Statistical Analysis Plan Template

BI Study Number 1237-0070.

Protocol Version 1.0. Date: 19 September 2017

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.

Author:

Version Number and Date: V1.0; 29 May 2019

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan <V1.0, 29 MAY 2019)> for Protocol 1237-0070.

	Name	Signature	Date
Author:			
Position:	Statistician		
Company:			

	Name	Signature	Date
Approved By:			
Position:	Project		
Company:			
Approved By:			
Position:	Medical Project		
Company:			
Approved By:			
Position:	Statistician		
Company:			

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1	20-JUL-2018		Not Applicable – First draft
0.2	20-FEB-2019		No
0.3	18-MAR-2019		No
0.4	24-APR-2019		No
0.5	07-MAY-2019		No
0.6	08-MAY-2019		No
0.7	21-MAY-2019		No

TABLE OF CONTENTS

1. ABBREVIATIONS

ACOS	Asthma COPD overlap syndrome
ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Confidence Interval
COTE	Copd cO-morbidity Test
ENR	Subjects enrolled
FEV_1	Forced expiratory volume in 1st second
FVC	Forced vital capacity
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
LABA	Long-acting beta2-agonist
mMRC	Modified Medical Research Council
TLF	Tables/Listings/Figures shells
SADR	Serious Adverse Drug Reaction
SABA	Short-acting beta2- agonists
SAMA	Short-acting muscarinic antagonist
SAP	Statistical Analysis Plan

2. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of treatment patterns and patient profile. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 1.0, dated 19 September 2017 and case report forms (CRFs) version 1.0, dated 28 June 2018.

3. STUDY 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.

3.1 Primary Objective

The primary objective is to describe the patient profile for patients treated with ICS at the time of study visit.

3.2 Secondary Objectives

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.

4. STUDY DESIGN

4.1 General Description

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 imposes 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.

4.2 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 Spain (Miravitlles, 2015), 66% of patients in usual clinical practice attending to primary care 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 1. Scenario for estimated proportions by 95% confidence intervals (95% CI)

	1	2	3	4	5	6	7	8
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)	(0.363;0.437)	(0.47;0.53)	(0.468;0.532)	(0.465;0.535)	(0.463;0.537)
Precision of estimation	0.030	0.032	0.035	0.037	0.030	0.032	0.035	0.037
N (at final analysis)	1000	900	753	674	1042	938	784	702
Dropout 10%	1112	1000	838	749	1159	1043	872	780

4.3 Description of the treatment

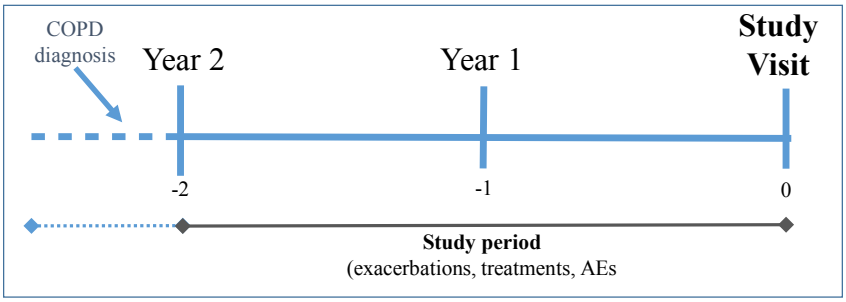
Patients in this study will have been prescribed a treatment for their COPD. They could have been prescribed ICS or not. Prescription of the treatments will have been done under the sole responsibility of the healthcare professional and before the study initiation visit.

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

4.4 Study flow/schedule

The design of the study imposes 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.

Figure 1. Study scheme for study periods



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.

4.5 Schedule of Events

The schedule of events can be found in Section 6 of the protocol (Milestones).

4.6 Changes to Analysis from Protocol

No changes in analysis or definitions included in the final protocol have been considered.

5. PLANNED ANALYSES

5.1 Interim Analysis

No interim analysis has been planned.

5.2 Final Analysis

All final, planned analyses identified in this SAP will be performed by Real-World Evidence Solutions (RWES) Biostatistics following SOPs. Final CSR will be performed using Boehringer Ingelheim template.

6. ANALYSIS SETS

6.1 Subjects enrolled (ENR)

Subjects enrolled (ENR) set will contain all subjects who provide informed consent for this study and are included in main database.

6.2 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will contain all subjects who provide informed consent for this study (ENR set) and fulfill all selection criteria. 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. This analysis set includes patients fulfilling these conditions:

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 FEV1/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, and will be excluded from this analysis set, 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.

6.3 Patients treated with ICS Analysis Set (PICAS)

The patients treated with ICS Analysis Set (PICAS) includes all patient in FAS set treated with ICS during the study period.

6.4 Safety Analysis Set - ICS

The patients in the Safety Analysis Set includes all patient in ENR set treated at least with one dose of ICS during the study period. All safety variables related with ICS will be analyzed using this analysis set.

6.5 Safety Analysis Set - SPIOLTO®, STRIVERDI®, SPIRIVA® or ATROVENT®

The patients in the Safety Analysis Set includes all patient in ENR set treated at least with one dose of SPIOLTO®, STRIVERDI®, SPIRIVA® or ATROVENT® during the study period. All safety variables related to Boehringer Ingelheim COPD drugs will be analyzed using this analysis set.

7. GENERAL CONSIDERATIONS

The design of the study imposes 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.

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.

The Investigator will enter the patient following the user guide during the study visit will fill in the CAT – COPD Assessment Test and mMRC data electronically into the eCRF system.

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

7.1 Reference Start/End Date

Reference start date is date of study visit, collected in the eCRF as mandatory variable. For this retrospective chart review study, index date is defined as date for data collection (patients attending to the participant site).

7.2 Common Calculations

7.2.1 Body Mass Index (BMI)

The formula to obtain Body Mass Index is the following: BMI (kg/ m^2) = weight (kg)/ height ^{2} (m) and BMI will be categorized into 5 categories according to the World Health Organization (WHO):

- Underweight: BMI< 18.5 kg/m^2
- Normal weight: 18.5 kg m^2<= BMI<= 25 kg/m^2
- Overweight: 25 kg/m^2< BMI<= 30 kg/m^2
- Obese: 30 kg/m^2<BMI<= 35 kg/m^2
- Severely Obese: BMI> 35 kg/m^2

7.2.2 Number of Pack-years

The number of **pack-years** is equal to the number of cigarettes smoked per day divided by 20 and multiplied by number of years smoked. The formula used for current smokers and ex-smokers will be:

Number of pack-years (for smokers) = (packs smoked per day) × (years smoking)

Number of pack-years (for Ex-Smokers) = (packs smoked per day) × (years smoking)

7.2.3 Time since COPD diagnosis

The number of years since diagnosis will be obtained as the difference between year of study visit and year of COPD diagnosis (+1). Years since diagnosis could be categorized according quartiles (or percentiles).

7.2.4 Time since Asthma diagnosis

In asthmatic patients, the number of years since diagnosis will be obtained as the difference between year of study visit and year of Asthma diagnosis (+1).

7.2.5 Spirometric values

Spirometric data are collected directly from clinical records. However, Predicted FEV_1/FVC pre and post bronchodilator and change in FEV_1 will be calculated using the formulas:

Predicted FEV1 (L) = 100 x FEV1 (L) / FEV1 (%)

Predicted FVC (L) = 100 x FVC (L) / FVC (%)

Change (L) in FEV1 = FEV1 Post (L) - FEV1 Pre (L)

Percentage (1) of change in FEV1 (%) = 100 x [FEV1 Post (L) - FEV1 Pre (L)] / Predicted FEV1 (L)

Percentage (2) of change in FEV1 (%) = 100 x [FEV1 Post (L) - FEV1 Pre (L)] / Predicted FEV1 Pre (L)

7.2.6 Number of exacerbations

7.2.6.1 Number of total exacerbations

The number of exacerbations (mild, moderate and severe) in the last two years will be the number of exacerbations registered in section 8 of CRF, whose date of exacerbation is included in the last 2 years or 730.50 days (365.25x2) before the study visit.

The number of exacerbations in the last year will be the number of exacerbations registered in section 8 of CRF, whose date of exacerbation is included in the last 365 days before the study visit.

In both cases, the number of exacerbations will be assumed as zero when “without exacerbation in the last 2 years” is ticked.

7.2.6.2 Number of severe exacerbations

The number of severe exacerbations in the last two years will be the number of exacerbations requiring hospitalization, registered in section 8 of CRF, whose date of exacerbation is included in the last 2 years or 730.5 days (365.25x2) before the study visit.

The number of severe exacerbations in the last year will be the number of exacerbations registered in section 8 of CRF, whose date of exacerbation is included in the last 365 days before the study visit and required hospitalization.

In both cases, the number of severe exacerbations will be assumed as zero when “without exacerbation in the last 2 years” is ticked.

7.2.7 Laboratory values

7.2.7.1 Eosinophils

Eosinophils will be categorized in two categories (for each unit) (Celli 2017) (GOLD 2019):

- If eosinophils are in %: <2% and ≥2 %
- If eosinophils are in cells/µl: <100, 100-299 and ≥300.

7.2.7.2 Immunoglobulin E

Immunoglobulin E (IgE) levels will be categorized according to these values, included in the Spanish Asthma guidelines (GEMA) and ACO (Cosio et al. 2016):

- ≤100 UI/ml
- >100 UI/ml

7.2.8 GOLD 2019

To determine the severity of all subjects with COPD (independently of FEV_1/FVC post-bronchodilation obtained), patients will be categorized into four levels, according to these criteria:

- Gold 1 (mild): FEV_1 (%)>= 80% predicted.
- Gold 2 (Moderate): 50% <= FEV_1 (%) <80% predicted.
- Gold 3 (Severe): 30% <= FEV_1 (%) <50% predicted.
- Gold 4 (Very serious): FEV_1 (%) <30% predicted.

In case the number of GOLD 4 subjects was less than 10, these will be grouped with the GOLD 3 subjects, forming a single category (GOLD 3-4).

7.2.9 BODEx Index

The BODEx index includes the body mass index (BMI), the degree of dyspnea measured with the mMRC scale, the pulmonary function measured with the FEV_1 (%) post-bronchodilation and the

number of severe exacerbations (only visits to hospital emergencies and admissions are included). It is a continuous variable with a range from 0 to 9 points.

Table A: Calculation of the BODEx Index for prognostic approach to COPD.

	Variables	Score			
		0	1	2	3
B	BMI (kg/m2)	>21	≤21		
O	FEV_1 (%)	≥65	50-64	36-49	≤35
D	Dyspnea (mMRC)*	0-1	2	3	4
Ex	Severe Exacerbations)	0	1-2	≥3	

Propuesto por (Soler-Cataluna et al. 2009)

Taking into account the score obtained in the BODEX index, they can be grouped into the following categories:

- Class I Mild: BODEx 0-2 points
- Class II Moderate: BODEx 3-4 points
- Class III Serious: BODEx 5-6 points
- Class IV Very serious: BODEx 7-9 points

7.2.10 COTE Index

The COTE comorbidity index was constructed from the 12 comorbidities that were associated with a statistically significant risk of death (Divo et al. 2012). Thus, comorbidities such as hypertension and hypercholesterolemia, which are very frequent in patients with COPD, would not be associated with higher mortality, while others would be, such as cancer (particularly lung, esophagus, pancreas and breast), anxiety, liver cirrhosis, atrial fibrillation, diabetes, pulmonary fibrosis, heart failure, gastroduodenal ulcer and coronary heart disease.

The sum of the points aims to capture the individual or combination of diseases that affect each patient. The total score ranges between 0 and 25 points. An increase of 1 point in the COTE index is associated with an increased risk of death from episodes related to COPD and not related to COPD.

Table B: Comorbidities associated with mortality and the COTE index

Disease	Points
Lung, esophagus, pancreas or breast cancer	6
Pulmonary fibrosis	2
Auricular Fibrillation / flutter	2
Congestive heart failure	1
Coronary artery disease	1
Gastroduodenal ulcer	1
Liver cirrhosis	2
Diabetic neuropathy	2
Anxiety	6
All other cancers	2
Total score	∑ (sum of all points)

The COTE index will also be described according to the mortality risk at this cut-off point:

- Low risk mortality: COTE index <4 points
- High risk mortality: COTE index ≥ 4 points.

7.2.11 Risk stratification

Patients will be classified according to their risk based on GesEPOC 2017 Spanish guideline:

- Low risk:
  - FEV_1(%) post-bronchodilation >= 50% and,
  - mMRC 0-2, and
  - 0 or 1 exacerbation in the last year, and
  - without hospitalization in the last year.
- High risk:
  - FEV_1(%) post-bronchodilation<50% or,
  - mMRC > 2 or mMRC = 2 with treatment or,
  - 2 or more exacerbation in the last year or,
  - 1 or more exacerbation with hospitalization in the last year.

7.2.12 Gold 2019 Classification

According to GOLD 2019 classification, four different types of patients will be considered:

- Patient A:
  - 0 or 1 exacerbations (not leading to hospital admission) and,
  - mMRC 0-1 and CAT < 10
- Patient B:
  - 0 or 1 exacerbations (not leading to hospital admission), and
  - mMRC >= 2 or CAT >= 10
- Patient C:
  - ≥ 2 exacerbations or >= 1 exacerbation leading to hospital admission, and
  - mMRC 0-1 and CAT < 10.
- Patient D:
  - ≥2 exacerbations or any >= 1 exacerbation leading to hospital admission, and
  - mMRC >= 2 or CAT >= 10.

7.2.13 CAT questionnaire score

The CAT questionnaire score will be obtained from the sum of the 8 items that each range from 0 (no symptoms) to 5 points (highest symptoms) (Available at http://www.catestonline.org/).

Table C: CAT questionnaire and responses

Item	Symptom	0 option	Range	5 option
1	Cough	I never cough	[0 5]	I cough all the time
2	Mucus	I have no phlegm (mucus) in my chest at all	[0 5]	My chest is completely full of phlegm (mucus)
3	Chest pressure	My chest does not feel tight at all	[0 5]	My chest feels very tight

Item	Symptom	0 option	Range	5 option
4	Dyspnea	When I walk up a hill or one flight of stairs I am not breathless	[0 5]	When I walk up a hill or one flight of stairs I am very breathless
5	Limitation in domestic activities	I am not limited doing any activities at home	[0 5]	I am very limited doing activities at home
6	Social limitation	I am confident leaving my home despite my lung condition	[0 5]	I am not at all confident leaving my home because of my lung condition
7	Sleep	I sleep soundly	[0 5]	I don't sleep soundly because of my lung condition
8	Energy	I have lots of energy	[0 5]	I have no energy at all
	TOTAL		[0-40]	

Missing or missing answers are not allowed to obtain a valid score. Therefore, the score range of this questionnaire ranges from 0 to 40 points. The score will be grouped into two categories:

- CAT <10: Low impact of COPD (Most days are good, the illness prevents the patient from doing one or two things he or she would like, coughing several days a week).
- CAT ≥10: Medium / high impact of COPD in the patient.

On the other hand, the CAT score will be categorized according to the impact of symptoms such as cough, mucus, chest pressure, dyspnea, limitation in domestic activities, social limitation and sleep and energy:

- Low impact: 0 <= CAT <= 10.
- Moderate impact: 11 <= CAT <= 20.
- High impact: 21 <= CAT <= 30.
- Very high impact: 31 <= CAT <= 40.

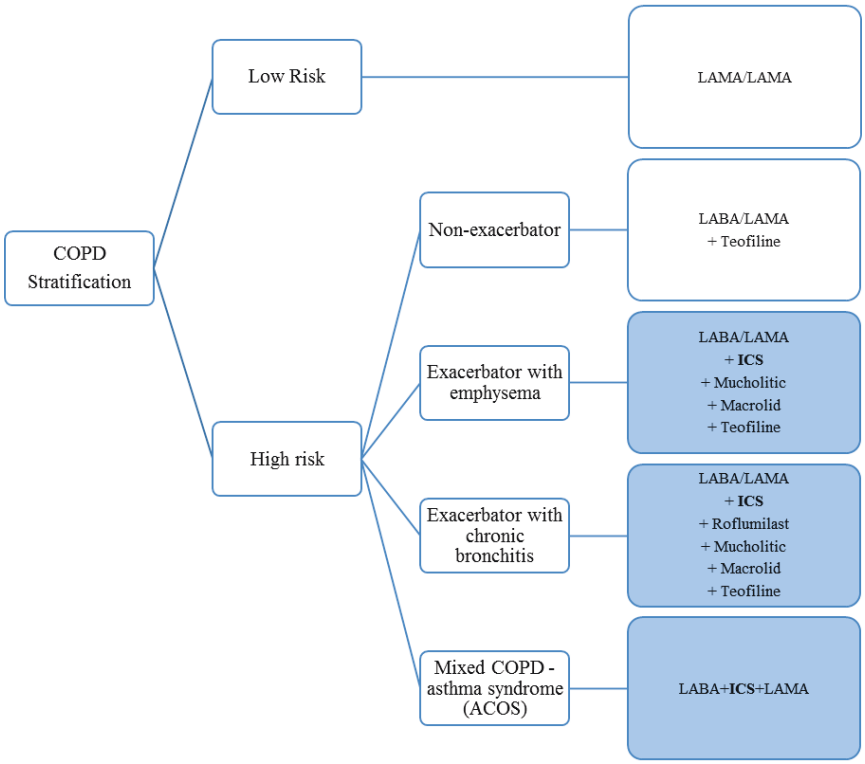
7.2.14 Adherence to ICS treatment recommendations according GesEPOC 2017 guideline.

GESEPOC 2017 guideline indicates different treatment options according to risk and COPD Phenotype, obtained from Figure 4 in "Guía española de la enfermedad pulmonar obstructiva crónica (GesEPOC) 2017. Tratamiento farmacológico en fase estable" in http://www.archbronconeumol.org/es-pdf-S0300289617300844.

The use of ICS is indicated only in these cases:

- Patients at high risk and,
  - Phenotypes: exacerbator with emphysema, exacerbator with chronic bronchitis or mixed COPD - asthma syndrome (ACOS). Only mixed phenotype allows the use of ICS as the first option. For exacerbator with chronic bronchitis and exacerbator with emphysema, the use of ICS is indicated after a first treatment of LAMA / LABA, when there is worsening of symptoms.

Table D: Treatment COPD scheme according to risk and phenotype



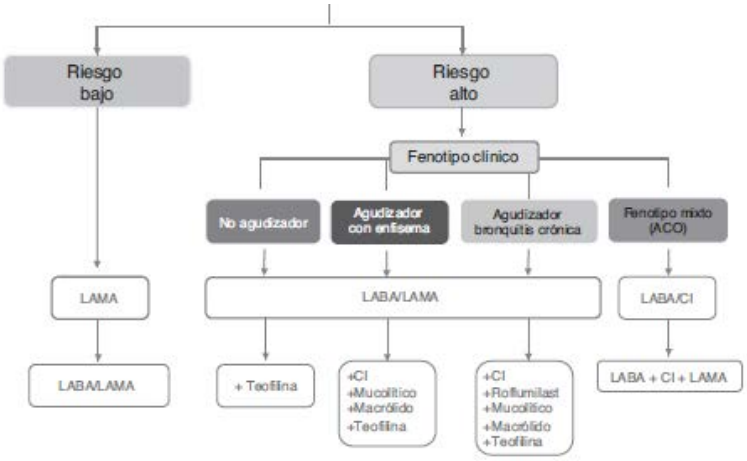


Figure 4 in "Guía española de la enfermedad pulmonar obstructiva crónica (GesEPOC) 2017. Tratamiento farmacológico en fase estable" (http://www.archbronconeumol.org/es-pdf-S0300289617300844)

Taking into account the algorithm of treatment recommendations included in GesEPOC (phenotype) guidelines, we will define patients as:

- Adherent to ICS (Adequate use of ICS):
  - Patients treated with ICS that according to GesEPOC guidelines should have been treated with ICS, or
  - Patients **not** treated with ICS that according to GesEPOC guidelines should **not** have been treated with ICS.
- Non-Adherent to ICS (Inadequate use of ICS):
  - Patients treated with ICS but according to GesEPOC guidelines should **not** have been treated with ICS, or
  - Patients **not** treated with ICS but according to GesEPOC guidelines should have been treated with ICS.

7.3 Software Version

All analyses will be conducted using SAS version 9.4. Other statistical packages that can be used are SPSS version 19.0 or higher.

8. STATISTICAL CONSIDERATIONS

8.1 Statistical Bias Reduction

Methods for handling bias will be discussed in the appropriate section for endpoints relating to missing values.

8.2 Statistical Tests and Confidence Intervals

Unless otherwise specified in the description of the analyses, a two-sided 95% confidence interval will be considered as a default (alpha = 5%). P-values are provided as descriptive representations of the data, since no confirmatory testing is planned.

8.3 Adjustments for Covariates and Factors to be Included in Analyses

For some of the endpoints, multivariate analyses will be performed using the following covariates and factors. For details of their inclusion in the models, see the specific analysis section. Fixed variables are:

- Age
- Gender

Some optional variables are:

- Smoking history
- Number of exacerbations in the previous year.
- FEV_1 (%) or COPD severity
- FVC (%)
- COPD Risk
- COPD Phenotype
- Gold 2019 Classification A, B, C, D
- Comorbidities as asthma and/or atopy
- CAT category

8.4 Missing data

Missing data will not be imputed, except in those variables described in their scoring system. According to general analysis, if patients have missing values for an outcome, those patients will be excluded for that outcome's analysis.

9. OUTPUT PRESENTATIONS

Tables and Figures on page 39 describe the presentations for this study and therefore the format and content of the summary TLFs to be provided by RWES Biostatistics.

10. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study. Subject disposition, withdrawals, and protocol violations (as defined in section 6.2), including inclusion and exclusion criteria will be presented for all enrolled patients.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the FAS. General statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be reported for this study:

- Age in study visit
- Sex
- Ethnicity
- Weight (kg), Height (cm), Body mass index (BMI) (kg/m^2) and categories
- Tobacco use (no-smoker, ex-smoker, smoker, packs/year)
- Time since diagnosis (years) - calculated relative to date of visit

11.1 Derivations

Derived variables are specified in section 7.2. Common Calculations on page 15 in this SAP.

12. SURGICAL AND MEDICAL HISTORY

Neither surgical nor medical history are collected in the eCRF.

13. COMORBIDITIES

Comorbidities are collected according to COTE index, plus asthma and athopy. Comorbidities will be presented for the FAS.

14. MEDICATIONS

Medications will be presented for the FAS and coded using the WHO Drug Dictionary (WHO-DD) and Anatomical Therapeutic Chemical (ATC) class coding (including ATC Level 3).

Medications (antibiotics and corticosteroids) used for exacerbations, will be considered only if start date is in the two years previous to the study visit. Medications started previously will not be considered for analysis due to the exacerbations are not included in the study period.

15. STUDY MEDICATION EXPOSURE

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.

16. PRIMARY OUTCOMES

16.1 Primary Endpoint

The primary endpoint for a patient, currently on ICS, is absence or presence of moderate/severe exacerbation in the year prior to the study visit.

16.1.1 Data Variables and Derivation

The data will be obtained from medical charts and it will be collected in “treatments” section (all treatment combinations including ICS will be considered as “yes” and also ICS discontinuation the same date of the study visit will be considered as “yes”). Treatments have to be started previously to the study visit and it have to be ongoing or stopped the same day of the study visit.

16.1.2 Missing Data Methods for Primary Endpoint

Missing data will not be imputed. If patients have missing values for this outcome, those patients will be excluded for the analysis and number of missing values will be presented.

16.1.3 Primary Analysis of Primary Endpoints

The primary analysis will consist of the proportion of patients, currently on ICS, who did not have or had moderate/severe exacerbation in the year prior to the study visit. The primary analysis will be performed for the FAS.

16.1.3.1 Current treatment with ICS

Main variable will be presented according to the presence or not of moderate/severe exacerbations in the previous 365 days.

The use of ICS will be analyzed using number of patients in each category and percentages (absolute and relative frequencies) and 95% confidence intervals will be provided based on Wald's (Normal Approximation) method for each group. Percentages will be compared using Chi-Square test or Fisher's Exact test.

Logistic regression will be used to assess the independent contribution of clinical and demographic factors to the estimation of the proportion of patients with COPD who use ICS inadequately. First, univariate and second, multiple logistic regression (MLR) methods will be used to investigate the impact of the following explanatory covariates (patient and disease characteristics) on ICS use. Potential covariates are:

- Age
- gender
- Smoking history
- Number of exacerbations in the previous year.
- History of asthma (yes/no)
- History of atopy (yes/no)
- COTE index
- COPD GesEPOC 2017 phenotype

- GOLD 2019 spirometric classifications (1, 2,3, 4)
- GOLD 2019 patient groups (A, B, C, D)
- mMRC score
- CAT - COPD Assessment Test

Backward selection procedures will be applied to generate the final MLR models which consider only covariates in the selection procedure with a p-value <0.1 in the corresponding univariate logistic regression analysis, using inadequate ICS use (yes/no) as response variable. A p-value <0.05 will be used for the covariates to stay in the model in a backward elimination step. Continuous variables can be replaced by categorical variables. Parameters estimated, exp(B) and C95% Wald Confidence Limits for OR will be presented.

Additionally, logistic regression model will be performed for each age subgroup, using the same procedure described in the previous paragraph. Age subgroups will be adjusted according to the distribution of patients.

16.1.3.2 Inadequate use of ICS

As a part of main analysis, inadequate use of ICS will be presented as in the previous section 16.1.3.1. Current treatment with ICS. This analysis will be presented only for patients without exacerbations in the previous year. This cohort will be used because only patients without exacerbations can receive ICS without requiring it, which is, making an inappropriate use of the treatment.

16.2 Secondary analysis

The secondary analyses will be performed for the FAS. According to previous statements, if patients have missing values for an outcome, those patients will be excluded for that outcome's analysis.

16.2.1 ICS use in the two years prior to the study visit

The secondary analyses is the 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 (see also section 16.1.1. Data Variables and Derivation on page 29).

This analysis will be presented according to the presence or not of moderate/severe exacerbations in the previous 2x365 days.

Use of ICS will be analyzed using number of patients in each category and percentages (absolute and relative frequencies) and 95% confidence intervals will be provided based on Wald's (Normal Approximation) method for each group. Percentages will be compared using Chi-Square test or Fisher's Exact test.

16.2.2 Moderate-to-severe exacerbations in COPD

This analysis consists of the number (count) of moderate-to-severe exacerbations in the previous 1 and 2 years previous to the study visit in COPD patients according to ICS use at time of study visit.

Patients with missing data related to exacerbations will be excluded from the analysis and number of missing values will be presented.

The objective is to describe the number (total count) of moderate-to-severe exacerbations in one and two years previous to the study visit according to ICS treatment at the time of study visit.

Results will be analyzed with measures of central tendency (mean and median), variability/dispersion (standard deviation and interquartile ranges) and ranges. The number of moderate-to-severe exacerbations will be analyzed using Mann-Whitney U test or Kruskal-Wallis non-parametric tests.

After that, at exploratory level, negative binomial regressions will be used for modelling discrete-count variables, not continuous and limited to non-negative values as the number of moderate-to-severe exacerbations (counts), both for first and second previous years. Covariates included in the model will be those used also in primary analysis, excluding the number of exacerbations in the previous year.

Backward selection procedures will be applied to generate the final model which consider only covariates in the selection procedure with a p-value <0.1 in the corresponding univariate analysis, using number of exacerbations as response variable. A p-value <0.05 will be used for the covariates to stay in the model in a backward elimination step. Continuous variables can be replaced by categorical variables.

16.2.3 General patient profile for COPD patients

To evaluate general patient profile for COPD patients, several variables will be described. In general, 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 and ranges) for continuous variables and distributions of absolute and relative frequencies for categorical variables. This analysis will be also performed for the FAS.

All results will be described according to the ICS treatment in the study visit: categorical variables will be analyzed using Chi-Square or Fisher's Exact test and quantitative variables by means t-test for independent groups or 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. Variables included are:

Table 2. Variables included in the eCRF

Group	Variable
Sociodemographic	Age (years),
	gender,
	ethnicity.
	BMI (Kg/m2)
	BMI grade
	Smoking history.
Clinical Variables	Spirometry - Bronchodilator test
	Spirometry - FEV1 absolute values pre and post-bronchodilator
	Spirometry - FEV1 % values pre and post-bronchodilator.
	Spirometry - FEV1 increase from pre to post-bronchodilator
	Blood Eosinophilia (number of eosinophils and %)
	Immunoglobulin E (Ig E)
Exacerbations	Episodes of exacerbations in the previous year
	Episodes of exacerbations in the two previous years
	Episodes of severe exacerbations in the previous year
	Episodes of severe exacerbations in the two previous years
	Treatments for exacerbations
COPD characteristics	Time since COPD diagnosis (years)
	COPD GesEPOC 2017 phenotypes
	GOLD 2019 spirometric classifications (Gold 1, Gold 2, Gold 3, Gold 4).
	GOLD 2019 patient groups (A, B, C, D).
	BODEx index (numerical and categories)
	Risk classification according GesEPOC.
	Breathlessness based on mMRC score.
	CAT - COPD Assessment Test (numerical and categories)
Comorbidities	COTE index (numerical and categories)
	History of asthma (yes/no)
	Time since asthma diagnosis (years)

Group	Variable
	History of atopy (yes/no).
Treatments	Current COPD treatment: With ICS: ICS, LABA+ICS, LABA+LAMA+ICS. Without ICS: SABA, SAMA, LABA, LAMA, LABA+LAMA, Others
	History of antibiotics for COPD
	History of corticosteriods for COPD
	Concomitant medication.
	Adherence to GesEPOC 2017 treatment recommendations guidelines

16.2.4 Rescue medication use

The description of Rescue medication used in patients treated with ICS and without ICS will include the active substance (ATC codes), dose, start date and end date. The main treatment is salbutamol (SABA) and it will be described the number and percentage of patients who used each treatment as rescue medication in the last year and in the last two years. This percentage will be calculated using as denominator FAS set.

Results will be stratified by ICS treatment in the study visit. Percentages will be compared using Chi-Square or Fisher's Exact test.

16.2.5 Adherence to GesEPOC 2017 treatment recommendations guidelines

Adherence to treatment recommendations according GesEPOC 2017 guidelines will be described using number and percentage of adherent patients (considered treated according to guidelines).
Tables will be described according to the number of exacerbations in the last year prior to study visit:

- patients with 0-1 exacerbations (not leading to hospital admission) vs.
- patients with ≥ 2 exacerbations or ≥ 1 exacerbation leading to hospital admission in the last 1 year;

Comparisons between groups will be performed using Chi-Square or Fisher's Exact test.

16.2.6 ICS-related adverse events

Percentage of patients treated with ICS who reported ICS-related events will be reported. All adverse event list will be presented (see Safety Outcomes).

17. PATIENT REPORTED OUTCOMES (PRO)

Quality of Life (QoL) was assessed using the COPD Assessment Test (CAT), a questionnaire for people with COPD designed to measure the impact of COPD on a person's life, and how these changes over time (http://www.catestonline.org/).

The analysis of CAT is included in analysis of patient profile in section 16.2.3. General patient profile for COPD patients (page 33).

18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set (see sections 6.4 and 6.5).

18.1 Adverse Drug Reactions

First of all, the percentage of patients experiencing ICS-related adverse drug reactions (ADRs) will be presented in patients using ICS. Only ADRs with onset date included in the last two years previous to study visit will be included.

Number and percentage of patients reporting each type of ADRs will be reported: Pneumonia, Fracture, Skin thinning/easy bruising, Cataract, Diabetes and Oropharyngeal candidiasis. ADRs will be described according to type, seriousness, reason for seriousness and outcome.

In the same way, the percentage of patients experiencing Adverse Drug Reactions related with BI products SPIOLTO®, STRIVERDI®, SPIRIVA® or ATROVENT® will be presented. Number and percentage of patients reporting each type of ADRs will be reported. ADRs will be described according to type, duration (days), seriousness, reason for seriousness and outcome.

Adverse Drug Reaction term (open string variable) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 20.0.

18.2 Serious Adverse Drug Reactions

Serious Adverse Drug Reactions (SADRs) are those ADRs recorded as "Serious" on the Adverse Events page of the (e)CRF. A summary of serious SADRs by SOC and PT will be prepared.

The percentage of patients experiencing serious ICS-related adverse drug reaction (SADRs) will be presented in patients using ICS. Only SADRs with onset date included in the last two years previous to study visit will be included.

Number and percentage of patients reporting each type of SADRs will be reported: Pneumonia, Fracture, Skin thinning/easy bruising, Cataract, Diabetes and Oropharyngeal candidiasis. Global SADRs will be described according to type of seriousness and outcome.

The percentage of patients experiencing serious related drug reactions (SADRs) with SPIOLTO®, STRIVERDI®, SPIRIVA® or ATROVENT® will be presented. Number and percentage of patients reporting each type of SADRs will be reported.

18.3 Deaths

If any subjects die during ICS-treatment or SPIOLTO®, STRIVERDI®, SPIRIVA® or ATROVENT® treatment, recorded on the "results in death" or outcome of event" as "fatal" on AEs and ADRs page of the (e)CRF, the information will be presented in a summary table and a data listing.

19. REFERENCES

Celli, B. (2017). Is the Blood Eosinophil Count a Useful Biomarker in COPD? The devil is in the Details! Arch Bronconeumol 53(8): 415-416.

Cosio, B. G., J. B. Soriano, J. L. Lopez-Campos, M. Calle-Rubio, J. J. Soler-Cataluna, J. P. de-Torres, J. M. Marin, C. Martinez-Gonzalez, P. de Lucas, I. Mir, G. Peces-Barba, N. Feu-Collado, I. Solanes, I. Alfageme, and C. Casanova. 2016. 'Defining the Asthma-COPD Overlap Syndrome in a COPD Cohort', Chest, 149: 45-52.

Divo, M., C. Cote, J. P. de Torres, C. Casanova, J. M. Marin, V. Pinto-Plata, J. Zulueta, C. Cabrera, J. Zagaceta, G. Hunninghake and B. Celli (2012). "Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease." Am J Respir Crit Care Med 186(2): 155-161.

Miravitlles, M. (2015). Frequency and characteristics of different clinical phenotypes of chronic obstructive pulmonary disease. Int J Tuberc Lung Dis, Aug; 19(8) 992-8.

19.1 Dated & Times

Depending on data available, dates and times will take the form <dd/mm/yyyy hh:mm:ss.>

19.2 Spelling Format

English UK.

19.3 Listings

All listings will be ordered by the following: group (ICS/non-ICS, etc..), center-subject ID, and date (where applicable).

20. TABLES AND FIGURES

20.1 Evaluability

Table 3. Evaluability criteria – Patients in the FAS

		Total
Total included patients (ENR)		
Evaluable patients	Evaluable patients (FAS)	
	Non-Evaluable patients	
Reasons for non-evaluable patients	Inclusion criteria 1	
	Inclusion criteria 2	

ICS Analysis Set (PICAS)		
Safety Analysis Set-ICS		
Safety Analysis Set- BI drug		

Table 4. Other protocol violations occurred in evaluable patients

		Total
Evaluable patients	Evaluable patients (FAS)	
Important protocol violations	ADR (serious or non-serious) or fatal event not notified to BI	
	Any other major or critical Non-Compliance detected during monitoring visit	

Table 5. Main stratification variables

		Total
Total evaluable (FAS)		
Current treatment on ICS	Total No (Non - ICS treatment) Yes (ICS treatment) 95% CI for current ICS treatment	
Moderate/severe exacerbations in the previous year	Total No (Without Moderate/severe Exacerbations) Yes (With Moderate/severe Exacerbations) 95% CI for presence of moderate/severe exacerbations in the previous year	
Inadequate use of ICS	Total Adherent patients: Adequate use of ICS	

		Total
	Non-adherent patients: Inadequate use of ICS (use of ICS in patients without moderate/severe exacerbations in the previous year) 95% CI for non-adherent patients (inadequate use of ICS)	

20.2 General patient profile for COPD patients according to ICS current use

Main analysis will be stratified by current ICS treatment (patients currently treated with ICS vs. patients currently non-treated with ICS). The same tables for general patient profile could be presented according to GOLD (I-IV), GOLD (A-D) and GesEPOC Phenotypes.

20.2.1 Socio-demographic characteristics

Table 6. Socio-demographic variables and habits according to current treatment on ICS.

		Non - ICS	ICS	Total
Age	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missings			
Age group	40-49 years 50-59 years 60-69 years 70-79 years 80+ years			
Gender	Male, n (%) Female, n (%)			
Ethnicity	Caucasian Asian African Unknown Other			
Weight (Kg)	Valid N Mean (SD) Median (Q1-Q3) Min-Max			

		Non - ICS	ICS	Total
	N missings			
Height (cm)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missings			
BMI (Kg/m2)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missings			
BMI cat	Underweight: BMI< 18.5 kg/m2 Normal weight: 18.5 kg/m2<= BMI<= 25 kg/m2 Overweight: 25 kg/m2< BMI<= 30 kg/m2 Obese: 30 kg/m2<BMI<= 35 kg/m2 Severely Obese: BMI> 35 kg/m2			
Smoking habit	Non-smoker Smoker Ex-smoker			
Smokers- Number of years smoking	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Smokers- Number of pack-years	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Ex-Smokers- Number of years smoking	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Ex-Smokers- Number of pack-years	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

20.2.2 Clinical variables

Table 7. Spirometry values in COPD patients according to current treatment on ICS.

			Non - ICS	ICS	Total
Pre-bronchodilator	FVC (L)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
	FVC (%)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
	FEV1 (L)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
	FEV1 (%)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
	FEV1/FVC (%)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Post-bronchodilator	FVC (L)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
	FVC (%)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
	FEV1 (L)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
	FEV1 (%)	Valid N			

			Non - ICS	ICS	Total
		Mean (SD) Median (Q1-Q3) Min-Max N missing			
	FEV1/FVC (%)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
	FEV1/FVC (%) - cat	FEV1/FVC (%) < 0.7 FEV1/FVC (%) ≥ 0.7			
Change	FEV1 Change (L)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
	FEV1 percentage of change (1)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
	FEV1 percentage of change (2)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

Table 8. Comorbidities according to current treatment on ICS.

		Non - ICS	ICS	Total
History of asthma	No Yes			
Time since asthma diagnosis (years)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
History of atopy	No Yes			
COTE Index -comorbidities	Lung cancer Esophagus cancer Pancreas cancer Breast cancer Pulmonary fibrosis			

		Non - ICS	ICS	Total
	Auricular Fibrillation / flutter Congestive heart failure Coronary artery disease Gastroduodenal ulcer Liver cirrhosis Diabetic neuropathy Anxiety All other cancers			
COTE Index	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
COTE Index (cat)	Low risk: COTE index <4 points High risk: COTE index ≥ 4 points.			

Table 9. COPD characteristics according to current treatment on ICS.

		Non - ICS	ICS	Total
Time since COPD diagnosis (years)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Time since COPD diagnosis (cat)	0-2 years >2-5 years >5 years			
COPD GesEPOC 2017 phenotypes	non-exacerbator, mixed COPD - asthma syndrome (ACOS) exacerbator with emphysema exacerbator with chronic bronchitis			
GOLD 2019 spirometric classification	Gold 1 – Mild Gold 2 – Moderate Gold 3 – Severe Gold 4 – Very severe			
GOLD 2019 patient groups (A, B, C, D).	Patient A Patient B Patient C Patient D			
BODEx Index	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

		Non - ICS	ICS	Total
BODEx Index (cat)	Class I Mild: BODEx 0-2 points Class II Moderate: BODEx 3-4 points Class III Serious: BODEx 5-6 points Class IV Very serious: BODEx 7-9 points			
CAT score	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
CAT score (cat)	CAT <10: Low impact of COPD. CAT ≥10: Medium / high impact of COPD Low impact: 0 <= CAT <= 10. Moderate impact: 11 <= CAT <= 20. High impact: 21 <= CAT <= 30. Very high impact: 31 <= CAT <= 40.			
mMRC score	Grade 0 Grade 1 Grade 2 Grade 3 Grade 4			

Table 10. Analytic results according to current treatment on ICS.

		Non - ICS	ICS	Total
Blood Eosinophilia (%)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Number of eosinophils (%)	<2% >= 2%			
Blood Eosinophilia (cel/µl)	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Number of eosinophils (cel/µl)	<100 cel/µl 100-299 cel//µl >= 300 cel/µl			
Immunoglobulin E (UI/ml)	Valid N Mean (SD) Median (Q1-Q3) Min-Max			

		Non - ICS	ICS	Total
	N missing			
Inmunoglobulin E (UI/ml)	≤100 UI/ml >100 UI/ml			

20.2.3 Exacerbations

Table 11. Previous exacerbations according to current treatment on ICS.

Period	Variable		Non - ICS	ICS	Total
Last 2 years	Total Exacerbations	No Yes			
	Number of total Exacerbations	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
	Moderate/Severe Exacerbations	No Yes			
	Number of Moderate/Severe Exacerbations	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
	Severe Exacerbations	No Yes			
	Number of Severe Exacerbations	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
Previous year	Total Exacerbations	No Yes			
	Number of total Exacerbations	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			
	Moderate/Severe Exacerbations	No Yes			
	Number of Moderate/Severe Exacerbations	Valid N Mean (SD) Median (Q1-Q3)			

Period	Variable		Non - ICS	ICS	Total
		Min-Max N missing			
	Severe Exacerbations	No Yes			
	Number of Severe Exacerbations	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missing			

Table 12. Treatments for Moderate/Severe Exacerbations according to current treatment on ICS.

		Non - ICS	ICS	Total patients with severe/moderate exacerbations
Treatments for exacerbations	No Yes			
Type of treatment (multirresponse)	Antibiotics for COPD β-Lactam antibiotics Amoxicillin/Clavulanic Acid Other Macrolides Azithromycin Other Fluoroquinolones Ciprofloxacin Levofloxacin Moxifloxacin Other Unknown antibiotic			
	Oral corticosteriods for COPD Systemic corticosteroids Prednisone Prednisolone Metilprednisolone Dexamethasone Deflazacort Other systemic corticosteroid Other Corticosteroid Unknown corticosteroid			

20.2.4 Current COPD treatment

Table 13. Current COPD treatment according to current treatment on ICS

		Non - ICS	ICS	Total
ICS treatment	No ICS ICS alone LABA + ICS LABA + LAMA + ICS	100%	0%	
Type of ICS	ICS alone Budesonide Fluticasone propionate	- - -		
	LABA + ICS Beclometasone / Formoterol Formoterol / Budesonide Salmeterol / Fluticasone propionate Fluticasone furoate/vilanterol	- - - - -		
	LABA + LAMA + ICS Fluticasone / Umeclidinium / Vilanterol Beclometasone / Formoterol / Glycopyrronium	- - -		
Other treatments	No Yes			
Type of treatment (multirresponse)	Inhaled therapy SABA Salbutamol Terbutaline SAMA Ipratropium LABA Formoterol Salmeterol Indacaterol Olodaterol LAMA Tiotropium Aclidinium Glycopyrronium Umeclidinium LABA+LAMA Indacaterol / Glycopyrronium Aclidinium / Formoterol Umeclidinium / vilanterol Tiotropium / Olodaterol Other therapies PDE4 inhibitors Roflumilast			

		Non - ICS	ICS	Total
	Methylxanthines Theophylline Mucolytics Ambroxol Bromhexine Erdosteine Carbocisteine N-Acetylcysteine Other mucolytic Vaccines Influenza Conjugated pneumococcal Non-conjugated pneumococcal Antitussives Alpha-1-Antitrypsin Immunoregulators Other treatment			

Percentages will be calculated over total of patients in each group (100%).

Table 14. Presentation of current COPD treatment pattern according to current treatment on ICS

		Non - ICS	ICS	Total
ICS alone		-		
Budesonide	□ TH: 100 mcg/inh □ TH: 200 mcg/inh □ TH: 400 mcg/inh	-		
Fluticasone propionate	□ PCI: 50 mcg/inh □ PCI: 125 mcg/inh □ PCI: 250 mcg/inh □ AH: 100 mcg/inh □ AH: 250 mcg/inh □ AH: 500 mcg/inh	-		
LABA + ICS		-		
Beclometasone / Formoterol	□ NH: 100/6 mcg/inh □ PCI Modulite: 100/6 mcg/inh	-		
Formoterol / Budesonide	□ TH: 4,5/160 mcg/inh □ TH: 9/320 mcg/inh □ SM: 4,5/160 mcg/inh □ SM: 9/320 mcg/inh □ EH: 4,5/160 mcg/inh □ EH: 9/320 mcg/inh	-		
Salmeterol / Fluticasone propionate	□ AH: 50/500 mcg/inh □ FP: 50/500 mcg/inh	-		
Fluticasone furoate/vilanterol	□ EL: 100/25 mcg/inh	-		

		Non - ICS	ICS	Total
LABA + LAMA + ICS		-		
Fluticasone / Umeclidinium / Vilanterol	□ EL: 92/65/22 mcg/inh	-		
Beclometasone / Formoterol / Glycopyrronium	□ PCI: 87/5/9mcg/inh	-		
Inhaled therapy				
SABA				
Salbutamol	□ PCI: 100mcg/inh			
Terbutaline	□ TH: 500 mcg/inh			
SAMA				
Ipratropium	□ PCI: 20mcg/inh			
LABA				
Formoterol	□ PCI: 12 mcg/inh □ TH: 9 mcg/inh □ AL: 12mcg/inh			
Salmeterol	□ PCI: 25 mcg/inh □ AH: 50 mcg/inh			
Indacaterol	□ BH: 150mcg/inh □ BH: 300 mcg/inh			
Olodaterol	□ RM: 2,5 mcg/inh			
LAMA				
Tiotropium	□ HA: 18 mcg/inh □ RM: 2,5 mcg/inh			
Aclidinium	□ GE: 400 mcg/inh			
Glycopyrronium	□ BH: 44 mcg/inh			
Umeclidinium	□ EL: 62,5 mcg/inh			
LABA+LAMA				
Indacaterol / Glycopyrronium	□ BH: 110/50 mcg/inh			
Aclidinium / Formoterol	□ GE: 340/12 mcg/inh			
Umeclidinium / vilanterol	□ EL: 62,5/25 mcg/inh			
Tiotropium / Olodaterol	□ RM: 2,5/2,5mcg/inh			
Other therapies				
PDE4 inhibitors				
Roflumilast	□ 250 mcg/tablet □ 500 mcg/tablet			
Metilxantines				
Theophylline	□ 100 retard mg/tablet □ 200 retard mg/tablet □ 300 retard mg/tablet □ Oral Solution 27mg/5ml			
Mucolytics				

		Non - ICS	ICS	Total
Ambroxol	□ Oral Solution 15mg/5ml □ Oral Solution 300mg/100ml □ Tablets 30 mg			
Bromhexine	□ Oral Solution 160mg/100ml □ Oral Solution 80mg/100ml □ Tablets 8mg			
Erdosteine	□ Oral Solution 3,5g/100ml □ Tablets 300 mg			
Carbocisteine	□ Oral Solution 50mg/100ml □ Oral Solution 100mg/ml □ Sachets: 750mg			
N-Acetylcysteine	□ Sachets 200mg □ Sachets 600mg			
Other mucolytic				

Percentages (each presentation) will be calculated over the patients receiving each treatment.

* AH: Accuhaler; AL: Aerolizer; BH: Breezhaler; IC: Inhaled capsules; EH: Easyhaler; EL: Ellipta; FP: Forspiro; GE: Genuair; HA: Handihaler; IPC: Inhaler in pressurized cartridge; inh: inhalation; NT: Nexthaler; RM: Respimat; SM: Spiromax; TH: Turbuhaler.

Table 15. Doses of current COPD treatment pattern according to current treatment on ICS

	Doses	Non - ICS	ICS	Total
ICS alone		-		
Budesonide	200-1600 mcg/24h ___ mcg/___ h ___ mcg/___ h Not available	-		
Fluticasone propionate	500 mcg/12h ___ mcg/___ h ___ mcg/___ h Not available	-		
LABA + ICS		-		
Beclometasone / Formoterol	200/12 mcg/12h ___/___ mcg/___ h ___/___ mcg/___ h Not available	-		
Formoterol / Budesonide	9/320 mcg/12h ___/___ mcg/___ h ___/___ mcg/___ h Not available	-		
Salmeterol / Fluticasone propionate	50/500 mcg/12h ___/___ mcg/___ h ___/___ mcg/___ h Not available	-		

	Doses	Non - ICS	ICS	Total
Fluticasone furoate/vilanterol	100/25 mcg/24h XX1/YY1 mcg/ZZ1 h XX2/YY2 mcg/ZZ2 h Not available	-		
LABA + LAMA + ICS		-		
Fluticasone / Umeclidinium / Vilanterol	92/65/22 mcg/24h ___/___/___ mcg/___ h ___/___/___ mcg/___ h Not available	-		
Beclometasone / Formoterol / Glycopyrronium	2 inhal 87/5/9 mcg/ 12h ___/___/___ mcg/___ h ___/___/___ mcg/___ h Not available	-		
Inhaled therapy				
SABA				
Salbutamol	200 mcg/4-6h ___ mcg/___ h ___ mcg/___ h Not available			
Terbutaline	500 mcg/6h ___ mcg/___ h ___ mcg/___ h Not available			
SAMA				
Ipratropium	20-40 mcg/6-8h ___ mcg/___ h ___ mcg/___ h Not available			
LABA				
Formoterol	12 mcg/12h ___ mcg/___ h ___ mcg/___ h Not available			
Salmeterol	50 mcg/12h ___ mcg/___ h ___ mcg/___ h Not available			
Indacaterol	150 mcg/24h ___ mcg/___ h ___ mcg/___ h Not available			
Olodaterol	5 mcg/24h ___ mcg/___ h ___ mcg/___ h Not available			

	Doses	Non - ICS	ICS	Total
LAMA				
Tiotropium	18 mcg/24h 05 mcg/24h ___ mcg/___ h ___ mcg/___ h Not available			
Aclidinium	400 mcg/12h ___ mcg/___ h ___ mcg/___ h Not available			
Glycopyrronium	44 mcg/24h ___ mcg/___ h ___ mcg/___ h Not available			
Umeclidinium	62,5 mcg/24h ___ mcg/___ h ___ mcg/___ h Not available			
LABA+LAMA				
Indacaterol / Glycopyrronium	110/50 mcg/24h ___/___ mcg/___ h ___/___ mcg/___ h Not available			
Aclidinium / Formoterol	340/12 mcg/12h ___/___ mcg/___ h ___/___ mcg/___ h Not available			
Umeclidinium / vilanterol	62,5/25 mcg/24h ___/___ mcg/___ h ___/___ mcg/___ h Not available			
Tiotropium / Olodaterol	5/5 mcg/24h ___/___ mcg/___ h ___/___ mcg/___ h Not available			
Other therapies				
PDE4 inhibitors				
Roflumilast	250-500 mcg/24h ___ mcg/___ h ___ mcg/___ h Not available			
Metilxantines				
Theophylline	400 mg/24h ___ mg/___ h ___ mg/___ h			

	Doses	Non - ICS	ICS	Total
	Not available			
Mucolytics				
Ambroxol	30 mg/8h ___ mg/___ h ___ mg/___ h Not available			
Bromhexine	8 mg/8h ___ mg/___ h ___ mg/___ h Not available			
Erdosteine	300 mg/12h ___ mg/___ h ___ mg/___ h Not available			
Carbocisteine	750 mg/8h ___ mg/___ h ___ mg/___ h Not available			
N-Acetylcysteine	200 mg/8h ___ mg/___ h ___ mg/___ h Not available			
Other mucolytic	___ mg/___ h ___ mg/___ h Not available			
Vaccines				
Influenza				
Conjugated pneumococcal				
Non-conjugated pneumococcal				
Antitussives	___ mg/___ h ___ mg/___ h Not available			
Alpha-1-Antitrypsin	___ mg/___ h ___ mg/___ h Not available			
Immunoregulators	___ mg/___ h ___ mg/___ h Not available			
Other treatment				

Percentages (each dose) will be calculated over the patients receiving each treatment.

Table 16. Time in treatment (months) of current COPD treatment pattern according to current treatment on ICS

	Doses	Non - ICS	ICS	Total
ICS alone	Mean (SD) Median (Q1-Q3) Min-Max	-		
Budesonide	Mean (SD) Median (Q1-Q3) Min-Max	-		
Fluticasone propionate	Mean (SD) Median (Q1-Q3) Min-Max	-		
LABA + ICS	Mean (SD) Median (Q1-Q3) Min-Max	-		
Beclometasone / Formoterol	Mean (SD) Median (Q1-Q3) Min-Max	-		
Formoterol / Budesonide	Mean (SD) Median (Q1-Q3) Min-Max	-		
Salmeterol / Fluticasone propionate	Mean (SD) Median (Q1-Q3) Min-Max	-		
Fluticasone furoate/vilanterol	Mean (SD) Median (Q1-Q3) Min-Max	-		
LABA + LAMA + ICS	Mean (SD) Median (Q1-Q3) Min-Max	-		
Fluticasone / Umeclidinium / Vilanterol	Mean (SD) Median (Q1-Q3) Min-Max	-		
Beclometasone / Formoterol / Glycopyrronium	Mean (SD) Median (Q1-Q3) Min-Max	-		
Inhaled therapy				
SABA	Mean (SD) Median (Q1-Q3) Min-Max			
Salbutamol	Mean (SD) Median (Q1-Q3) Min-Max			
Terbutaline	Mean (SD) Median (Q1-Q3) Min-Max			
SAMA	Mean (SD) Median (Q1-Q3)			

	Doses	Non - ICS	ICS	Total
	Min-Max			
Ipratropium	Mean (SD) Median (Q1-Q3) Min-Max			
LABA	Mean (SD) Median (Q1-Q3) Min-Max			
Formoterol	Mean (SD) Median (Q1-Q3) Min-Max			
Salmeterol	Mean (SD) Median (Q1-Q3) Min-Max			
Indacaterol	Mean (SD) Median (Q1-Q3) Min-Max			
Olodaterol	Mean (SD) Median (Q1-Q3) Min-Max			
LAMA	Mean (SD) Median (Q1-Q3) Min-Max			
Tiotropium	Mean (SD) Median (Q1-Q3) Min-Max			
Aclidinium	Mean (SD) Median (Q1-Q3) Min-Max			
Glycopyrronium	Mean (SD) Median (Q1-Q3) Min-Max			
Umeclidinium	Mean (SD) Median (Q1-Q3) Min-Max			
LABA+LAMA	Mean (SD) Median (Q1-Q3) Min-Max			
Indacaterol / Glycopyrronium	Mean (SD) Median (Q1-Q3) Min-Max			
Aclidinium / Formoterol	Mean (SD) Median (Q1-Q3) Min-Max			
Umeclidinium / vilanterol	Mean (SD) Median (Q1-Q3) Min-Max			

	Doses	Non - ICS	ICS	Total
Tiotropium / Olodaterol	Mean (SD) Median (Q1-Q3) Min-Max			
Other therapies				
PDE4 inhibitors	Mean (SD) Median (Q1-Q3) Min-Max			
Roflumilast	Mean (SD) Median (Q1-Q3) Min-Max			
Metilxantines	Mean (SD) Median (Q1-Q3) Min-Max			
Theophylline	Mean (SD) Median (Q1-Q3) Min-Max			
Mucolytics	Mean (SD) Median (Q1-Q3) Min-Max			
Ambroxol	Mean (SD) Median (Q1-Q3) Min-Max			
Bromhexine	Mean (SD) Median (Q1-Q3) Min-Max			
Erdosteine	Mean (SD) Median (Q1-Q3) Min-Max			
Carbocisteine	Mean (SD) Median (Q1-Q3) Min-Max			
N-Acetylcysteine	Mean (SD) Median (Q1-Q3) Min-Max			
Other mucolytic	Mean (SD) Median (Q1-Q3) Min-Max			
Vaccines				
Influenza	Mean (SD) Median (Q1-Q3) Min-Max			
Conjugated pneumococcal	Mean (SD) Median (Q1-Q3) Min-Max			

	Doses	Non - ICS	ICS	Total
Non-conjugated pneumococcal	Mean (SD) Median (Q1-Q3) Min-Max			
Antitussives	Mean (SD) Median (Q1-Q3) Min-Max			
Alpha-1-Antitrypsin	Mean (SD) Median (Q1-Q3) Min-Max			
Immunoregulators	Mean (SD) Median (Q1-Q3) Min-Max			
Other treatment				

20.2.5 Previous COPD treatment

Table 17. Previous COPD treatment according to current treatment on ICS

		Non - ICS	ICS	Total
Previous 2 years	No ICS ICS alone LABA + ICS LABA + LAMA + ICS			
	ICS alone Budesonide Fluticasone propionate			
	LABA + ICS Beclometasone / Formoterol Formoterol / Budesonide Salmeterol / Fluticasone propionate Fluticasone furoate/vilanterol			
	LABA + LAMA + ICS Fluticasone / Umeclidinium / Vilanterol Beclometasone / Formoterol / Glycopyrronium			
Last year	No ICS ICS alone LABA + ICS LABA + LAMA + ICS			
	ICS alone Budesonide Fluticasone propionate			
	LABA + ICS Beclometasone / Formoterol Formoterol / Budesonide			

		Non - ICS	ICS	Total
	Salmeterol / Fluticasone propionate Fluticasone furoate/vilanterol			
	LABA + LAMA + ICS Fluticasone / Umeclidinium / Vilanterol Beclometasone / Formoterol / Glycopyrronium			

Percentages will be calculated over total of patients in each group (100%).

Table 18. Presentation of previous COPD treatment according to current treatment on ICS

		Presentation	Group1	Group2	Total
Previous 2 years	ICS alone				
	Budesonide	□ TH: 100 mcg/inh □ TH: 200 mcg/inh □ TH: 400 mcg/inh			
	Fluticasone propionate	□ PCI: 50 mcg/inh □ PCI: 125 mcg/inh □ PCI: 250 mcg/inh □ AH: 100 mcg/inh □ AH: 250 mcg/inh □ AH: 500 mcg/inh			
	LABA + ICS				
	Beclometasone / Formoterol	□ NH: 100/6 mcg/inh □ PCI Modulite: 100/6 mcg/inh			
	Formoterol / Budesonide	□ TH: 4,5/160 mcg/inh □ TH: 9/320 mcg/inh □ SM: 4,5/160 mcg/inh □ SM: 9/320 mcg/inh □ EH: 4,5/160 mcg/inh □ EH: 9/320 mcg/inh			
	Salmeterol / Fluticasone propionate	□ AH: 50/500 mcg/inh □ FP: 50/500 mcg/inh			
	Fluticasone furoate/vilanterol	□ EL: 100/25 mcg/inh			
	LABA + LAMA + ICS				
	Fluticasone / Umeclidinium / Vilanterol	□ EL: 92/65/22 mcg/inh			
	Beclometasone / Formoterol / Glycopyrronium	□ PCI: 87/5/9mcg/inh			
Last year	ICS alone				
	Budesonide	□ TH: 100 mcg/inh □ TH: 200 mcg/inh □ TH: 400 mcg/inh			
	Fluticasone propionate	□ PCI: 50 mcg/inh			

		Presentation	Group1	Group2	Total
		□ PCI: 125 mcg/inh □ PCI: 250 mcg/inh □ AH: 100 mcg/inh □ AH: 250 mcg/inh □ AH: 500 mcg/inh			
	LABA + ICS				
	Beclometasone / Formoterol	□ NH: 100/6 mcg/inh □ PCI Modulite: 100/6 mcg/inh			
	Formoterol / Budesonide	□ TH: 4,5/160 mcg/inh □ TH: 9/320 mcg/inh □ SM: 4,5/160 mcg/inh □ SM: 9/320 mcg/inh □ EH: 4,5/160 mcg/inh □ EH: 9/320 mcg/inh			
	Salmeterol / Fluticasone propionate	□ AH: 50/500 mcg/inh □ FP: 50/500 mcg/inh			
	Fluticasone furoate/vilanterol	□ EL: 100/25 mcg/inh			
	LABA + LAMA + ICS				
	Fluticasone / Umeclidinium / Vilanterol	□ EL: 92/65/22 mcg/inh			
	Beclometasone / Formoterol / Glycopyrronium	□ PCI: 87/5/9mcg/inh			

Percentages (each presentation) will be calculated over the patients receiving each treatment.

Table 19. Doses of previous COPD treatment according to current treatment on ICS

		Doses	Group1	Group2	Total
Previous 2 years	ICS alone				
	Budesonide	200-1600 mcg/24h ___ mcg/___ h ___ mcg/___ h Not available			
	Fluticasone propionate	500 mcg/12h ___ mcg/___ h ___ mcg/___ h Not available			
	LABA + ICS				
	Beclometasone / Formoterol	200/12 mcg/12h ___/___ mcg/___ h ___/___ mcg/___ h Not available			
	Formoterol / Budesonide	9/320 mcg/12h ___/___ mcg/___ h ___/___ mcg/___ h			

		Doses	Group1	Group2	Total
		Not available			
	Salmeterol / Fluticasone propionate	50/500 mcg/12h ___/___ mcg/___ h ___/___ mcg/___ h Not available			
	Fluticasone furoate/vilanterol	100/25 mcg/24h XX1/YY1 mcg/ZZ1 h XX2/YY2 mcg/ZZ2 h Not available			
	LABA + LAMA + ICS				
	Fluticasone / Umeclidinium / Vilanterol	92/65/22 mcg/24h ___/___/___ mcg/___ h ___/___/___ mcg/___ h Not available			
	Beclometasone / Formoterol / Glycopyrronium	2 inhal 87/5/9 mcg/ 12h ___/___/___ mcg/___ h ___/___/___ mcg/___ h Not available			
Last year	ICS alone				
	Budesonide	200-1600 mcg/24h ___ mcg/___ h ___ mcg/___ h Not available			
	Fluticasone propionate	500 mcg/12h ___ mcg/___ h ___ mcg/___ h Not available			
	LABA + ICS				
	Beclometasone / Formoterol	200/12 mcg/12h ___/___ mcg/___ h ___/___ mcg/___ h Not available			
	Formoterol / Budesonide	9/320 mcg/12h ___/___ mcg/___ h ___/___ mcg/___ h Not available			
	Salmeterol / Fluticasone propionate	50/500 mcg/12h ___/___ mcg/___ h ___/___ mcg/___ h Not available			
	Fluticasone furoate/vilanterol	100/25 mcg/24h XX1/YY1 mcg/ZZ1 h XX2/YY2 mcg/ZZ2 h Not available			
	LABA + LAMA + ICS				

		Doses	Group1	Group2	Total
	Fluticasone / Umeclidinium / Vilanterol	92/65/22 mcg/24h ___/___/___ mcg/___ h ___/___/___ mcg/___ h Not available			
	Beclometasone / Formoterol / Glycopyrronium	2 inhal 87/5/9 mcg/ 12h ___/___/___ mcg/___ h ___/___/___ mcg/___ h Not available			

Percentages (each dose) will be calculated over the patients receiving each treatment.

20.2.6 Rescue medication

Table 20. Use and type of rescue medication in the previous 2 years according to current treatment on ICS

		Non - ICS	ICS	Total
Use of rescue medication	No Yes Not available in Clinical records			
Rescue medication	SABA (salbutamol) Other treatments Treatment 1 Treatment 2 ….			
Time (days) with salbutamol Within 2 years	Mean (SD) Median (Q1-Q3) Min-Max			
Time (days) with Treatment 1 * Within 2 years	Mean (SD) Median (Q1-Q3) Min-Max			

Percentages will be calculated over total of patients in each group (100%). (*): If there is a high number of other rescue medication, time in treatment will be analyzed for each medication.

Table 21. Use and type of rescue medication in the previous year according to current treatment on ICS

		Group1	Group2	Total
Use of rescue medication	No Yes Not available in Clinical records			
Rescue medication	SABA (salbutamol)			

		Group1	Group2	Total
	Other treatments Treatment 1 Treatment 2 ….			
Time (days) with salbutamol Within previous year	Mean (SD) Median (Q1-Q3) Min-Max			
Time (days) with Treatment 1 * Within previous year	Mean (SD) Median (Q1-Q3) Min-Max			

Percentages will be calculated over total of patients in each group (100%). (*): If there is a high number of other rescue medication, time in treatment will be analyzed for each medication.

20.2.7 Concomitant treatments (ATC code classification)

Table 22. Concomitant treatments according to current treatment on ICS

	Doses	Non - ICS	ICS	Total
Other treatments	No Yes			
Type of treatment	A Alimentary tract and metabolism A10 Drugs used in diabetes A10B Blood glucose lowering drugs, excl. insulins A10BA Biguanides A10BA01 Phenformin A10BA02 Metformin A10BA03 Buformin .. N Nervous System. N02 Analgesics. N02B Other analgesics and antipyretics. N02BE Anilides. N02BE01 Paracetamol (acetaminophen). N02BE01 Paracetamol N02BE03 Phenacetin N02BE04 Bucetin N02BE05 Propacetamol …			

Percentages will be calculated over total of patients in each group (100%).

Table 23. Comorbidities (receiving treatment) according to current treatment on ICS

	Doses	Non - ICS	ICS	Total
Comorbidities receiving concomitant treatment	Total Comorbidity 001 Comorbidity 002 ….			

Percentages will be calculated over total of patients in each group (100%).

20.3 Endpoints

20.3.1 ICS treatment

Table 24. Current treatment on ICS according to the absence or presence of moderate/severe exacerbations in the year prior to the study visit.

ICS treatment	Moderate/severe Exacerbations in the previous year		Total
	No	Yes	
Total patients	N (100%)	N (100%)	N (100%)
Currently non treated with ICS	XXX (XX.X%) [95%CI: XX.X%-XX.X]	XXX (XX.X%) [95%CI: XX.X%-XX.X]	XXX (XX.X%) [95%CI: XX.X%-XX.X]
Currently treated with ICS	XXX (XX.X%) [95%CI: XX.X%-XX.X]	XXX (XX.X%) [95%CI: XX.X%-XX.X]	XXX (XX.X%) [95%CI: XX.X%-XX.X]

*Note: Percentages will be column percentages. Each percentage will correspond to percentage of patients currently treated with ICS, according to the presence of moderate/severe exacerbations in the previous year.

Table 25. Inadequate use of ICS (use of ICS without moderate/severe exacerbations in the previous year) according to clinical and demographic factors (univariate logistic regression analysis)

Variable	Category	Inadequate use of ICS	Odds-Ratio (OR)	p-value
Age	Cont (1 year)	n/N (%)		
Age (cat)	40-49 years 50-59 years 60-69 years 70-79 years 80+ years	n/N (%) n/N (%) n/N (%) n/N (%) n/N (%)	(ref)	

Variable	Category	Inadequate use of ICS	Odds-Ratio (OR)	p-value
Gender	Male Female		(ref)	
BMI cat	Underweight: BMI< 18.5 kg/m2 Normal weight: 18.5 kg/m2<= BMI<= 25 kg/m2 Overweight: 25 kg/m2< BMI<= 30 kg/m2 Obese: 30 kg/m2<BMI<= 35 kg/m2 Severely Obese: BMI> 35 kg/m2		(ref)	
Smoking habit	Non-smoker Smoker Ex-smoker		(ref)	
History of asthma	No Yes		(ref)	
History of atopy	No Yes		(ref)	
BODEx Index (cat)	Class I Mild: BODEx 0-2 points Class II Moderate: BODEx 3-4 points Class III Serious: BODEx 5-6 points Class IV Very serious: BODEx 7-9 points		(ref)	
COTE Index (cat)	Low risk: COTE index <4 points High risk: COTE index ≥ 4 points.		(ref)	
Time since COPD diagnosis (cat)	0-2 years >2-5 years >5 years		(ref)	
COPD GesEPOC 2017 phenotypes	non-exacerbator, mixed COPD - asthma syndrome (ACOS), exacerbator with emphysema exacerbator with chronic bronchitis		(ref)	
GOLD 2019 spirometric classification	Gold 1 – Mild Gold 2 – Moderate Gold 3 – Severe Gold 4 – Very severe		(ref)	
GOLD 2019 patient groups (A, B, C, D)	Patient A Patient B Patient C Patient D		(ref)	
CAT score (cat)	CAT <10: Low impact of COPD. CAT ≥10: Medium / high impact of COPD		(ref)	
mMRC score	Grade 0 Grade 1 Grade 2 Grade 3 Grade 4		(ref)	
Number of eosinophils (%)	<2% >= 2%		(ref)	

Variable	Category	Inadequate use of ICS	Odds-Ratio (OR)	p-value
Inmunoglobulin E (UI/ml)	<= 100 UI/ml >100 UI/ml		(ref)	
Presence of exacerbations in previous 2 years	None 1-2 exacerbations 3-4 exacerbations 5+ exacerbations		(ref)	
Presence of moderate/severe exacerbations in previous 2 years	None 1-2 moderate/severe exacerbations 3-4 moderate/severe exacerbations 5+ moderate/severe exacerbations		(ref)	
Presence of severe exacerbations in previous 2 years	None 1-2 severe exacerbations 3-4 severe exacerbations 5+ severe exacerbations		(ref)	
Presence of exacerbations in previous year	None 1-2 exacerbations 3-4 exacerbations 5+ exacerbations		(ref)	
Presence of moderate/severe exacerbations in previous year	None 1-2 moderate/severe exacerbations 3-4 moderate/severe exacerbations 5+ moderate/severe exacerbations		(ref)	
Presence of severe exacerbations in previous year	None 1-2 severe exacerbations 3-4 severe exacerbations 5+ severe exacerbations		(ref)	
Antibiotics for COPD exacerbations	No Yes		(ref)	
Oral corticosteriods for COPD exacerbations	No Yes		(ref)	
Type of ICS	ICS alone LABA + ICS LABA + LAMA + ICS			

Inadequate use of ICS: use of ICS without moderate/severe exacerbations in the previous year in patients.

Table 26. Multivariate logistic regression model of inadequate use of ICS (use of ICS without moderate/severe exacerbations in the previous year)

Parameter	Cat	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Exp(Est)
Intercept							

Parameter	Cat	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq	Exp(Est)
Variable 1							
Variable 2	Cat 2 Cat 3 Cat 4						
…							
Variable n							

Effect	OR Point Estimate	95% Wald Confidence Limits
Variable 1		
Variable 2		
…		
Variable n		

Table 27. Multivariate logistic regression model of inadequate use of ICS (use of ICS without moderate/severe exacerbations in the previous year) by age subgroups

	Patients aged ≤ xx years		Patients aged xx- xx years				Patients aged > xx years	
Effect	OR (95% CI)	p-value	OR (95% CI)	OR (95% CI)	OR (95% CI)	p-value	OR (95% CI)	p-value
Variable 1								
Variable 2								
…								
Variable n								

20.3.2 Exacerbations

Table 31. Presence of moderate/severe exacerbations in COPD patients in the year previous to the study visit according to current treatment on ICS

		Non treated with ICS	Currently treated with ICS	Total
Number of moderate/severe exacerbations	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missings			
Presence of moderate/severe exacerbations	Total Without exacerbations With exacerbations			
	None 1-2 moderate/severe exacerbations 3-4 moderate/severe exacerbations 5+ moderate/severe exacerbations			

Table 32. Negative binomial model for number of moderate-to-severe exacerbations in COPD patients in the year previous to the study visit

Parameter	DF	Estimate	Std Error	Wal 95% CI	Chi-Square	Pr>ChiSq
Variable 1						
Variable 2						
…						
Variable n						
Dispersion						

Table 33. Presence of total exacerbations in COPD patients in the year previous to the study visit according to current treatment on ICS

		Non treated with ICS	Currently treated with ICS	Total
Number of total exacerbations	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missings			
Presence of exacerbations	Total Without exacerbations With exacerbations			
	None 1-2 exacerbations			

		Non treated with ICS	Currently treated with ICS	Total
	3-4 exacerbations 5+ exacerbations			

Table 34. Presence of severe exacerbations in COPD patients in the year previous to the study visit according to current treatment on ICS

		Non treated with ICS	Currently treated with ICS	Total
Number of severe exacerbations	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missings			
Presence of severe exacerbations	Total Without exacerbations With exacerbations			
	None 1-2 exacerbations 3-4 exacerbations 5+ exacerbations			

Table 35. Presence of moderate/severe exacerbations in COPD patients in the two previous years to the study visit according to current treatment on ICS

		Non treated with ICS	Currently treated with ICS	Total
Number of moderate/severe exacerbations	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missings			
Presence of moderate/severe exacerbations	Total Without exacerbations With exacerbations			
	None 1-2 moderate/severe exacerbations 3-4 moderate/severe exacerbations 5+ moderate/severe exacerbations			

		Non treated with ICS	Currently treated with ICS	Total

Table 36. Presence of total exacerbations in COPD patients in the two previous years to the study visit according to current treatment on ICS

		Non treated with ICS	Currently treated with ICS	Total
Number of total exacerbations	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missings			
Presence of exacerbations	Total Without exacerbations With exacerbations			
	None 1-2 exacerbations 3-4 exacerbations 5+ exacerbations			

Table 37. Presence of severe exacerbations in COPD patients in the two previous years to the study visit according to current treatment on ICS

		Non treated with ICS	Currently treated with ICS	Total
Number of severe exacerbations	Valid N Mean (SD) Median (Q1-Q3) Min-Max N missings			
Presence of severe exacerbations	Total Without exacerbations With exacerbations			
	None 1-2 exacerbations			

		Non treated with ICS	Currently treated with ICS	Total
	3-4 exacerbations 5+ exacerbations			

20.3.3 Adherence to treatment recommendations according GesEPOC 2017 guidelines.

Table 38. Adherence to treatment recommendations according to GesEPOC 2017 Guidelines, according to number of exacerbations in the last year

		0-1 * exacerbations	>= 2 ** exacerbations	Total
Adherence	Adherent (Adequate ICS use) ICS-Treated who should be treated with ICS Non ICS-treated who should not be treated with ICS Non-Adherent (Non-adequate ICS use) ICS-Treated who should not be treated with ICS Non ICS-treated who should be treated with ICS			

* 0-1 exacerbations (not leading to hospital admission). ** ≥ 2 exacerbations or ≥ 1 exacerbation leading to hospital admission in the last 1 year prior to index date.

20.4 Safety

20.4.1 Adverse Drug Reactions - related with ICS

Table 39. Patients with ADRs related with ICS treatment according to current treatment on ICS

		Current Non - ICS	Current ICS	Total ICS patients
ADRs related with ICS treatment	Total Patients No Yes			
Type of ADR (multi-response)	□ Pneumonia □ Fracture □ Skin thinning/easy bruising			

		Current Non - ICS	Current ICS	Total ICS patients
	□ Cataract □ Diabetes □ Oropharyngeal candidiasis			
ADR outcome (multi-response)	Recovered Not yet recovered Recovered with secuelae Unknown Fatal			

Patients in the Safety Analysis Set. Including patients treated with ICS at some time during the previous two years.

Table 40. Description of ADRs related with ICS treatment according to current treatment on ICS

		Current Non - ICS	Current ICS	Total ICS patients
Number of ADRs related with ICS treatment	Total ADRs ICS-related			
Type of ADR	□ Pneumonia □ Fracture □ Skin thinning/easy bruising □ Cataract □ Diabetes □ Oropharyngeal candidiasis			
ADR outcome	Recovered Not yet recovered Recovered with secuelae Unknown Fatal			

Patients in the Safety Analysis Set. Including patients treated with ICS at some time during the previous two years

Table 41. List of ADRs related with ICS treatment

PATCOD	Adverse Event Term	MedDRA Code	Onset date	End date	SAE?	Reason for seriousness	Outcome

Patients in the Safety Analysis Set. Including patients treated with ICS at some time during the previous two years

20.4.2 Serious Adverse Drug Reactions (SADRs) - related with ICS

Table 42. Patients with SADRs related with ICS treatment according to current treatment on ICS

		Current Non - ICS	Current ICS	Total ICS patients
SADRs related with ICS treatment	Total patients No Yes			
Type of SADR (multi-response)	□ Pneumonia □ Fracture □ Skin thinning/easy bruising □ Cataract □ Diabetes □ Oropharyngeal candidiasis			
Reason for seriousness (multi-response)	Results in death Immediately life-threatening Persistent or significant disability/incapacity Requires/prolongs hospitalization Congenital anomaly/birth defect Other comparable medical criteria			
SADR outcome (multi-response)	Recovered Not yet recovered Recovered with secuelae Unknown Fatal			

Patients in the Safety Analysis Set. Including patients treated with ICS at some time during the previous two years

Table 43. Description of SADRs related with ICS treatment according to current treatment on ICS

		Current Non - ICS	Current ICS	Total ICS patients
Number of SADRs related with ICS treatment	Total SADRs ICS-related			
Type of SADR	□ Pneumonia □ Fracture □ Skin thinning/easy bruising □ Cataract □ Diabetes □ Oropharyngeal candidiasis			

		Current Non - ICS	Current ICS	Total ICS patients
Reason for seriousness	Results in death Immediately life-threatening Persistent or significant disability/incapacity Requires/prolongs hospitalization Congenital anomaly/birth defect Other comparable medical criteria			
SADR outcome	Recovered Not yet recovered Recovered with secuelae Unknown Fatal			

Patients in the Safety Analysis Set. Including patients treated with ICS at some time during the previous two years

20.4.3 Adverse Drug Reactions associated to BI product (SPIOLTO®, STRIVERDI®, SPIRIVA® or ATROVENT®)

Table 44. Patients with ADRs associated to BI product according to current treatment on ICS

		Current Non - ICS	Current ICS	Total ICS patients
ADRs associated to BI product	Total Patients No Yes			
Type of ADR (multi-response)	Term 1 Term 2 … Term n			
ADR outcome (multi-response)	Recovered Not yet recovered Recovered with secuelae Unknown Fatal			

Patients in the Safety Analysis Set. Including patients treated with BI product at some time during the previous two years.

Table 45. Description of ADRs associated to BI product according to current treatment on ICS

		Current Non - ICS	Current ICS	Total ICS patients

		Current Non - ICS	Current ICS	Total ICS patients
ADRs associated to BI product	Total ADRs			
Type of ADR	Term 1 Term 2 … Term n			
ADR outcome	Recovered Not yet recovered Recovered with secuelae Unknown Fatal			

Patients in the Safety Analysis Set. Including patients treated with BI product at some time during the previous two years

Table 46. List of ADRs associated with BI product.

PATCOD	Adverse Event Term	MedDRA Code	Onset date	End date	SAE?	Reason for seriousness	Outcome	Relationship With BI product	BI product

Patients in the Safety Analysis Set. Including patients treated with BI product at some time during the previous two years

20.4.4 Serious Adverse Drug Reaction (SADRs)related with BI product

Table 47. Patients with SADRs related with BI product according to current treatment on ICS

		Current Non - ICS	Current ICS	Total ICS patients
SADRs associated to BI product	Total patients No			

		Current Non - ICS	Current ICS	Total ICS patients
	Yes			
Type of SADR (multi-response)	Term 1 Term 2 … Term n			
Reason for seriousness (multi-response)	Results in death Immediately life-threatening Persistent or significant disability/incapacity Requires/prolongs hospitalization Congenital anomaly/birth defect Other comparable medical criteria			
SADR outcome (multi-response)	Recovered Not yet recovered Recovered with secuelae Unknown Fatal			

Patients in the Safety Analysis Set. Including patients treated with BI product at some time during the previous two years

Table 48. Description of SADR related with BI product according to current treatment on ICS

		Current Non - ICS	Current ICS	Total ICS patients
Number of SADRs associated to BI product	Total SADRs			
Type of SADR	Term 1 Term 2 … Term n			
Reason for seriousness	Results in death Immediately life-threatening Persistent or significant disability/incapacity Requires/prolongs hospitalization Congenital anomaly/birth defect Other comparable medical criteria			
SADR outcome	Recovered Not yet recovered Recovered with secuelae Unknown Fatal			

Patients in the Safety Analysis Set. Including patients treated with BI product at some time during the previous two years

20.4.5 Deaths

Table 49. List of deaths

PATCOD	Adverse Event Term	MedDRA Code	Onset date	End date	Outcome	Relationship With BI product	BI product