Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	**c19714253-01**
BI Study Number:	1237- 0070
BI Investigational Product(s):	Spiolto® Respimat®
Title:	Non-interventional, cross-sectional, multicenter study to describe the exacerbations profile of C**OP**D patients **T**reated with **I**CS in a real-life primary care population in Spain. OPTI Study.
Brief lay title	The OPTI study in Spain looks at the history flare-ups in patients with Chronic Obstructive Pulmonary Disease (COPD) treated with inhaled steroids.
Protocol version identifier:	1.0
Date of last version of protocol:	19 September 2017
PASS:	No
EU PAS register number:	The study will be registered in EU PAS Register (ENCePP) and clinicaltrials.gov
Active substance:	R03AL06 Tiotropium bromide + Olodaterol
Medicinal product:	Spiolto® Respimat® 2.5 microgram/2.5 microgram, inhalation solution; tiotropium/olodaterol
Product reference:	*NL/H/3157/001/DC*
Procedure number:	Not applicable
Marketing authorisation holder(s):	MAH: This study is initiated, managed and sponsored by:
Joint PASS:	*No*

Research question and objectives:	**Primary objective:** To describe the patient profile for patients treated with ICS at the time of study visit. The **secondary objectives** are: - To describe the patient profile for patients not treated with ICS at the time of study visit - To assess the proportion and the number (count) of patients with COPD treated with ICS at the time of study visit with or without moderate-to-severe exacerbations, both in the previous 1 year and previous 2 years before the study visit. - To assess the proportion and the number (count) of patients with COPD not treated with ICS at the time of study visit with or without moderate-to-severe exacerbations, both in the previous 1 year and previous 2 years before the study visit. - Use of rescue medication. - Adherence to treatment recommendations according GesEPOC guidelines. - To describe ICS-related adverse events.
Country(-ies) of study:	Spain
Author:	Mobile:
Marketing authorisation holder(s):	
Date:	19 September 2017

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ACOS	Asthma COPD overlap syndrome
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
ANOVA	Analysis of Variance
BMI	Body Mass Index
CA	Competent Authority
CI	Confidence Interval
CML	Clinical Monitor Local
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DMP	Data Management Plan
CTP	Clinical Trial Protocol
eCRF	Electronic Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1st second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
IB	Investigator's Brochure
ICS	Inhaled corticosteroid
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
LABD	Long-acting bronchodilators
mMRC	Modified Medical Research Council
MAH	Marketing Authorisation Holder
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
QoL	Quality of Life
TCM	Trial Clinical Monitor
TMMA	Team Member Medical Affairs
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

3. RESPONSIBLE PARTIES

Team Member Medical Affairs (TM MA)	
Trial Statistician (TSTAT)	
Medical Advisor	
Trial Clinical Monitor (TCM)	
Coordinating Investigator	
Coordinating Investigator	
Coordinating Investigator	

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®			
Name of active ingredient: R03AL06 Tiotropium bromide + Olodaterol			
Protocol date: 19 September 2017	**Study number:** 1237- 0070	**Version/Revision:** Version 1.0	**Version/Revision date:**
Title of study:	Non-interventional, cross-sectional, multicenter study to describe the exacerbations profile of COPD patients **T**reated with **I**CS in a real-life primary care population in Spain. OPTI Study.		
Rationale and background:	Chronic obstructive pulmonary disease (COPD) is essentially characterized by chronic airflow limitation that is not fully reversible and mainly associated with tobacco smoke. It is an underdiagnosed disease with high morbidity and mortality and is a very significant public health problem. COPD is a complex disease with a very heterogeneous clinical presentation. Within what we know as COPD, different phenotypes can be defined that have clinical, prognostic and therapeutic repercussions. GesEPOC guidelines identify four clinical phenotypes with differential treatment: non-exacerbator, mixed COPD - asthma syndrome (ACOS), exacerbator with emphysema and exacerbator with chronic bronchitis (1). Exacerbation is defined as an acute episode of clinical instability that occurs in the natural course of the disease and is characterized by a sustained deterioration of respiratory symptoms that goes beyond their daily variations. The main symptoms referred to are worsening of the dyspnoea, cough, increased volume and / or changes in the colour of the sputum. (1). Different clinical practice guidelines (2) recognize the usefulness of using inhaled corticosteroid (ICS) in patients who present frequent exacerbations despite optimal bronchodilator treatment, and their use associated with long-acting bronchodilators (LABD) produces a significant decrease in the number of exacerbations and an improved quality of life, even though they have not been shown to have a beneficial effect on mortality (3). However, clinical evidence has showed a higher prevalence and incidence of side effects when ICS is long-term used (such as pneumonias) (2). According to the new GOLD 2017 report (2) patients with 0-1 exacerbations (not leading to hospital admission – group A/B) treatment with ICS is not recommended and for patients with ≥ 2 exacerbations or ≥ 1 exacerbation leading to hospital admission (group		

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	C/D) the preferred option is Long acting bronchodilation. It is known that almost 2/3 of the COPD patients are non-exacerbators (4). In these patients, an inhaled corticosteroids (ICS) therapy is not recommended and despite of this, 61% of these patients are being treated with ICS (4). Additionally, a Spanish consensus in the use of ICS in COPD patients recommends that the ICS therapy should be withdrawn in those patients without evidence of exacerbations in the previous two years (5). However there are discrepancies between guidelines and real-life practice, as ICS are still being overused.		
Research question and objectives:	**Primary objective**: To describe the patient profile for patients treated with ICS at the time of study visit. The **secondary objectives** are: a) To describe the patient profile for patients not treated with ICS at the time of study visit b) To assess the proportion and the number (count) of patients with COPD treated with ICS at the time of study visit with or without moderate-to-severe exacerbations, both in the previous 1 year and previous 2 years before the study visit. c) To assess the proportion and the number (count) of patients with COPD not treated with ICS at the time of study visit with or without moderate-to-severe exacerbations, both in the previous 1 year and previous 2 years before the study visit. d) Use of rescue medication. e) Adherence to treatment recommendations according GesEPOC guidelines. f) To describe ICS-related adverse events.		
Study design:	Non-Interventional, descriptive, cross-sectional cohort and multicentre study with COPD patients attended at Spanish Primary Care offices.		
Population:	Approximately 1,000 patients with COPD are planned to be included in the study. To minimize selection bias at the patient level, the first 5 consecutive patients from each site who met all inclusion criteria and none of the exclusion criteria will be enrolled. Inclusion criteria: 1. Written informed consent prior to participation.		

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	2. Female and male patient ≥ 40 years of age. 3. COPD diagnosis more than two years before the study visit. 4. Previously confirmed COPD diagnosis (post-bronchodilator FEV_1/FVC ratio <70%) 5. Clinical data available 2 years before the study visit. 6. Ability to complete CAT – COPD Assessment Test. <u>Exclusion criteria:</u> 1. Current participation in any clinical trial involving a drug or device. 2. A moderate or severe exacerbation (requiring oral corticosteroid, antibiotics or hospitalization) during the study visit or within 4 weeks before the study visit.		
Variables:	- Age, gender, ethnicity. - Height & weight (BMI auto calculated). - Smoking history. - Pulmonary Function Test – Spirometry. - Bronchodilator test. - History and details of Exacerbations (last 2 years). - Episodes of wheezing in exacerbations. - COPD diagnosis (year). - History of asthma (yes/no) and year of diagnosis. - History of atopy (yes/no). - Blood Eosinophilia (number of eosinophils and %). - Inmunoglobulin E (Ig E). - Current COPD treatment (including ICS). - History of antibiotics and oral corticosteroids for COPD. - Rescue medication. - Comorbidities (COTE index). - Concomitant medication. - Occurrence of pneumonias, candidiasis and other AEs related		

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	with ICS treatment. - COPD GesEPOC 2017 phenotypes. - GOLD 2017 spirometric classifications (1, 2, 3, 4). - GOLD 2017 patient groups (A, B, C, D). - BODEx. (BMI / % FEV_1 / mMRC / severe Exacerbations) - Breathlessness based on mMRC score. - QoL: CAT – COPD Assessment Test.
Data sources:	Data will be obtained from patient medical records and during the study visit. Most of data will be available in the charts but as a routine clinical practice, some data could be missing. Data will be collected through an eCRF which will include all the study variables. CAT – COPD Assessment Test will be filled in by the patient following the user guide during the study visit and data will be entered electronically into the CRF system by the Investigator.
Study size:	It is planned that a total of approximately 1000 patients will be recruited in 200 sites for the study. Additional details regarding sample size considerations are provided in Section 9.5
Data analysis:	The **primary outcome** is to describe the proportion of patients currently on ICS who did not have moderate/severe exacerbation in the year prior to the study visit. Secondary outcomes are provided in Section 9.3.2.2 Since the study is descriptive, the variables included in the study objectives will be summarized overall and by factors of interest. All results will be summarized with measures of central tendency (mean and median), variability/dispersion (standard deviation and interquartile ranges), absolute and relative frequencies, and ranges. The analysis population will consist of all eligible patients (i.e. all patients fulfilling all inclusion criteria and no exclusion criteria). If patients have missing values for an outcome, those patients will be

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	excluded for that outcome's analysis. Missing data will not be imputed.		
Milestones:	Note that the times described below may be modified by the administrative processing periods for study initiation: - Final Protocol: September 2017 - Start of data collection: April 2018 - End of data collection: April 2019 - Final study report: November 2019		

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	**Planned Date**
IRB/IEC approval	December 2017
Start of data collection	April 2018
End of data collection	April 2019
Registration in the EU PAS register	November 2017
Final report of study results:	November 2019

7. RATIONALE AND BACKGROUND

Chronic obstructive pulmonary disease (COPD) is essentially characterized by chronic airflow limitation that is irreversible and mainly associated with tobacco smoke. It is an underdiagnosed disease with high morbidity and mortality and is a very significant public health problem.

COPD is a complex disease with a very heterogeneous clinical presentation. Within what we know as COPD, different phenotypes can be defined that have clinical, prognostic and therapeutic repercussions.

GesEPOC guidelines identify four clinical phenotypes with differential treatment: non-exacerbator, mixed COPD-asthma (ACOS), exacerbator with emphysema and exacerbator with chronic bronchitis. Exacerbation is defined as an acute episode of clinical instability that occurs in the natural course of the disease and is characterized by a sustained deterioration of respiratory symptoms that goes beyond their daily variations. The main symptoms referred to are worsening of the dyspnoea, cough, increased volume and / or changes in the colour of the sputum (1).

Different clinical practice guidelines (2) recognize the usefulness of using inhaled corticosteroid (ICS) in patients who present frequent exacerbations despite optimal bronchodilator treatment, and their use associated with long-acting bronchodilators (LABD) produces a significant decrease in the number of exacerbations and an improved quality of life, even though they have not been shown to have a beneficial effect on mortality (3). However, clinical evidence has showed a higher prevalence and incidence of side effects when ICS is long-term used (such as pneumonias) (2).

According to the new GOLD 2017 report (2) for patients with 0-1 exacerbations (not leading to hospital admission – group A/B) treatment with ICS is not recommended and for patients with ≥ 2 exacerbations or ≥ 1 exacerbation leading to hospital admission (group C/D) the preferred option is Long acting bronchodilation. It is known that almost 2/3 of the COPD patients are non-exacerbators; in these patients, an inhaled corticosteroids (ICS) therapy is not recommended and despite of this, 61% of these patients are being treated with ICS (4). Additionally, a Spanish consensus in the use of ICS in COPD patients recommends that the ICS therapy should be withdrawn in those patients without evidence of exacerbations in the previous two years (5). However there are discrepancies between guidelines and real-life practice, as ICS are still being overused.

8. RESEARCH QUESTION AND OBJECTIVES

This study has been designed in order to describe the COPD patient profile of patients treated with or without ICS in primary care, in Spain.

Primary objective:
To describe the patient profile for patients treated with ICS at the time of study visit.

Secondary objectives:

a) To describe the patient profile for patients not treated with ICS at the time of study visit.
b) To assess the proportion and the number (count) of patients with COPD treated with ICS at the time of study visit with or without moderate-to-severe exacerbations, both in the previous 1 year and previous 2 years before the study visit.
c) To assess the proportion and the number (count) of patients with COPD not treated with ICS at the time of study visit with or without moderate-to-severe exacerbations, both in the previous 1 year and previous 2 years before the study visit.
d) Use of rescue medication.
e) Adherence to treatment recommendations according GesEPOC guidelines.
f) To describe ICS-related adverse events.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This non-Interventional, descriptive, cross-sectional cohort and multicentre study will be conducted with COPD patients attended at Spanish Primary Care offices.

The design of the study impose an only visit to be performed that will coincide with one of those performed by the patients as part of routine follow-up of their disease, without interfering with usual clinical practice of the investigator.

A specific therapeutic strategy has already been assigned to each included patient, based on routine practice and without interference with the physician's prescription habits. The observational nature of the study is ensured as no diagnostic or therapeutic intervention outside of routine clinical practice will be applied.

9.2 SETTING

Approximately 1,000 patients with COPD are planned to be included in the study. To minimize selection bias at the patient level, the first 5 consecutive patients from each site who met all inclusion criteria and none of the exclusion criteria will be enrolled from approximately April 2018 and during one year.

It is necessary to ensure that study population is representative of the entire national territory. Therefore, patients will be recruited from primary care centers in different geographical areas according to the distribution of the overall population in this area. Site selection will be performed in order to secure representativeness of the COPD population.

9.2.1 Study sites

Approximately 200 primary care centers, who regularly attend COPD patients, will be selected to participate. It is necessary to ensure that study population is representative of the entire national territory, including sites of all 17 autonomous communities. Number of sites/patients in each Autonomous Communities will be approached according COPD population distribution extracted from Spanish Statistic National Institute (data available for 2014). Site feasibility assessments will be performed by the CRO during the site selection process.

9.2.2 Study population

To be eligible to participate in the study, patients must meet the following selection criteria. The patient will be considered included when he/she agrees to participate in the study by signing the informed consent.

Patients will be <u>included</u> in the study if all of the following criteria are met:

1) Written informed consent prior to participation.
2) Female and male patient ≥ 40 years of age.

3) COPD diagnosis more than 2 years before the study visit.
4) Previously confirmed COPD diagnosis (post-bronchodilator FEV_1/FVC ratio <70%)
5) Clinical data available 2 years before the study visit.
6) Ability to complete CAT – COPD Assessment Test.

Patients will be excluded from participating in this study if the following criterion is met:

1) Current participation in any clinical trial involving a drug or device.
2) A moderate or severe exacerbation (requiring oral corticosteroid, antibiotics or hospitalisation) during the study visit or within 4 weeks before the study visit.

In addition, a log of all patients included into the study (i.e. having given informed consent) will be maintained in the study file (ISF) at the study site.

9.2.3 Study visits

The design of the study impose an only one visit to be performed that will coincide with one of those performed by the patients as part of routine follow-up of their disease, without interfering with usual clinical practice of the investigator.

After signing the informed consent (if patient agreed to participate in the study) patients will be asked to answer the breathlessness scale (mMRC) and the CAT – COPD Assessment Test at the unique study visit. Other variables needed to answer study objectives will be obtained directly from patient medical records. The end of the study visit is the end of the study for each patient.

9.2.4 Study discontinuation

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

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any efficacy/safety information that could significantly affect continuation of the study
3. Violation of the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

The investigator / the study site will be reimbursed for reasonable expenses incurred in case of study termination (except in case of the third reason).

9.3 VARIABLES

9.3.1 Exposures

Patients in this study will have been prescribed a treatment for their COPD. They could have been prescribed ICS or not. Prescription of the treatments will have been done under the sole responsibility of the healthcare professional and before the study initiation visit.

In addition, no intervention, either diagnostic or therapeutic, will be applied to patients other than that used for routine clinical practice.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The primary outcome is to describe the proportion of patients currently on ICS who did not have moderate/severe exacerbation in the year prior to the study visit.

Table 9.3.2.1:1 Variable related to primary outcome

	Data from Medical Charts	Data Measured at Study Visit
History and details of Exacerbations (last 1 year).	X	

9.3.2.2 Secondary outcomes

The secondary outcomes are:

a) To describe the proportion of patients currently on ICS who have had moderate/severe exacerbation in the year prior to the study visit.
b) Proportion of patients with COPD treated with ICS at the time of study visit with or without moderate-to-severe exacerbations, in the previous 2 years before the study visit.
c) Proportion of patients with COPD not treated with ICS at the time of study visit with or without moderate-to-severe exacerbations, both in the previous 1 year and previous 2 years before the study visit.
d) Number (count) of moderate-to-severe exacerbations in COPD patients treated with ICS at the time of study visit, both in the previous 1 year and previous 2 years before the study visit.
e) Number (count) of moderate-to-severe exacerbations in COPD patients not treated with ICS at the time of study visit, both in the previous 1 year and previous 2 years before the study visit.
f) General patient profile for patients treated with ICS and patients not treated with ICS. These data will be obtained from medical charts.
g) Description of Rescue medication used in patients treated with ICS and without ICS (active substance, dose, start date, end date). These data will be obtained from medical charts.
h) Adherence to treatment recommendations according GesEPOC 2017 guidelines. For this analysis, patients will be stratified between patients with 0-1 exacerbations (not leading to hospital admission) and for patients with ≥ 2 exacerbations or ≥ 1 exacerbation leading to hospital admission in the last 1 year prior to index date. Taking into account the algorithm of treatment recommendations included in GesEPOC (phenotype) guidelines, we will define:

- Adherence:
  - Those patients (%) treated with ICS that according to GesEPOC guidelines should have been treated with ICS.
  - Those patients (%) not treated with ICS that according to GesEPOC guidelines should not have been treated with ICS.

- Non-Adherence:
  - Those patients (%) treated with ICS but according to GesEPOC guidelines should not have been treated with ICS.
  - Those patients (%) not treated with ICS but according to GesEPOC guidelines should have been treated with ICS.

i) To describe ICS-related adverse events (Pneumonia, Fracture, Skin thinning/easy bruising, Cataract, Diabetes, Oropharyngeal candidiasis). These data will be obtained from medical charts.

An exacerbation is defined as an acute worsening of respiratory symptoms that result in additional therapy (6):

- Moderate exacerbation: increase in, or new onset of, ≥ 2 respiratory symptoms (cough, sputum, dyspnea, wheezing, chest tightness) with ≥ 1 symptom lasting ≥ 3 days and leading the patient's attending physician to initiate treatment with systemic corticosteroids and/or antibiotics.
- Severe exacerbation: increase in or new onset of ≥ 2 respiratory symptoms (cough, sputum, dyspnoea, wheezing, chest tightness) with ≥ 1 symptom lasting ≥ 3 days and leading to patient's hospitalization.

9.3.3 Covariates

Table 9.3.3:1 Covariates related to patient profile

	Data from Medical Charts	Data Measured at Study Visit
Age, gender, ethnicity.	X	
Height & weight (BMI auto-calculated) *	X	
Smoking history.	X	
Pulmonary function test - Spirometry # *	X	
Bronchodilator test # * (FEV_1 increase, absolute values).	X	
Episodes of wheezing in exacerbations.	X	
COPD diagnosis (year)	X	

History of asthma (yes/no) and year of diagnose	X	
History of atopy (yes/no).	X	
Blood Eosinophilia (number of eosinophils and %) *	X	
Inmunoglobulin E (Ig E) *	X	
Current COPD treatment (including ICS: start and stop dates, dose, reason) §	X	
History and details of Exacerbations (last 2 years).	X	
History of antibiotics and oral corticosteriods for COPD	X	
Comorbidities (COTE index)	X	
Concomitant medication.	X	
COPD GesEPOC 2017 phenotypes	X	
GOLD 2017 spirometric classifications (1, 2, 3, 4).	**Auto-calculated**	
GOLD 2017 patient groups (A, B, C, D).	**Auto-calculated**	
BODEx (BMI / % FEV_1 / mMRC / severe Exacerbations)	**Auto-calculated**	
Breathlessness based on mMRC score.		X
QoL: CAT - COPD Assessment Test		X

* Last measure available

available in medical charts <12 months

§ Not including possible changes or new prescriptions done at study visit

The covariates will also be included as independent variables for multivariable analysis: COPD phenotypes, GOLD group, BODEx index, mMRC score and CAT – COPD Assessment Test.

9.4 DATA SOURCES

Data collection will be limited to those variables available in the medical records and data obtained / measured during the study visit (see Table 9.3.2.1:1 and Table 9:3:3: 1) of selected patients.

CAT – COPD Assessment Test will be filled in by the patient following the user guide during the study visit and data will be entered electronically into the CRF system.

9.5 STUDY SIZE

Due to the descriptive design of the proposed non interventional study, a formal sample size calculation has not been performed based on statistical power and protection for type I error.

In previously published studies in usual clinical practice in primary care in Spain (4), 66% of patients are non-exacerbators and of these, 61% are treated with ICS, therefore approximately 40% of all patients are currently treated with ICS without having exacerbations in the prior year.

Assuming a sample size of 900 patients and 40% of the patients are treated with ICS at the study visit and did not have a moderate or severe COPD exacerbation in the prior year, the 95% confidence interval for this proportion would be between 36.8% (lower limit) and 43.2% (upper limit). To account for a 10% drop-out rate (patients with inconsistent, incomplete or missing data), the sample size becomes 1,000 patients.

Table 9.5:1 Scenario for estimated proportions by 95% CI

Scenario for estimated proportions by 95% confidence intervals (95% CI)	1	2	3	4	5	6
Expected proportion	0.4			0.5		
Lower and Upper limit of 95% CI	(0.37;0.43)	(0.368;0.432)	(0.365;0.435)	(0.47;0.53)	(0.468;0.532)	(0.465;0.535)
Precission of estimation	0.03	0.032	0.035	0.03	0.032	0.035
N (at final analysis)	1000	900	753	1042	938	784
Dropout 10%	**1112**	**1000**	**838**	**1159**	**1043**	**872**

9.6 DATA MANAGEMENT

The data will be entered by the investigators themselves and/or authorized personnel directly in the electronic case report form (eCRF). A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous.

AE reconciliation will be performed by the CRO, quarterly after study initiation.

When data management is outsourced, the designated contract organization will be responsible for the development and implementation of the data management plan and preparation of the data handling report according to the sponsor´s standards.
The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system will meet the standards of the International Committee on Harmonization guideline E6R1 regarding electronic study data handling. Patient confidentiality will be strictly maintained.

9.7 DATA ANALYSIS

Analyses will be performed by Boehringer Ingelheim's designees. The analysis population will consist of all eligible patients (i.e. all patients fulfilling all inclusion criteria and no exclusion criteria).

In this non-interventional study, retrospective data from medical charts and data at the study visit will be collected for COPD patients. Once the study has been completed and all data

from the last patient have been recorded, the database will be closed and statistical analysis will be performed.

The proposed methods for statistical analysis presented below are a summary of the methods that will be applied in the study to analyze the data collected and to answer the study objectives.

Since the study is essentially descriptive the variables included in the study objectives will be summarized by factors of interest and globally. All results will be analysed with measures of central tendency (mean and median), variability/dispersion (standard deviation and interquartile ranges), absolute and relative frequencies, and ranges. 95% confidence intervals will be provided as appropriate. The level of significance will be established at the 0.05 level (two-sided).

A Statistical Analysis Plan (SAP), will be prepared to describe all processes, treatment and specifications for data collection, cleaning, validation and analysis.

9.7.1 Main analysis

All patients who have signed the informed consent and fulfil all selection criteria will be included in the analysis. If patients have missing values for an outcome, those patients will be excluded for that outcome's analysis. Missing data will not be imputed. Number of missing values will be presented for each outcome.

Descriptive statistics will be used for describing the patient profile. All results will be analyzed with measures of central tendency (mean and median), variability/dispersion (standard deviation and interquartile ranges), distributions of absolute and relative frequencies, and ranges. 95% confidence intervals will be provided as appropriate. The level of significance will be established at the 0.05 level (two-sided).

9.7.2 Further analysis

<u>For the secondary objectives:</u>

Categorical variables will be analysed using Fisher's Exact test and quantitative variables by means t-test for independent groups. In case of more than two groups, One-Way ANOVA will be used and an appropriated post-hoc analysis will be done. For quantitative variables that do not meet parametric applicability criteria, adequate statistical analysis will be used, as Mann-Whitney U test or Kruskal Wallis test.

Logistic regression will be used to assess the independent contribution of clinical and demographic factors to the estimation of proportions of interest-dependent variables, such as inadequate use of ICS in patients with COPD. Additionally, multivariate logistic regression models will be used to propose estimation of proportion of these patients of interest.

Descriptive statistics will be used for describing the use of rescue medication and adverse events ICS-related.

Any update of GesEPOC /GOLD guidelines and treatment recommendations during the study will be taken into account for analysis.

9.8 QUALITY CONTROL

The eCRF will include programmable edit checks to obtain feedback if data is missing, out of range, illogical or potentially erroneous. These checks will be performed once data is entered into the eCRF. Thus the data entered in to the eCRF will be validated within the system and the physician will receive alerts for missing or inconsistent data. In case any changes of already entered data will be required, an audit trail will be available.

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

Strict and continuous quality control will be maintained to ensure the accuracy and scientific rigor of the data obtained, maintaining uniform conditions for collecting the information. Quality control will be carried out by qualified personnel designated for this purpose.
A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent document of this study.

9.9 LIMITATIONS OF THE RESEARCH METHODS

A NIS is the most suitable design to obtain information about the use of medicines in everyday therapeutic practice and thus for investigating questions in everyday therapeutic practice. However, there are some limitations inherent to this design.

Consecutive enrolment will be employed to minimize selection bias. The entry criteria are less restrictive than the ones of a randomised clinical trial, which will permit the enrolment of a broader patient population. Additionally, as the setting is limited to the primary care setting, patients treated in other clinical settings may not be part of this study.

Another limitation is that data in medical records may have missing values and could reduce the validity of conclusions. However, the data included as variables in this study are those most frequent for COPD in world real practice.

Finally, recruitment period will include winter season. Due to seasonality of exacerbations in COPD, with higher incidence of exacerbations in winter season, this may account for the over-representation of exacerbator patients. To avoid this limitation, a full year for recruitment has been stablished.

Due to the cross-sectional study design no conclusion on any causal association can be drawn.

9.10 OTHER ASPECTS

Not applicable

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, either on paper or via remote data capture.

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

For eCRFs all data must be derived from source documents.

9.10.2.2 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. US Food and Drug Administration (FDA)). The Clinical Research Associate (CRA) / Clinical Monitor Local (CML) and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1.

9.10.3 Completion of study

The EC/competent authority in Spain needs to be notified about the end of the study (last patient out), or early termination of the study.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Quality Medicine auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the

study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IEC and the competent authority.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

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

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)
The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring

and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

The following are considered as AESIs:
No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

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

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

The following must be collected by the investigator in the (e)CRF from signing the informed consent onwards until the end of the study:

- All adverse drug reaction (ADRs) (serious and non-serious).
- All AEs with fatal outcome.

All ADRs , including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:
- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced

- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

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

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

Expedited Reporting of AEs and Drug Exposure During Pregnancy
The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study:

Table 11.2:1 Type of reports and timelines

Type of Report	Timeline
All **serious ADRs** associated with SPIOLTO®, STRIVERDI®, SPIRIVA® or ATROVENT®	immediately within 24 hours
All **AEs with fatal outcome** in patients	immediately within 24 hours

exposed to SPIOLTO®, STRIVERDI®, SPIRIVA® or ATROVENT®	
All **non-serious ADRs** associated with SPIOLTO®, STRIVERDI®, SPIRIVA® or ATROVENT®	7 calendar days
All **pregnancy monitoring** forms	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF pages and the NIS AE form.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than SPIOLTO®, STRIVERDI®, SPIRIVA® or ATROVENT® according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

Final study report will be distributed to national health authority and ethics committees.
The results of this study may be published in a national journal and presented in regional or national congresses.

13. REFERENCES

13.1 PUBLISHED REFERENCES

[1] Miravitlles et al. Clinical Practice Guideline for the Diagnosis and Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD) – the Spanish COPD Guideline (GesEPOC). 2017 version. Arch Bronconeumol 2017;53 (Supl 1):2-64.

[2] Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: goldcopd.org [accessed 15 November 2016]

[3] Nannini et al. Combined corticosteroid and long-acting beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev, 4 (2007), pp. CD006829

[4] Miravitlles et al. Frequency and characteristics of different clinical phenotypes of chronic obstructive pulmonary disease. Int J Tuberc Lung Dis. 2015 Aug; 19(8): 992-8.

[5] Alcázar Navarrete et al. Correct use of inhaled corticosteroids in chronic obstructive pulmonary disease: a consensus document. Working Group "Consensus document on the appropriate use of inhaled corticosteroids in COPD". Arch Bronconeumol. 2015 Apr; 51(4):193-8.

[6] Beeh et al. Characterisation of exacerbation risk and exacerbator phenotypes in the POET-COPD trial. Respiratory Research 2013, 14:116

13.2 UNPUBLISHED REFERENCES

Not applicable

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Title
<1>	Patient information and Informed Consent Form
<2>	Investigator List
<3>	Statistical Analysis Plan (SAP)
<4>	Data Management Plan (DMP)
<5>	Serious Adverse Event Report in Non-Interventional Studies (NIS (S)AE Form)
<6>	Pregnancy Monitoring Form

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Non-interventional, cross-sectional, multicenter study to describe the exacerbations profile of C**OP**D patients **T**reated with **I**CS in a real-life primary care population in Spain. OPTI Study.

Study reference number:

1237- 0070

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Study progress reports for EC and authorities will be done annually.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Descriptive study and measures of association

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.3
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Descriptive study and measures of association (logistic regression / negative binomial).

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.2 Age and sex?	☒	☐	☐	9.2.2
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Cross-sectional study. No follow-up is carried out

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Observational study. Patients treated as per routine clinical practice.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3

Comments:

Descriptive outcomes. For QoL: CAT – COPD Assessment Test.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7.1
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☒	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.2
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☒	☐	
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.7

Comments:

Descriptive study and measures of association (logistic regression / negative binomial)

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10.2

Comments:

Unique patient identification code numbers will be used.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Descriptive study and measures of association.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.2

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.2 Information bias?	☐	☐	☒	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.2

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10.1

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

ANNEX 3. ADDITIONAL INFORMATION

CAT – COPD Assessment Test

COPD Assessment Test Página 1 de 1

Name: Today's Date:

CAT™
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

Example: I am very happy	0 X 2 3 4 5	I am sad	
			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
			CLICK TO GET YOUR TOTAL SCORE!

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http://www.catestonline.org/english/indexEN.htm 11/08/2017

APPROVAL / SIGNATURE PAGE

Document Number: c19714253 **Technical Version Number:1.0**

Document Name: non-interventional-study-protocol-version-1.0

Title: Non-interventional, cross-sectional, multicenter study to describe the exacerbations profile of COPD patients Treated with ICS in a real-life primary care population in Spain. OPTI Study.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval- Safety Evaluation Therapeutic Area		21 Sep 2017 12:29 CEST
Approval-Medical		21 Sep 2017 14:09 CEST
Author-Trial Statistician		21 Sep 2017 16:00 CEST
Approval-Therapeutic Area		22 Sep 2017 11:45 CEST
Approval-Team Member Medical Affairs		02 Oct 2017 11:19 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed