set- Primary and secondary endpoint- Therapeutic success and change between baseline and Visit 2

org. name; org.city	patient. no	ccq.q_01-ccq.q_10													
Site	Patient-No.	Symptom (Q1; Q2; Q5; Q6)			Functional state (CCQ-4) (Q7-Q10)				Mental state (Q3; Q4)			Total CCQ score			
		Baseline	Visit 2	Change	Baseline	Visit 2	Change	Success	Baseline	Visit 2	Change	Baseline	Visit 2	Change	Success

Listing 15: Full Analysis Set- Secondary endpoints

org. name; org.city	patient. no	anamnesis. general_condition	visit.general_ condition	visit.satisfaction_spiolto	visit.satisfaction_inhalator	visit.satisfaction_handling
Site	Patient-No.	Baseline- PGE score	Week 6 (appr.)- PGE score	Patient overall satisfaction with Spiolto® Respimat® treatment	Patient satisfaction with inhaling from the Respimat® device	Patient satisfaction with handling of the Respimat® inhalation device

Listing 16: Treated Set - Drug-related adverse events

org. name; org.city	patient.no	Age	patient. gender	sae.nci	Coded by	Coded by	sae.start; anamnesis. spiolto_date; visit.date; visit.spiolto_last_date	sae. start	sae. end	sae.therapy	sae. outcome	sae.spiolto_ action_taken	sae.sae
Site	Patient-No.	Age	Sex	Event	SOC term	PT term	Point in time*	Start date	End date	Therapy required	Outcome	Action taken	Serious?

Listing 17: Treated Set - Serious adverse events

org. name; org.city	patient. no	Age	patient. gender	sae.nci	Coded by	Coded by	sae.start; anamnesis. spiolto_date; visit.date; visit.spiolto_ last_date	sae. start	sae. end	sae. outcome	sae.spiolto _causality	sae.spiolto_ action_taken	sae.criteria_[fatal; life_ threatening; disability; hospital; prolonged; congenital; other]
Site	Patient-No.	Age	Sex	Event	SOC term	PT term	Point in time*	Start date	End date	Outcome	Relation	Action taken	Reason

*** Point in time ∈ {Screening; Treatment; Post-treatment}**

Listing 18: Treated Set – Cause of death

org. name; org.city	patient.no	Age	patient.gender	sae.death_date	sae.death_cause
Site	Patient-No.	Age	Sex	Date of death	Cause of death

Tables

Table 15.3.2 10: Treated Set- Drug-related AE leading to treatment discontinuation by MedDRA system organ class and preferred term
Table 15.3.2 11: Treated Set- Drug-related AE- Improvement after stop of therapy (patient based; multiple answers possible)
Table 15.3.2 12: Treated Set- Drug-related AE- Re-exposition done for at least one event
Table 15.3.2 13: Treated Set- Drug-related AE- Recurrence of at least one TEAE after re-exposition
Table 15.3.2 14: Treated Set- Incorrect administration of medication (multiple answers possible)
Table 15.3.2 15: Treated Set- Serious AE according to MedDRA-SOC and PT (event based)
Table 15.3.2 16: Treated Set- Serious AE- Reason for seriousness (patient based; multiple answers possible)
Table 15.3.2 17: Treated Set- Serious AE by MedDRA system organ class and preferred term- Maximum NCI grade per patient
Table 15.3.2 18: Treated Set- Serious AE- Worst outcome per patient
Table 15.3.2 19: Treated Set- Serious AE- Action taken concerning treatment (patient based; multiple answers possible)
Table 15.3.2 20: Treated Set- Serious AE leading to treatment discontinuation by MedDRA system organ class and preferred term
Table 15.3.2 21: Treated Set- Serious AE- Number of patients with at least one serious AE with causal relationship to treatment
Table 15.3.2 22: Treated Set- Serious AE by relationship with Spiolto® Respimat® by MedDRA system organ class and preferred term

Sensitivity analyses

Sensitivity analysis- Table 1: Full Analysis Set- Time between Visit 1 and Visit 2 [weeks]
Sensitivity analysis- Table 2: Full Analysis Set- Time between Visit 1 and Visit 2 [categorical]
Sensitivity analysis- Table 3: Analysis stratified by time between Visit 1 and Visit 2- Full Analysis Set- Total CCQ score- Share of patients with therapeutic success after 6 weeks (approximately)- defined as 0.4-point decrease of total CCQ score between baseline and week 6 (approximately)
Sensitivity analysis- Table 4: Analysis stratified by time between Visit 1 and Visit 2- Full Analysis Set- Total CCQ score- Share of patients with therapeutic success- χ^2-Test (Fisher's Exact test)
Sensitivity analysis- Table 5: Analysis stratified by time between Visit 1 and Visit 2- Full Analysis Set- CCQ score
Sensitivity analysis- Table 6: Full Analysis Set- Patients with non-estimated number of exacerbations
Sensitivity analysis- Table 7: Full Analysis Set- Patients with non-estimated number of exacerbations- Exacerbations in the last 12 months
Sensitivity analysis- Table 8: Full Analysis Set- Patients with non-estimated number of exacerbations- Exacerbations in the last 12 months [categorical]
Sensitivity analysis- Table 9: Full Analysis Set- Patients with non-estimated number of exacerbations- COPD degree of severity (GOLD group)
Sensitivity analysis- Table 10: Full Analysis Set- Patients with non-estimated number of exacerbations- COPD degree of severity (GOLD group) [grouped]

Sensitivity analysis- Table 11: Full Analysis Set- Patients with non-estimated number of exacerbations- COPD degree of severity (GOLD group) – Distribution

Sensitivity analysis- Table 12: Full Analysis Set- Patients with non-estimated number of exacerbations- Total CCQ score- Share of patients with therapeutic success after 6 weeks (approximately)- defined as 0.4-point decrease of total CCQ score between baseline and week 6 (approximately)

Sensitivity analysis- Table 13: Full Analysis Set- Patients with non-estimated number of exacerbations- CCQ score

Subgroup analyses

Subgroup analysis- Table 1: Analysis stratified by subgroup- Full Analysis Set- Total CCQ score- Share of patients with therapeutic success after 6 weeks (approximately), defined as 0.4-point decrease of total CCQ score between baseline and week 6 (approximately)

Subgroup analysis- Table 2: Analysis stratified by subgroup- Full Analysis Set- Total CCQ score- Share of patients with therapeutic success- χ^2-Test (Fisher's Exact test)

Subgroup analysis- Table 3: Analysis stratified by subgroup- Full Analysis Set- CCQ score

Subgroup analysis- Table 4: Analysis stratified by subgroup- Full Analysis Set- Absolut change of CCQ score between visit 1 and visit 2

Subgroup analysis- Table 5: Analysis stratified by subgroup- Full Analysis Set- Absolut change of CCQ- Wilcoxon Rank-Sum Test (Mann-Whitney-U-Test)/Kruskal-Wallis Test

Subgroup analysis- Table 6: Analysis stratified by subgroup- Full Analysis Set- General condition of patient (PGE score)

Subgroup analysis- Table 7: Analysis stratified by subgroup- Full Analysis Set- General condition of patient (PGE score)- χ^2-Test

Subgroup analysis- Table 8: Analysis stratified by subgroup- Full Analysis Set- Patient satisfaction with Spiolto® Respimat®

Subgroup analysis- Table 9: Analysis stratified by subgroup- Full Analysis Set- Patient satisfaction with Spiolto® Respimat®- χ^2-Test

Appendix

Appendix 1: Other reason for not performing corresponding visit (free text)

Appendix 2: Other concomitant diseases during observation (free text)

Appendix 3: Concomitant medication during observation (free text)

Appendix 4: Concomitant medication during observation- Other diseases treated

Appendix 5: Other respiratory therapeutics prior/during observation (free text)

Appendix 6: Respiratory therapeutics prior/during observation- Trade name (free text)

Appendix 7: Other reasons for irregular treatment with Spiolto® Respimat® (free text)

Appendix 8: Other reasons for no continuation of Spiolto® Respimat® treatment (free text)

Appendix 9: Adverse events- No causality with Spiolto®- Suspected context (free text)

Appendix 10: Adverse events- Other reason for seriousness (free text)

Appendix 11: Cause of death (free text)

Listings

Listing 1: Patients with visit 1- Violation of inclusion or exclusion criteria (Patients with violations only)