Title Page

Protocol Title:

Comparison of 1-year treatment with inhaled long acting bronchodilators (LABD) plus inhaled glucocorticosteroids (ICS) versus LABD without ICS on re-hospitalizations and/or death in elderly patients with chronic obstructive pulmonary disease (COPD) recently hospitalized because of an acute exacerbation of COPD (ICS-Life study).

Protocol Number: AIFA-ICSLIFE-001

Compound Number: n/a

Short Title:

Inhaled long-acting bronchodilators with or without inhaled glucocorticosteroids for preventing hospitalizations and death in elderly patients with chronic obstructive pulmonary disease.

Sponsor Name: Professor Alberto Papi (Principal Investigator)

Legal Registered Address:

Dipartimento di Scienze Mediche

Università degli Studi di Ferrara

Via L. Borsari 46

44121 Ferrara Italy

Regulatory Agency Identifying Number(s): EudraCT number 2018-000739-28

Approval Date: March 12, 2018

Sponsor Signatory:

Professor Alberto Papi	**Date**

Medical Monitor Name and Contact Information will be provided separately

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

Comparison of 1-year treatment with inhaled long acting bronchodilators (LABD) plus inhaled glucocorticosteroids (ICS) versus LABD without ICS on re-hospitalizations and/or death in elderly patients with chronic obstructive pulmonary disease (COPD) recently hospitalized because of an acute exacerbation of COPD (ICS-Life study).

Short Title:

Inhaled long-acting bronchodilators with or without inhaled glucocorticosteroids for preventing hospitalizations and death in elderly patients with chronic obstructive pulmonary disease.

Rationale:

Chronic obstructive pulmonary disease occurs mainly in the elderly and has important comorbidities, particularly cardiovascular, which increase its severity (Roversi et al 2016). Chronic obstructive pulmonary disease affects 5% of people globally, increasing to 10% in the elderly. According to data from the World Health Organisation (WHO), there were 384 million cases of COPD in 2010, with a global prevalence of 12% (www.who.int). Deaths due to COPD are 3 million/year globally (GOLD 2018) and >20,000/year in Italy (Ministero Della Salute www.salute.gov.it).

Acute exacerbation of COPD is one of the most common clinical diagnoses in patients presenting to the hospital with increased dyspnoea and hypoxemia as chief complaints or signs. In Italy, patients with a main diagnosis of AECOPD are primarily classified under the diagnosis related group (DRG) code 087 (pulmonary oedema and respiratory failure). In Italy, DRG 087 is the 5th most common cause of admission to the hospital; 139,000 patients classed as DRG 087 were discharged in 2014 (Ministero Della Salute www.salute.gov.it). Patients hospitalized due to exacerbations of respiratory symptoms are mostly elderly (average age 75 years), frail, and have multiple comorbidities (Shah et al 2016). Up to 20% of patients hospitalized for AECOPD are re-hospitalized (Shah et al 2016) or even die (Serra-Picamal et al 2018) within 30 days, and >30% are re-hospitalized or die within a year (Tokgoz et al 2016). The most important risk factors for re-hospitalization and death after AECOPD are comorbidities (Shah et al 2016, Vanflateren et al 2016), particularly HF/IHD/AF (Roversi et al 2016). Thus, re-hospitalizations and death are a major risk for the patient and a major burden on society, particularly in the year following the first hospitalization due to AECOPD (Shah et al 2016, Tokgoz et al 2016).

Compared to randomized clinical trials conducted in younger patients with milder cases of chronic obstructive pulmonary disease (COPD) (Calverley et al 2007, Vestbo et al 2016(a)), meta-analyses and registry studies suggest that long-acting bronchodilators plus inhaled steroids (LABD+ICS) reduce hospitalizations and mortality in elderly, frail patients (Gershon et al 2014, Sin et al 2005) with COPD.

According to the Global Initiative for Obstructive Lung Disease (www.goldcopd.org), for GOLD D patients, GOLD recommends LABD either alone (LAMA or LABA) or in combination (LAMA+LABA), mainly to reduce symptoms and exacerbations (Wedzicha et al 2016). GOLD also recommends adding ICS to LABD, but only if patients are young and/or have eosinophilia and/or a history of asthma, mainly because LABA+ICS is the most prescribed treatment in these patients.

We speculated that multimorbid elderly COPD patients recently hospitalized due to an acute exacerbation of COPD (AECOPD) and who have concomitant cardiovascular disease may have fewer re-hospitalizations and increased survival in the following year if treated with LABD+ICS rather than with LABD alone.

The aim of this study is to examine the efficacy and safety of currently recommended and prescribed inhalation therapies to elderly, frail and multimorbid COPD patients with a recent hospitalization due to an AECOPD. The study involves a group of patients who have never before been selected for a clinical trial and who represent the 5th most common cause of hospitalization and the 3rd most common cause of death in Italy.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• to demonstrate that in elderly COPD patients with one or more cardiac comorbidities (heart failure, and/or ischemic heart disease, and/or atrial fibrillation) who have been recently hospitalized due to AECOPD, 1-years treatment with LABD+ICS will prolong the time to first re-hospitalization and/or the death for any cause when compared to 1-years treatment with LABD alone	• composite event of the time to first re-hospitalization and/or death (all cause)
Secondary	
• to compare the number of moderate/severe exacerbations of COPD in the two patient groups • to compare the number of re-hospitalizations and deaths (all cause) in the two patient groups • to compare quality of life (QoL) scores measured using the COPD Assessment Test (CAT) and mMRC dyspnoea scale between the two patient groups • to verify if one year of treatment with combination therapy including ICS increases the risk of pneumonia • to compare the number of acute cardiac events in this frail, elderly COPD population • to compare the incidence of deaths due to cardiovascular events • to compare changes in lung function	• number of moderate/severe COPD exacerbations • number of re-hospitalizations and deaths (all cause) • QoL variation measured as change in CAT total score from baseline to end of treatment period. • change in mMRC dyspnea score from baseline to end of treatment period. • number of pneumonia events • number of acute cardiac events • number of cardiovascular deaths • change in FEV1 from baseline to the end of treatment period • change in FVC from baseline to the end of treatment period

Overall Design:

This will be a phase IV, open label, multicenter, randomized pragmatic study in frail elderly patients with COPD. Participants will be treated with either inhaled LABD alone or LABD combined with inhaled glucocorticosteroids. The choice of the specific LABD and ICS to be used will be left to the discretion of the clinical investigator, according to the treatments available from their pharmacy department.

The center will be considered as a unique stratifying factor, so the study will have a balanced-block center-stratified design.

The main aim of the study is to assess whether, in elderly patients with COPD and one or more cardiac comorbidities (heart failure, and/or ischemic heart disease, and/or atrial fibrillation) recently hospitalized because of an acute exacerbation of COPD, 12 months treatment with LABD(s)+ICS can increase the time to first re-hospitalization (all cause) and/or death for any cause when compared with LABD(s) alone. Patients will be followed-up for 3 months after completion of the 12 month treatment period.

Randomization to treatment will occur after screening.

A Data Monitoring Committee (DMC) will periodically review and evaluate the accumulated study data for safety, study conduct and progress, scientific validity and integrity. The DMC will monitor the progress of the study, enrollment, study performance in terms of data management metrics and will undertake a review of the safety data including adverse events.

Participants will be recruited according to the following inclusion and exclusion criteria:

Inclusion criteria

1. Participant must be older than 60 years of age, at the time of signing the informed consent.
2. Recently (within 6 months) discharged from hospital with a diagnosis of acute exacerbation of COPD (usually coded as DRG 087 or DRG 088).
3. Participants with a clinical diagnosis of COPD (i.e. previous diagnosis of COPD and/or treatment with short acting bronchodilators (SABD), LABD or LABD+ICS
4. Spirometry confirmed diagnosis of COPD, post-bronchodilator (30 minutes after 400 μg salbutamol) FEV1/FVC ratio <0.7. The diagnostic spirometry test can have been performed up to three years prior to randomization, or if never performed before, should be performed not earlier than 4 weeks since last exacerbation
5. Smokers or ex-smokers with a smoking history of >10 pack years (a pack year is defined as 20 cigarettes smoked every day for a year)
6. Clinical diagnosis documented in the patient's medical records of one or more major chronic cardiac disease (heart failure, ischemic heart disease or atrial fibrillation).
7. Currently receiving at least one of the specified treatments (either alone or in combination, see Appendix 10.5) for heart failure, ischemic heart disease or atrial fibrillation.
8. Participant must be willing and able to perform pulmonary function tests
9. Male or female. Contraception is not considered necessary in this cohort of elderly (> 60 years) patients receiving treatment with commercially available licensed products.

10. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Exclusion criteria

1. Patients with a primary discharge diagnosis of DRG 087 or DRG 088 but clearly judged by the clinical investigator to be due to other causes, i.e. patients presenting to the hospital with symptoms of AECOPD but due mainly to other conditions (pulmonary embolism, pneumonia, pneumothorax, anemia, acute kidney failure, decompensated heart failure, acute ischemic heart disease, new onset atrial fibrillation, stroke, etc.)
2. Patients who required invasive mechanical ventilation during hospitalization
3. Patients with Asthma as primary and principal diagnosis
4. Patients with severe cardiovascular (CV) disease who in the opinion of the investigator are unlikely to survive the 15 month study period
5. Patients considered unable to comply with the study procedures and follow-up in the opinion of the investigator (eg, evidence of alcohol or drug abuse, psychiatric disorder, physical disability, social or geographical obstacles)
6. Patients in whom spirometry is contraindicated (eg, hemoptysis, detached retina, active tuberculosis, last trimester of pregnancy)
7. Patients with other mechanical or overt causes of respiratory symptoms, particularly dyspnea (such as pneumothorax, chest wall trauma, lung fibrosis, lung cancer, anemia, severe obesity (BMI >40) or cachexia (BMI <18))
8. Patients with any major disease which in the opinion of the investigator would prevent study participation, such as dementia, end-stage disease, cachexia, chronically bedridden patient and life expectancy <15 months.
9. Participation in any other interventional study within the last 3 months or concurrent participation in an observational clinical study.

Number of Participants:

The aim is to randomize 464 participants to each intervention group

Adjusting for an expected 10% dropout rate, a total of 516 patients per group will need to be randomized.

The study will be performed at 39 centers in Italy.

Intervention Groups and Duration:

In this study patients will be randomised to receive one of the following two treatment regimens for up to 12 months:

1) Usual and optimized treatment for concomitant cardiovascular (CV) diseases plus inhaled long acting bronchodilator(s) (LABD(s))

2) Usual and optimized treatment for concomitant CV diseases plus inhaled long acing bronchodilator(s) and inhaled glucocorticosteroids (ICS).

The choice of the specific LABD(s) and/or ICS for each patient will be left to the discretion of the clinical investigator. All treatments will be administered at licensed dosages. During the study, the doses of all medications may be adjusted by the investigator according to licensed dosages. Both study groups will receive prescriptions for study medication, which will be collected by the patients from their local pharmacy or hospital pharmacy department. Prescription data will be captured on the electronic case report form (eCRF).

All diagnostic procedures and medical treatments will be performed according to best medical practice (Percorsi Diagnostico Terapeutici Assistenziali (PDTA) at the study centre. Best medical practice is usually based on the most recent and credited international guidelines for these chronic diseases such as the ESC guidelines for cardiac diseases (www.esc.org) and GOLD guidelines (www.goldcopd.org) for COPD.

Additional therapeutic or diagnostic procedures (i.e. use of concomitant medication) will be performed according to local guidelines (PDTA).

Both study groups will receive prescriptions for study medication, which will be collected by the patients from their local pharmacy or hospital pharmacy department. Study treatments will be stored and dispensed by the pharmacy in accordance with normal dispensing practice.

The total duration of study participation for each participant will be 15 months (12 month treatment period and 3 month follow-up) plus up to an additional 10 days for the study screening to be completed.

Participants will be instructed in the correct method of using the inhaler device(s) at the randomization visit and their technique will be checked at each follow-up visit to ensure that they are using the device(s) correctly.

Participants will be requested to bring their medication when they attend for their next visit and the investigator will make an assessment of the participant's compliance with their treatment from the quantity of medication returned and by directly asking the participant about their compliance with their COPD treatment.

During the study, the doses of all medications can be adjusted by the investigator according to licensed dosages.

Treatment with ICS in the only LABDs group will be permitted if, on clinical Investigators judgement, it would be necessary for patient temporary conditions for at maximum 15 days in case of patient treated at home or for 15 days (at maximum) after hospital discharge in case of hospitalised patient. If the ICS treatment will surpass these periods, the patient will be considered being switched to the LABD + ICS group and considered as protocol violator

Statistical Considerations

Sample Size

The sample size calculation is based on the superiority criteria of the LABD+ICS group vs. LABD alone group in terms of re-hospitalization and/or death. With 464 patients in each group, the

percentage of patients experiencing the composite event (re-hospitalization and/or death) is expected to be 9% in the LABD+ICS group and 15% in the LABD alone group. A log-rank test (two-sided 5% significance level) will have 80% power to detect a difference between treatment groups in terms of time to first re-hospitalization and/or death (primary efficacy endpoint).

Statistical Hypothesis

The superiority of the LABD(s)+ICS group vs. LABD(s) group in terms of time to first re-hospitalization and/or death will be tested. The following hypothesis scheme will be considered:

H_0: there is no difference in the time to first re-hospitalization and/or death between the two treatment groups.

H_1: there is a difference in the time to first re-hospitalization and/or death between the two treatment groups

Patient Populations

The following populations will be considered for the analysis:

- **Randomized population**: all randomized patients.
- **Safety population**: all randomized patients who receive at least one administration of the study treatment in a given treatment period.
- **Intention-to-Treat population (ITT)**: all randomized patients from the safety population with at least one available post-baseline efficacy evaluation during the treatment period.
- **Per-protocol population (PP)**: all randomized patients from the ITT population without any major protocol deviations (e.g., wrong inclusions, forbidden concomitant medications, etc.). The exact definition of major protocol deviations will be discussed with the clinical team case by case during the review of the data and will be described in the Data Review Report.

The primary efficacy variable will be analysed both in the ITT and in the PP populations. As this is a superiority study, the primary analysis population will be the ITT. All the other efficacy variables will be analysed in the ITT population only.

Analysis of safety variables will be performed on the safety population.

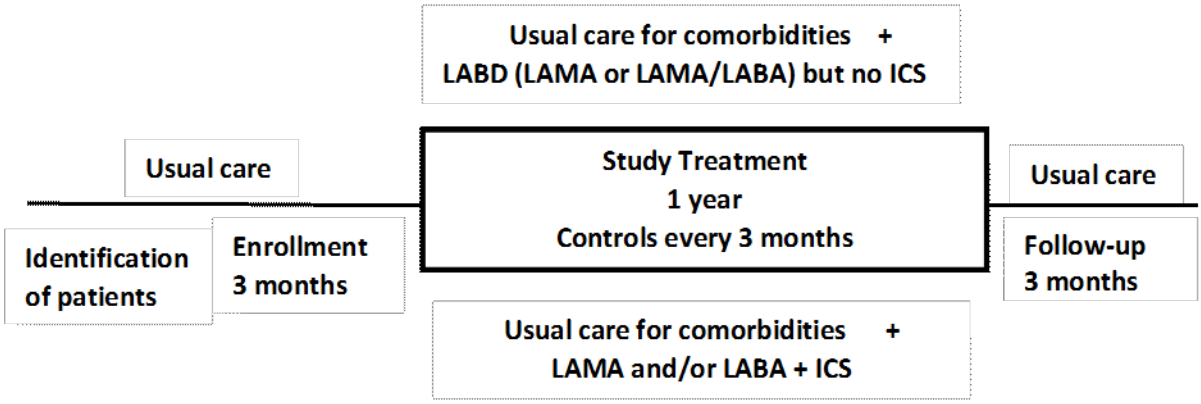
The primary efficacy variable will be analyzed using the Kaplan-Meier estimator. Comparison between treatment groups will be performed using the log-rank test stratified by center. A Kaplan-Meier plot for time to first re-hospitalization and/or death will also be presented by treatment group.

The LABD(s)+ICS group will be declared to prolong time to first re-hospitalization and/or death, compared to the LABD(s) group, if the difference between the two treatments is significantly in favour of LABD(s)+ICS (i.e. the p-value from the log-rank test is ≤ 0.050).

A detailed Statistical Analysis Plan (SAP) will be described in a separate document to be completed after the protocol is finalised and before database lock.

Data Monitoring Committee: Yes

1.2. Schema



1.3. Schedule of Activities (SoA)

Procedure	Screening (up to 10 days before Day 1)	Intervention Period [months]					Follow-up (3 months after last study treatment)	Notes
		day 1 (randomization)	3 months	6 months	9 months	12 months (or early withdrawal)		
Visit number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	
Informed consent	X							
Inclusion and exclusion criteria	X	X						Recheck clinical status before randomization and/or 1st dose of study medication.
Spirometry*		X				X		Participant must have a diagnosis of COPD confirmed by spirometry (performed within the last 3 years) prior to randomization.
COPD assessment test (CAT)	X	X	X	X	X	X	X	
mMRC dyspnea scale	X	X	X	X	X	X	X	
Demography	X							
Physical examination including height and weight	X	X	X	X	X	X	X	
Medical history (including substance usage (review and update after screening if necessary)*	X	X	X	X	X	X	X	Substances: alcohol, tobacco, and caffeine Medical history will be reviewed and updated at the follow-up visits

Procedure	Screening (up to 10 days before Day 1)	Intervention Period [months]					Follow-up (3 months after last study treatment)	Notes
		day 1 (randomization)	3 months	6 months	9 months	12 months (or early withdrawal)		
Visit number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	
History of COPD and cardiovascular disease (particularly HF, IHD or AF)	X	X	X	X	X	X	X	Participants must have concomitant CV disease (HF, IHD or AF) and must be receiving treatment (see Appendix 10.5) to be eligible for the study
Past and current medical conditions	X							Participants must have at least one concomitant major CV condition (HF, IHD or AF)
Laboratory assessments	X							
12-lead ECG	X					X		For stable patients a previous ECG recording (within the last 3 months) can be used
Chest x-ray	X (Optional)							Chest x-ray data will be collected if available
Vital signs (blood pressure and heart rate)	X	X	X	X	X	X		
Randomization		X						
Study treatment checked and prescribed		X	X	X	X			
Assessment of symptoms and hospitalizations			X	X	X	X	X	Also assessed via monthly telephone contact between visits

Procedure	Screening (up to 10 days before Day 1)	Intervention Period [months]					Follow-up (3 months after last study treatment)	Notes
		day 1 (randomization)	3 months	6 months	9 months	12 months (or early withdrawal)		
Visit number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	
Vaccination check (to be recorded in concomitant form)		X	X	X	X			Anti-influenza and anti-pneumococci. To be checked also during monthly telephone call
Adverse event review		X	X	X	X	X		
Serious adverse event review		X	X	X	X	X	X	
Concomitant medication review	X	X	X	X	X	X	X	

CV = cardiovascular, HF = heart failure, IHD = ischemic heart disease, AF = atrial fibrillation, CAT = COPD Assessment Test, mMRC = modified Medical Research Council.

* Participants with a diagnosis of COPD confirmed by spirometry within the last 3 years, will be immediately eligible for the study after hospital discharge. Participants without a previous spirometric confirmation must have a spirometry test, which must be performed not earlier than 4 weeks since last exacerbation. If confirmed then they can be recruited to the study.

**Participants will be contacted by telephone each month, by the clinical investigator or by a research staff member, to check compliance with the study procedures and treatment. Information about any hospitalizations or any unexpected medical events, particularly moderate exacerbations treated with antibiotics and/or steroids will be collected Information on anti-influenza and anti-pneumococci vaccination will also be collected.

2. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation caused mostly by cigarette smoking. In up to 30% of patients, COPD is punctuated by acute exacerbations that may cause hospitalization and death.

Chronic obstructive pulmonary disease occurs mainly in the elderly and has important comorbidities, particularly cardiovascular, which increase its severity (Roversi et al 2016). Chronic obstructive pulmonary disease affects 5% of people globally, increasing to 10% in the elderly. According to data from the World Health Organisation (WHO), there were 384 million cases of COPD in 2010, with a global prevalence of 12% (www.who.int). Deaths due to COPD are 3 million/year globally (GOLD 2018) and >20,000/year in Italy (Ministero Della Salute www.salute.gov.it).

With the increase in smoking and aging populations, the global prevalence of COPD is expected to rise over the next 14 years, with >4.5 million expected deaths/year in 2030 from COPD and related conditions. Hospitalizations for acute exacerbations of COPD (AECOPD) are estimated to cost about 25% ($13.2 billion) of the total direct costs of COPD in the U.S. ($50 billion). Acute exacerbations of COPD and hospitalizations are a significant burden on the healthcare system (May et al 2015), particularly due to comorbidities (Lisspers et al 2018).

Severe acute respiratory symptoms, in particular, dyspnoea, are important causes of hospitalization, healthcare resource utilization, and death. They are mainly due to AECOPD but may be due to other causes such as cardiac failure, ischaemic heart disease, acute kidney failure, anaemia, or pulmonary thromboembolisms (Roca et al 2013, Wedzicha et al 2014, Vanfleteren, et al 2016; GOLD 2018).

Acute exacerbations of COPD are defined as acute episodes characterized by a significant worsening of respiratory symptoms, particularly dyspnoea, cough, and sputum that can become purulent, that force a change in medication, use of healthcare resources, or hospitalization. Acute exacerbations of COPD are complex events usually associated with increased airway inflammation, increased mucus production and marked air trapping, which contribute to dyspnoea in particular. Sputum purulence and volume, together with increased cough and wheezing, may also be present (Anthonisen et al 1987, GOLD 2018), and possibly specifically distinguish exacerbations of respiratory symptoms due to AECOPD from the many other causes that may worsen dyspnoea (Roca et al 2013).

As comorbidities are common in COPD patients, exacerbations of dyspnoea must be differentiated clinically from other causes of acute dyspnoea, such as acute heart failure (HF) and/or ischemic heart disease (IHD) and/or atrial fibrillation (AF), anaemia, pulmonary embolism, pneumonia and others (Roca et al 2013).

Acute exacerbation of COPD is one of the most common clinical diagnoses in patients presenting to the hospital with increased dyspnoea and hypoxemia as chief complaints or signs. In Italy, patients with a main diagnosis of AECOPD are primarily classified under the diagnosis related group (DRG) code 087 (pulmonary oedema and respiratory failure). In Italy, DRG 087 is the 5th most common cause of admission to the hospital; 139,000 patients classed as DRG 087 were

discharged in 2014 (Ministero Della Salute www.salute.gov.it). Patients hospitalized due to exacerbations of respiratory symptoms are mostly elderly (average age 75 years), frail, and have multiple comorbidities (Shah et al 2016). Up to 20% of patients hospitalized for AECOPD are re-hospitalized (Shah et al 2016) or even die (Serra-Picamal et al 2018) within 30 days, and >30% are re-hospitalized or die within a year (Tokgoz et al 2016). The most important risk factors for re-hospitalization and death after AECOPD are comorbidities (Shah et al 2016, Vanflateren et al 2016), particularly HF/IHD/AF (Roversi et al 2016). Thus, re-hospitalizations and death are a major risk for the patient and a major burden on society, particularly in the year following the first hospitalization due to AECOPD (Shah et al 2016, Tokgoz et al 2016).

The global initiative for chronic obstructive lung disease (GOLD) guidelines recommend pharmacological and non-pharmacological treatments with the main aims of reducing symptoms, exacerbations and hospitalizations, and improving quality of life (www.goldcopd.org Apart from long-term oxygen treatment and smoking cessation, no treatment so far has been shown to reduce COPD hospitalizations or mortality. The most important limit of the GOLD guidelines, as with all guidelines for chronic diseases, is that they are based on randomized clinical trials (RCT) conducted in patients who are usually younger, with less severe symptoms and fewer comorbidities compared to patients treated in the general population (NICE Guidelines 2016, Fried et al 2012, Tinetti et al 2012). In particular, no properly powered RCT has ever been conducted in elderly, frail, multimorbid COPD patients after a recent hospitalization due to AECOPD, a large population at particular risk of re-hospitalization and death (vide supra).

For GOLD D patients, GOLD recommends LABD either alone (LAMA or LABA) or in combination (LAMA+LABA), mainly to reduce symptoms and exacerbations (Wedzicha et al 2016). GOLD also recommends adding ICS to LABD, but only if patients are young and/or have eosinophilia and/or a history of asthma, mainly because LABA+ICS is the most prescribed treatment in these patients.

While patients with COPD are at increased risk of cardiovascular diseases (Sin et al 2003) new initiation of LABAs or LAMAs in patients with COPD is associated with an increased severe cardiovascular risk (Wang et al 2018), particularly in the elderly (Gershon et al, 2013). Previous studies (Macie et al 2006) meta-analyses (Sin et al 2005) and registry studies (Gershon et al 2014) have suggested that treatment of COPD including ICS in addition to LABD may reduce mortality and hospitalizations, particularly in elderly, frail patients with severe COPD and multimorbidities. Two randomized clinical trials conducted in non-hospitalized, younger patients with milder COPD (Calverley et al 2007, Vestbo et al 2016(a)) resulted in a barely significant (Calverley et al 2007) or non-significant (Vestbo et al 2016(a)) reduction of mortality. In these studies, patients were treated for 4 years (Calverley et al 2007) and up to 3 years (Vestbo et al 2016(a)) with a combination of a LABA (salmeterol or vilanterol) and an ICS (fluticasone propionate or fluticasone furoate), respectively. Interestingly, the study by Vestbo et al was the first ever conducted in patients with COPD and concomitant cardiovascular disease or at risk for cardiovascular disease (Vestbo et al 2016(a), but the patients were relatively milder and younger compared to the usual COPD population. The study showed a non-significant reduction in mortality, but 1) patients were relatively young (mean age, 65 years), 2) airflow limitation was moderate (mean FEV1, 60% of predicted), and most importantly, 3) only 15% of patients had a previous history of hospitalization. Nonetheless, the 3-year treatment with the LABA+ICS

combination (vilanterol/fluticasone furoate) was associated with a non-significant 11.8% reduction of mortality for all causes as compared with 9% with the LABA vilanterol alone and a 22% reduction of hospitalizations as compared to 15% with vilanterol alone (Vestbo et al 2016(a). By contrast, a more recent RCT showed that, compared to a LABA/LAMA combination in a single inhaler, both a triple LABA/LAMA/ICS combination and a LABA/ICS combination in a single inhaler reduced all-cause mortality in symptomatic patient with COPD and history of exacerbations, with a marginally increased risk of pneumonia (Lipson et al 2018). A similar even if smaller head-to-head study showed not only superiority of LABA/LAMA/ICS over LABA/LAMA in reducing AECOPD but also an interesting reduction in some major cardiovascular adverse events (Papi et al 2018).

We speculated that multimorbid elderly COPD patients recently hospitalized due to AECOPD may have reduced re-hospitalizations and increased survival in the following year if treated with LABD+ICS rather than LABD without ICS.

The 2017 revision of the GOLD guidelines introduced an interesting refinement of the previous ABCD assessment tool that separates spirometric grades (GOLD 1, 2, 3, 4) depending on the percentage of predicted FEV1: post-bronchodilator FEV1/FVC <0.7 and FEV1 >80% (GOLD 1), FEV1 50-80% (GOLD 2), FEV1 30-50% (GOLD 3), or FEV1<30% (GOLD 4) from clinical severity GOLD A,B,C,D groups, that were defined only by symptom severity and frequency of exacerbations/hospitalizations in the previous year (www.goldcopd.org). Treatment recommendations are no longer based on spirometric severity but only on clinical GOLD A, GOLD B, GOLD C and GOLD D severity.

Thus pharmacological treatment recommendations are mainly based on results of RCTs assessing the effects on patient related outcomes, i.e. patient symptoms and history of exacerbation/hospitalization.

For GOLD D patients, GOLD recommends LABD either alone (LAMA or LABA) or in combination (LAMA+LABA), mainly to reduce symptoms and exacerbations (Wedzicha et al 2016). GOLD also recommends adding ICS to LABD, but only if patients are young and/or have eosinophilia and/or a history of asthma, mainly because LABA+ICS is the most prescribed treatment in these patients.

The reasons for limiting combinations including ICS are 1) that they may be equally effective (Magnussen et al 2014) or even less effective (Wedzicha et al 2016), than LABA+LAMA without ICS and, more importantly, 2) because ICS are associated with the risk of pneumonia (Jannella et al 2016). Finally, in GOLD D patients, GOLD recommends stepping up to triple therapy (LAMA+LABA+ICS) only when the above mentioned options are not effective enough (GOLD 2018). This recommendation is today supported by at least four recent studies that clearly show that LAMA+LABA+ICS in a single inhaler is superior to LABA+ICS (Singh et al 2016), to LAMA alone (Vestbo et al 2017), and to LABA+LAMA (Papi et al 2018, Lipson et al 2018).

Interestingly, neither of these studies on triple therapy (Singh et al 2016, Vestbo et al 2017) nor a recent large, real-life study confirming reduction of exacerbations by adding LABA+ICS to usual care (Vestbo et al 2016(b)), showed a clinically relevant increased risk of pneumonia, thus lessening concerns associated with the use of ICS (Jannella et al 2016). No or marginal risk of

pneumonia has been reported in two recent studies comparing triple with LABA/LAMA (Papi et al 2018, Lipson et al 2018

As previously mentioned, however, these recommendations are based on RCTs conducted in relatively young (average age 65 years) patients with less severe and less comorbid COPD, along with a very small (<1%) cohort of elderly frail patients with multimorbid COPD who had recent hospitalizations.

For this reason, considering the potential beneficial effects of ICS in this population, we propose to conduct a real-life study in which we will randomize elderly frail, multimorbid COPD patients recently hospitalized due to AECOPD to one of two regimens: 1) usual and optimized treatment for concomitant chronic diseases plus LABD but no ICS, and 2) usual and optimized treatment for concomitant chronic diseases plus LABD+ICS. The choice of the particular LABD and ICS will be left to the discretion of the clinical investigator. Thus, the proposed study will be a real-life but randomized study with a 12 month treatment period and 3 months follow-up. All diagnostic procedures and medical treatments will be performed according to best medical practice (PDTA) which is usually based on the most recent and credited international guidelines for both of these chronic diseases, e.g., European Society of Cardiology (ESC) guidelines for cardiac diseases (www.esc.org) and GOLD guidelines (www.goldcopd.org) for COPD.

2.1. Study Rationale

Re-hospitalizations and death are major concerns for patients hospitalized due to AECOPD. By limiting this study to include only patients admitted to the hospital because of exacerbation of respiratory symptoms and discharged with the DRG 087 (pulmonary edema or respiratory failure), we are referring to a population that in 2014 accounted for about 139,000 hospitalizations in Italy (Vestbo et al 2016(b), Ministero della Salute www.salute.gov.it). Many AECOPD may also be included in other DRG codes, such as DRG 127 (cardiac failure and shock, 190,000), DRG 89 (pneumonia, 73,000), DRG 125 (other cardiovascular diseases, 63,000) and DRG 088 (COPD, 42,000) (Roca et al 2013, Vanfleteren et al 2016).

The reason why AECOPD are coded as DRG 087 and not DRG 088 (COPD) is administrative, as reimbursement is much higher if COPD patients are admitted for respiratory failure than for stable disease. In the last 15 years there has been a significant decrease in admissions with DRG 088 and a simultaneous increase in DRG 087.

Compared to randomized clinical trials conducted in younger patients with milder cases of COPD (Calverley et al 2007, Vestbo et al 2016(a)), meta-analyses and registry studies suggest that, while new initiation of LABAs or LAMAs in patients with COPD is associated with an increased severe cardiovascular risk (Wang et al 2018) particularly in the elderly (Gershon et al 2013), long-acting bronchodilators plus inhaled steroids (LABD+ICS) reduce hospitalizations and mortality in elderly, frail patients (Macie et al 2006, Sin et al 2005, Gershon et al 2014) with COPD.

For GOLD D patients, GOLD recommends LABD either alone (LAMA or LABA) or in combination (LAMA+LABA), mainly to reduce symptoms and exacerbations (Wedzicha et al 2016). GOLD also recommends adding ICS to LABD, but only if patients are young and/or have eosinophilia and/or a history of asthma, mainly because LABA+ICS is the most prescribed treatment in these patients.

We speculated that elderly COPD patients recently hospitalized due to AECOPD may have fewer re-hospitalizations and increased survival in the following year if treated with LABD+ICS rather than with LABD alone.

The aim of this study is to examine the efficacy and safety of currently recommended and prescribed inhalation therapies to elderly, frail and multimorbid COPD patients with a recent hospitalization due to an AECOPD. The study involves a group of patients who have never before been selected for a clinical trial and who represent the 5th most common cause of hospitalization and the 3rd most common cause of death in Italy.

2.2. Background

For GOLD D patients, GOLD recommends LABD either alone (LAMA or LABA) or in combination (LAMA+LABA), mainly to reduce symptoms and exacerbations (Wedzicha et al 2016). GOLD also recommends adding ICS to LABD, but only if patients are young and/or have eosinophilia and/or a history of asthma, mainly because LABA+ICS is the most prescribed treatment in these patients.

We speculate that multimorbid elderly COPD patients recently hospitalized with an AECOPD and concomitant cardiovascular disease may have fewer re-hospitalizations and increased survival in the following year if treated with LABD+ICS rather than with LABD alone.

In this study patients will be randomised to one of two treatment regimens:

1) Usual and optimized treatment for concomitant chronic diseases plus LABD(s) but no ICS
2) Usual and optimized treatment for concomitant chronic diseases plus LABD(s)+ICS.

The choice of the particular LABD(s); (1 or 2) and ICS will be left to the discretion of the clinical investigator. Thus, the proposed study will be a real-life but randomized study with a 12 month treatment period followed by 3 months follow-up. All diagnostic procedures and medical treatments will be performed according to best medical practice (Percorsi Diagnostico Terapeutici Assistenziali (PDTA)) at the study centre. Best medical practice is usually based on the most recent and credited international guidelines for these chronic diseases such as the ESC guidelines for cardiac diseases (www.esc.org) and GOLD guidelines (www.goldcopd.org) for COPD.

2.3. Benefit/Risk Assessment

The key aim of this study is to examine the efficacy and safety of currently recommended and prescribed inhalation therapies to elderly, frail and multimorbid COPD patients with a recent hospitalization due to AECOPD. The study involves a group of patients who have never before been selected for a clinical trial and who represent the 5th most common cause of hospitalization and the 3rd most common cause of death in Italy.

The main objective of this study is to determine whether a long-term inhalation treatment including LABD(s) and ICS, that is currently recommended and shown to reduce symptoms and exacerbations, may also reduce re-hospitalizations and/or death in elderly, frail and multimorbid COPD patients with a recent hospitalization due to AECOPD.

Despite attempts to define the risk of re-hospitalization and death in this population, we could not go beyond an estimated re-hospitalization rate of 20% at 1 month in severe AECOPD (Shah et al 2016), and a re-hospitalization/death rate of 30% at 1 year (Tokgoz et al 2016). However, these estimates were obtained from retrospective studies reported in the literature (Shah et al 2016, Tokgoz et al 2016) that included patients with respiratory failure if they required non-invasive as well as invasive ventilation. In addition, as previously mentioned, the characterization of AECOPD in real life is quite inaccurate, not only as to the nature of the exacerbation of respiratory symptoms (Roca et al 2013) but also in confirming the diagnosis of COPD by spirometry.

For all these reasons, we estimated that by selecting patients with a diagnosis of COPD confirmed by spirometry, even if elderly, frail and with comorbidities, particularly the main chronic heart diseases (CHF, IHD, AF); excluding patients with respiratory failure requiring invasive mechanical ventilation, up to 20% of whom are expected to be re-hospitalized within the first month after a hospitalized AECOPD; and optimizing diagnosis and treatment at the beginning of the study, the rate of re-hospitalization or death will decrease to a maximum of 15% in patients treated with usual care plus LABD(s) but no ICS, whereas we expect that this number will decrease to 9% (40% reduction) by treating them with LABD(s)+ICS.

This reduction would be considered clinically relevant, a reduction of about 60 cases in the study that would translate to a hypothetical population of 100,000 similar patients in Italy, and a reduction of 6,000 hospitalizations/deaths in 1 year (Vestbo et al 2016(b), Ministero della Salute www.salute.gov.it).

In addition to the above-mentioned advantages, the study will provide a unique learning exercise for the 39 hospital centers planned to participate in the study, enabling them to improve their ability to characterize and treat this difficult population of patients who are often encountered not only in hospital pulmonary units but also in many hospital internal medicine units.

Since this will be a pragmatic real-life study, there are no anticipated additional risks to the standard medical procedures for patients who agree to participate in this study. The choice of the specific LABD(s) and ICS used to treat each patient will be left to the discretion of the clinical investigator, according to the ICS and LABD(s) treatments available in their pharmacy department.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of the study interventions may be found in the study Participant Information Sheet. Information may also be found in the Patient Information Leaflet and Summary of Product Characteristics for the specific licensed products prescribed for the individual participants.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• to demonstrate that in elderly COPD patients with one or more cardiac comorbidities (heart failure, and/or ischemic heart disease, and/or atrial fibrillation) who have been recently hospitalized due to AECOPD, 1-years treatment with LABD+ICS will prolong the time to first re-hospitalization and/or the death for any cause when compared to 1-years treatment with LABD alone	• composite event of the time to first re-hospitalization and/or death (all cause)
Secondary	
• to compare the number of moderate/severe exacerbations of COPD in the two patient groups • to compare the number of re-hospitalizations and deaths (all cause) in the two patient groups • to compare quality of life (QoL) scores measured using the COPD Assessment Test (CAT) and mMRC dyspnoea scale between the two patient groups • to verify if one year of treatment with combination therapy including ICS increases the risk of pneumonia • to compare the number of acute cardiac events in this frail, elderly COPD population • to compare the incidence of deaths due to cardiovascular events • to compare changes in lung function	• number of moderate/severe COPD exacerbations • number of re-hospitalizations and deaths (all cause) • QoL variation measured as change in CAT total score from baseline to end of treatment period. • change in mMRC dyspnea score from baseline to end of treatment period. • number of pneumonia events • number of acute cardiac events • number of cardiovascular deaths • change in FEV1 from baseline to the end of treatment period • change in FVC from baseline to the end of treatment period

4. Study Design

4.1. Overall Design

This will be a phase IV, open label, multicenter, randomized pragmatic study in frail elderly patients with COPD. Participants will be treated with either inhaled LABD alone or LABD combined with inhaled glucocorticosteroids. The choice of the specific LABD and ICS to be used will be left to the discretion of the clinical investigator, according to the treatments available from their pharmacy department.

The center will be considered as a unique stratifying factor, so the study will have a balanced-block center-stratified design.

The main aim of the study is to assess whether, in elderly patients with COPD and one or more cardiac comorbidities (heart failure, and/or ischemic heart disease, and/or atrial fibrillation) recently hospitalized because of an acute exacerbation of COPD, 12 months treatment with LABD(s)+ICS can increase the time to first re-hospitalization (all cause) and/or death for any cause when compared with LABD(s) alone. Patients will be followed-up for 3 months after completion of the 12 month treatment period.

4.2. Scientific Rationale for Study Design

This is a pragmatic, randomized, open study. Pragmatic studies are designed to evaluate the effectiveness of different treatment strategies in real-life clinical practice.

The key aim of this study is to examine the efficacy and safety of currently recommended and prescribed inhalation therapies to elderly, frail and multimorbid COPD patients with a recent hospitalization due to AECOPD. The study involves a group of patients who have never before been selected for a clinical trial and who represent the 5th most common cause of hospitalization and the 3rd most common cause of death in Italy. The main objective is to determine whether a long-term inhalation treatment including LABD(s) and ICS, can reduce re-hospitalizations and/or death in elderly, frail and multimorbid COPD patients with a recent hospitalization due to AECOPD.

The pragmatic study design means that the choice of the particular LABD(s) and ICS to be prescribed for each patient will be left to the discretion of the clinical investigator and all diagnostic procedures and medical treatments will be performed according to best medical practice at the study centre.

The randomized pragmatic design of this study will help to provide information about treatment choices in real clinical practice and the results will help physicians to make informed choices about the most appropriate treatments in frail elderly COPD patients with multiple comorbidities. The study will also provide a unique learning exercise for the study centers, enabling them to improve their ability to characterize and treat this difficult population of patients.

4.3. Justification for Dose

The choice of the specific LABD(s) and ICS used to treat each patient will be left to the discretion of the clinical investigator. All COPD treatments will be administered using licenced dosages.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit (Visit 7).

The end of the study is defined as the date of the last visit of the last participant in the study.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be older than 60 years of age, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Recently (within 6 months) discharged from hospital with a diagnosis of acute exacerbation of COPD (usually coded as DRG 087 or DRG 088).
3. Participants with a clinical diagnosis of COPD (i.e. previous diagnosis of COPD and/or treatment with short acting bronchodilators (SABD), LABD or LABD+ICS
4. Spirometry confirmed diagnosis of COPD, post-bronchodilator (30 minutes after 400 µg salbutamol) FEV1/FVC ratio <0.7. The diagnostic spirometry test can have been performed up to three years prior to randomisation, or if never performed before, should be performed not earlier than 4 weeks since last exacerbation
5. Smokers or ex-smokers with a smoking history of >10 pack years (a pack year is defined as 20 cigarettes smoked every day for a year)
6. Clinical diagnosis documented in the patient's medical records of one or more major chronic cardiac disease (heart failure, ischaemic heart disease or atrial fibrillation).
7. Currently receiving at least one of the specified treatments (either alone or in combination, see Appendix 10.5) for heart failure, ischemic heart disease or atrial fibrillation.
8. Participant must be willing and able to perform pulmonary function tests

Sex

9. Male or female. Contraception is not considered necessary in this cohort of elderly (> 60 years) patients receiving treatment with commercially available licensed products.

Informed Consent

10. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Patients with a primary discharge diagnosis of DRG 087 or DRG 088 but clearly judged by the clinical investigator to be due to other causes, i.e. patients presenting to the hospital with symptoms of AECOPD but due mainly to other conditions (pulmonary embolism, pneumonia, pneumothorax, anaemia, acute kidney failure, decompensated heart failure, acute ischemic heart disease, new onset atrial fibrillation, stroke, etc.)
2. Patients who required invasive mechanical ventilation during hospitalization
3. Patients with Asthma as primary and principal diagnosis
4. Patients with severe cardiovascular (CV) disease who in the opinion of the investigator are unlikely to survive the 15 month study period
5. Patients considered unable to comply with the study procedures and follow-up in the opinion of the investigator (eg, evidence of alcohol or drug abuse, psychiatric disorder, physical disability, social or geographical obstacles)
6. Patients in whom spirometry is contraindicated (eg, haemoptysis, detached retina, active tuberculosis, last trimester of pregnancy)
7. Patients with other mechanical or overt causes of respiratory symptoms, particularly dyspnoea (such as pneumothorax, chest wall trauma, lung fibrosis, lung cancer, anaemia, severe obesity (BMI >40) or cachexia (BMI <18))
8. Patients with any major disease which in the opinion of the investigator would prevent study participation, such as dementia, end-stage disease, cachexia, chronically bedridden patient and life expectancy <15 months.

Prior/Concurrent Clinical Study Experience

9. Participation in any other interventional study within the last 3 months or concurrent participation in an observational clinical study

5.3. Lifestyle Considerations

No lifestyle restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened at a later date.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

In this study patients will be randomised to receive one of the following two treatment regimens for up to 12 months:

1) Usual and optimized treatment for concomitant cardiovascular (CV) diseases plus inhaled long acting bronchodilator(s) (LABD(s))

2) Usual and optimized treatment for concomitant CV diseases plus inhaled long acing bronchodilator(s) and inhaled glucocorticosteroids (ICS).

The choice of the specific LABD(s) and/or ICS for each patient will be left to the discretion of the clinical investigator. All treatments will be administered at licensed dosages. During the study, the doses of all medications may be adjusted by the investigator according to licensed dosages. Both study groups will receive prescriptions for study medication, which will be collected by the patients from their local pharmacy or hospital pharmacy department. Prescription data will be captured on the electronic case report form (eCRF).

6.2. Preparation/Handling/Storage/Accountability

Participants enrolled in the study will receive medication dispensed from the local pharmacy or hospital pharmacy department in the usual way, there are no additional preparation, handling, or storage requirements.

Participants will be requested to bring any unused medication and the used empty device inhalers when they attend for their next visit and the investigator will make an assessment of the participant's compliance with treatment from the quantity of medication returned and by directly asking the participant about their compliance with the prescribed COPD treatment.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to randomized study intervention using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and instructions for the IWRS will be provided to each site.

The center will be considered as a unique stratifying factor, so the randomization will follow a balanced-block center-stratified design.

Study intervention will be dispensed at the study visits summarized in the SoA.

This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an IWRS. The site will contact the IWRS prior to the start of study intervention

administration for each participant. The site will record the intervention assignment on the applicable case report form.

Potential bias will be reduced by using central randomization.

Since this is an open label study, no unblinding procedures are foreseen.

6.4. Study Intervention Compliance

Participants will be instructed in the correct method of using the inhaler device(s) at the randomization visit (Visit 2) and their technique will be checked at each follow-up visit to ensure that they are using the device(s) correctly.

Participants will be requested to bring their medication when they attend for their next visit and the investigator will make an assessment of the participant's compliance with their treatment from the quantity of medication returned, including the empty drug device inhalers and by directly asking the participant about their compliance with their COPD treatment. The investigator will then provide a response to the following question in the eCRF: "Has the subject been compliant with the study medication up to this visit?"

6.5. Concomitant Therapy

Additional therapeutic or diagnostic procedures (i.e. use of concomitant medication) will be performed according to local guidelines (PDTA).

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the eCRF at each visit. Information recorded will include:

- Name of medication
- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Treatment with ICS in the only LABDs group will be permitted if, on clinical Investigators judgement, it would be necessary for patient temporary conditions for at maximum 15 days in case of patient treated at home or for 15 days (at maximum) after hospital discharge in case of hospitalised patient. If the ICS treatment will surpass these periods, the patient will be considered being switched to the LABD + ICS group and considered as protocol violator.

6.5.1. Rescue Medicine

The study site can prescribe inhaled short acting beta agonists (SABAs) as rescue medication to be taken on an as required (prn) basis. Rescue medications that may be used include:

1. salbutamol
2. terbutaline

Use of rescue medication is forbidden 6 hours before visits when lung function is assessed; if already taken, spirometry can be postponed to 6 hours after last inhalation

6.6. Dose Modification

During the study, the doses of all medications can be adjusted by the investigator according to licensed dosages, providing they remain in the correct treatment arm (see also paragraph 6.5).

6.7. Intervention after the End of the Study

This is a pragmatic study, so participants will be treated according to consolidated standards of care. On completion of the randomized treatment period, patients will not be withdrawn from the treatment but will continue to be treated according to accepted standards of care based on their clinical (respiratory and non-respiratory) condition and lung function. Patients will continue with their treatment.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Participants who are hospitalized during the study period will be allowed to continue in the study until the end at the discretion of the principal investigator and/or the participant. The investigator/ participant can decide to discontinue the study drug for safety or efficacy reasons.

Albeit we will invite patients and doctors to stick to the initial treatment unless required by changed medical condition, the specific COPD treatment regimen (LABD(s) without ICS or LABD(s) + ICS) can be changed at any point during the study. Treatment with ICS in the only LABDs group will be permitted if, on clinical Investigators judgement, it would be necessary for patient temporary conditions for at maximum 15 days in case of patient treated at home or for 15 days (at maximum) after hospital discharge in case of hospitalised patient. If the ICS treatment will surpass these periods, the patient will be considered being switched to the LABD + ICS group and considered as protocol violator.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local

equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness, to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (such as spirometry, ECG and chest x-ray) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.

Identification of suitable participants

In order to identify suitable participants, investigators at each centre will screen the medical records of all patients hospitalized in their department during the 6 month period before the beginning of the study, who were discharged with a diagnosis of pulmonary oedema/respiratory failure (usually, but not limited to DRG 087 or DRG 088).

Potential participants identified through this search of the medical records will be contacted by the research staff in person or over the phone to ascertain if they are eligible and whether they are interested in participating in the study. If the potential participant is eligible and willing to take part, the investigator or the research staff member will provide a copy of the informed consent form (ICF) for the potential participant to review or will proceed to schedule a time for the participant to come to the clinic to review the informed consent and for the screening visit (Visit 1).

Visit 1: Screening

Eligibility to participate will be assessed from the study inclusion and exclusion criteria.

Eligible participants will be asked to read the Participant Information Sheet and ICF. The participant will be given time to ask questions. Signed informed consent must be obtained from each participant before any study specific procedures are initiated. A copy of the signed consent form and the Participant Information Sheet will be given to each participant to keep.

Participants will be asked to complete both the CAT and mMRC dyspnoea scale questionnaires.

The participant's demography and medical history (including drug, alcohol, tobacco, and caffeine usage) will be recorded.

A physical examination including height and weight will be performed.

Past and current medical conditions, including the participant's history of COPD and the presence of concomitant cardiovascular diseases (in particular HF, IHD and AF) and all related treatment

will be recorded. To be eligible for recruitment into the study the participant must be receiving at least one of the CV treatments specified in Appendix 10.5.

Information about any moderate/severe exacerbations of COPD in the previous year, in addition to the index severe exacerbation, should also be recorded on the eCRF. This information should be assessed from the participant's clinical records and prescription history.

A blood sample will be taken for measurement of baseline laboratory parameters as described in Appendix 2.

A medical examination, including measurement of vital signs (blood pressure and heart rate), will be performed. A 12-lead ECG will also be performed unless a previous ECG recording (taken within the previous 3 months) is available and the participant is also considered to be in a stable condition.

If available, a chest x-ray taken within the last year when the participant was in a stable condition (and at least 4 weeks before the current acute COPD exacerbation) will be used for the screening assessment. In case of no x-ray available, it will be a discretionary choice of each centre to perform a chest x-ray at the screening visit (the chest x-ray must be performed at least 4 weeks after the most recent acute exacerbation of COPD).

Concomitant medications will be reviewed and updated if necessary (at the discretion of the investigator). Doses of all COPD medications can be adjusted by the clinical investigator according to licenced dosages for each inhaled drug, at any time during the study.

Visit 2: Randomization

The randomisation visit can be completed on the same day as the screening visit (in which case tests do not need to be repeated) or up to 10 days afterwards.

Vital signs, including blood pressure and heart rate, will be measured.

If the randomisation visit is completed on a different day to the screening visit the patient's eligibility to participate will be reassessed again prior to randomization, vital signs will be recorded and concomitant medications will be reviewed again. Participants will be asked to complete the CAT and mMRC questionnaires.

All participants will undergo a spirometry test at the randomization visit, this will be the baseline value.

The diagnostic spirometry test (to confirm the presence of COPD and eligibility to enter the study) can have been performed up to three years prior to randomization. For participants who have not had a diagnostic spirometry test within the last 3 years, the spirometry test performed at the randomization visit will also be the diagnostic test. The diagnostic spirometry test must be performed at least 4 weeks after discharge from hospital following hospitalization for an acute moderate to severe exacerbation of COPD.

Spirometry will be performed in accordance with American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines (Miller et al 2005). The spirometry test will be performed before and 30 minutes after bronchodilation (4 inhalations of 100 µg salbutamol). The key

objective diagnostic criterion for COPD is a FEV1/FVC ratio <0.7 after bronchodilation. If this criterion is not met the patient cannot be recruited into the study.

The participant's medical history including details of COPD and CV diseases will be reviewed and updated as necessary.

Participants will be questioned about the occurrence of any pre-treatment adverse events or serious adverse events and details will be recorded on the eCRF.

The participant will be randomized to receive the study treatment for a period of 12 months. Participants in both study intervention groups will receive prescriptions for study medication, which will be collected from the local pharmacy or hospital pharmacy department. Prescription data will be captured on the eCRF. Participants will be instructed in the correct method of using the inhaler device(s).

The participant will be given a study participation card which will include details about the study and emergency contact information for the investigational site. Participants will be instructed to contact the centre in case of worsening of the clinical conditions, particularly for acute exacerbations of respiratory symptoms.

Concomitant medications will be reviewed. Doses of all COPD medications can be adjusted by the clinical investigator according to licenced dosages for COPD for each inhaled drug, at any time during the study.

Information on anti-influenza and anti-pneumococci vaccine will be recorded.

Participants will be contacted by telephone each month, by the clinical investigator or by a research staff member, to check compliance with the study procedures and treatment (including any anti-influenza and anti-pneumococci vaccinations). Information about any hospitalizations or any unexpected medical events, particularly moderate exacerbations treated with antibiotics and/or steroids will be collected.

Visit 3: Follow-up after 3 months of treatment

Participants will be asked to complete the CAT and mMRC questionnaires.

Vital signs, including blood pressure and heart rate, will be measured.

Medical history and history of COPD and CV disease will be reviewed and updated as necessary.

Participants will be asked to bring back all the unused medication and the empty drug devices and they will also be asked about their compliance with the study procedures and treatment. Inhaler use and technique will be checked to ensure that the participant is using the device(s) correctly.

Information about any hospitalizations or any unexpected medical events, particularly moderate exacerbations treated with antibiotics and/or steroids will be collected. Information will be obtained by reviewing the patient's medical records and prescribed medication and also from direct questioning of the participant. Participants will also be contacted by telephone each month between the study visits (by the clinical investigator or by a research staff member) to assess this information.

The participant's ongoing treatments (concomitant medications, including any anti-influenza and anti-pneumococci vaccinations) will be reviewed and updated as necessary both for COPD and CV comorbidities, particularly HF, IHD and/or AF. Details of all concomitant medications will be recorded. Doses of all COPD medications can be adjusted by the clinical investigator according to licenced dosages for COPD for each inhaled drug, at any time during the study.

Participants will be questioned about the occurrence of any adverse events and details will be recorded on the eCRF.

Prescriptions for further supplies of the study medication, for collection from the local pharmacy or hospital pharmacy department, will be issued. Prescription data will be captured on the eCRF.

Visit 4: Follow-up after 6 months of treatment

Participants will be asked to complete the CAT and mMRC questionnaires.

Vital signs, including blood pressure and heart rate, will be measured.

Medical history and history of COPD and CV disease will be reviewed and updated as necessary.

Participants will be asked to bring back all the unused medication and the empty drug devices and they will also be asked about their compliance with the study procedures and treatment. Inhaler use and technique will be checked to ensure that the participant is using the device(s) correctly.

Information about any hospitalizations or any unexpected medical events, particularly moderate exacerbations treated with antibiotics and/or steroids will be collected. Information will be obtained by reviewing the patient's medical records and prescribed medication and also from direct questioning of the participant. Participants will also be contacted by telephone each month between the study visits (by the clinical investigator or by a research staff member) to assess this information.

The participant's ongoing treatments (concomitant medications including any anti-influenza and anti-pneumococci vaccinations) will be reviewed and updated as necessary both for COPD and CV comorbidities, particularly HF, IHD and/or AF. Details of all concomitant medications will be recorded. Doses of all COPD medications can be adjusted by the clinical investigator according to licenced dosages for COPD for each inhaled drug, at any time during the study.

Participants will be questioned about the occurrence of any adverse events and details will be recorded on the eCRF.

Prescriptions for further supplies of the study medication, for collection from the local pharmacy or hospital pharmacy department, will be issued. Prescription data will be captured on the eCRF.

Visit 5: Follow-up after 9 months of treatment

Participants will be asked to complete the CAT and mMRC questionnaires.

Vital signs, including blood pressure and heart rate, will be measured.

Medical history and history of COPD and CV disease will be reviewed and updated as necessary.

Participants will be asked to bring back all the unused medication and the empty drug devices and they will also be asked about their compliance with the study procedures and treatment. Inhaler use and technique will be checked to ensure that the participant is using the device(s) correctly.

Information about any hospitalizations or any unexpected medical events, particularly moderate exacerbations treated with antibiotics and/or steroids will be collected. Information will be obtained by reviewing the patient's medical records and prescribed medication and also from direct questioning of the participant. Participants will also be contacted by telephone each month between the study visits (by the clinical investigator or by a research staff member) to assess this information.

The participant's ongoing treatments (concomitant medications including any anti-influenza and anti-pneumococci vaccinations) will be reviewed and updated as necessary both for COPD and CV comorbidities, particularly HF, IHD and/or AF. Details of all concomitant medications will be recorded. Doses of all COPD medications can be adjusted by the clinical investigator according to licenced dosages for COPD for each inhaled drug, at any time during the study.

Participants will be questioned about the occurrence of any adverse events and details will be recorded on the eCRF.

Prescriptions for further supplies of the study medication, for collection from the local pharmacy or hospital pharmacy department, will be issued. Prescription data will be captured on the eCRF.

Visit 6: End of Study after 12 months of treatment or early withdrawal

Participants will be asked to complete the CAT and mMRC questionnaires.

Spirometry will be performed in accordance with ATS and ERS guidelines (Miller et al 2005). The spirometry test will be performed before and 30 minutes after bronchodilation (4 inhalations of 100 µg salbutamol).

Vital signs, including blood pressure and heart rate, will be measured. A 12-lead ECG will also be performed.

Medical history and history of COPD and CV disease will be reviewed and updated as necessary.

Participants will be asked to bring back all the unused medication and the empty drug devices and they will also be asked about their compliance with the study procedures and treatment.

Information about any hospitalizations or any unexpected medical events, particularly moderate exacerbations treated with antibiotics and/or steroids will be collected. Information will be obtained by reviewing the patient's medical records and prescribed medication and also from direct questioning of the participant.

Participants will be questioned about the occurrence of any adverse events and details will be recorded on the eCRF.

For participants who are withdrawn before the end of the study the reason for early withdrawal will be recorded on the eCRF.

Participants who complete the 12 month randomized treatment period will continue to be prescribed the most appropriate treatment for their condition at the discretion of the investigator. Doses of all COPD medications can be adjusted by the clinical investigator according to licenced dosages for COPD for each inhaled drug, at any time during the study.

Visit 7: Follow-up 3 months after End of Study

Participants will be asked to complete the CAT and mMRC questionnaires.

Medical history and history of COPD and CV disease will be reviewed and updated as necessary.

Participants will be asked about treatment. Information about any hospitalizations or any unexpected medical events, particularly moderate exacerbations treated with antibiotics and/or steroids will be collected. Information will be obtained by reviewing the patient's medical records and prescribed medication and also from direct questioning of the participant.

The participant's ongoing treatments (concomitant medications) will be reviewed and updated as necessary both for COPD and CV comorbidities, particularly HF, IHD and/or AF. Details of all concomitant medications will be recorded.

Participants will be questioned about the occurrence of any serious adverse events and details will be recorded on the eCRF.

8.1. Efficacy Assessments

At each follow-up visit, participants will be questioned about any hospitalizations or any unexpected medical events, particularly moderate exacerbations treated with antibiotics and/or steroids and all information will be collected on the eCRF. In addition, the participant's medical records will be reviewed and details of any relevant medical events and any medication prescribed will be recorded in the eCRF. Participants will also be contacted by telephone each month between the study visits (by the clinical investigator or by a research staff member) to assess this information.

An emergency telephone number contact will be set up in each center, in case the patients require hospitalization, particularly for acute exacerbations of respiratory symptoms.

8.1.1. Assessment of re-hospitalizations and deaths (all cause)

Information on deaths (all cause) will be collected from the participant's medical records.

Information on re-hospitalizations (all cause) will be collected by reviewing the participant's medical records, from direct questioning of the participant during the follow-up visits and during monthly phone calls with the participant.

8.1.2. Assessment of moderate/severe COPD exacerbations

Moderate/ severe exacerbations of COPD will be recorded based on the clinical evaluation.

A moderate/ severe COPD exacerbation is defined as a sustained worsening of respiratory symptoms that requires treatment with systemic corticosteroids, antibiotics (moderate) , or hospital admission (or any combination thereof). Events are classified as moderate or severe according to the European Medicines Agency Guideline 2012. Moderate exacerbations are those that require treatment with additional rescue bronchodilators systemic corticosteroids and/or antibiotics. Severe exacerbations are defined as those requiring treatment with additional rescue bronchodilators systemic corticosteroids and/or antibiotics. Hospital admission, or resulting in death.

8.1.3. Assessment of number of pneumonia events

Pneumonia events will be recorded based on the clinical diagnosis and will be confirmed by chest x-ray where possible.

8.1.4. Acute cardiac events

Acute cardiac events will be recorded based on the clinical evaluation.

Acute CV events are defined as an inpatient or emergency department visit with a primary diagnosis of any of the following conditions (International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes are also shown). Coronary heart disease (ICD-9-CM codes 410‑414), cardiac arrhythmia (ICD-9-CM code 427), heart failure (ICD-9-CM code 428), or ischemic stroke (ICD-9-CM codes 433-434) (Wang et al 2018).

8.1.5. Cardiovascular death

Cause of death will be assessed based on the coded cause of death recorded in the participant's records. Cardiovascular death will be defined as death resulting from an acute myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedure, cardiovascular hemorrhage, or death due to other cardiovascular causes. (Hicks et al 2015)

8.1.6. Quality of Life

Participants will be asked to provide responses to the CAT questionnaire and the mMRC dyspnoea scale which will be completed by the investigator.

The CAT questionnaire measures the impact of COPD on the participant's wellbeing and daily life. It includes 8 questions which are rated on a 6-point scale of 0 to 5. Participants are assigned an overall score ranging from 0 to 40. Higher scores indicate a poorer quality of life.

The mMRC dyspnoea scale rates the participant's breathlessness on a scale of 0 to 4, with higher scores indicating worse symptoms.

8.1.7. Spirometry

Participants must have their diagnosis of COPD confirmed by spirometry. The key objective diagnostic criterion for COPD is a FEV1/FVC ratio <0.7 after bronchodilation. If this criterion is not met the patient cannot be recruited into the study.

The diagnostic spirometry test (to confirm the presence of COPD and eligibility to enter the study) can be performed up to three years prior to randomization. For participants who have not had a diagnostic spirometry test within the last 3 years, the spirometry test performed at the randomization visit will be the diagnostic test. The diagnostic spirometry test must be performed *not earlier than 4 weeks since last exacerbation*or discharge from hospital following hospitalization for an acute COPD episode.

All participants will undergo a pre- and post-bronchodilator spirometry test at the randomization visit, this will be the baseline value.

A spirometry test will also be performed at the end of the study (Visit 6).

Spirometry tests will be performed in accordance with ATS and ERS guidelines (Miller et al 2005). The test will be performed before and 30 minutes after bronchodilation (4 inhalations of 100 µg salbutamol).

The following parameters will be recorded:

- Forced vital capacity (FVC)
- Forced expiratory volume in one second (FEV1)
- The FEV1/FVC ratio will be calculated

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A physical examination will be performed at each visit.
- The physical examination will include, as a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Vital signs will be measured at the screening visit, random visit and at each of the follow-up visits during the treatment period (Visits 2-6).
- Blood pressure and pulse measurements can be assessed using a completely automated device or manual techniques
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.3. Electrocardiograms

- A 12-lead electrocardiogram (ECG) will be performed at the screening visit.
- If the patient is in a “stable condition” at the screening visit and has an ECG which was recorded within the last 3 months no further ECG measurements will be recorded.
- For unstable patients and patients with no previous ECG recording available, an ECG test will be performed at the screening visit.
- A 12-lead ECG will also be performed at Visit 6 which will be completed after 12 months treatment or following early withdrawal of the participant from the study.

8.2.4. Chest x-ray

- A chest x-ray taken within the last year when the participant was in a stable condition (and at least 4 weeks before the current acute COPD exacerbation) can be used for the screening assessment.
- Optionally (centre choice) , for all other participants a chest x-ray will be performed at the screening visit (the chest x-ray must be performed at least 4 weeks after the most recent acute exacerbation of COPD).

- In case of suspected pneumonia occurring during the study, the investigator is invited to confirm the diagnosis with a chest x-ray.

8.2.5. Clinical Safety Laboratory Assessments

- Laboratory tests will be performed for screening purposes only.
- All tests will be performed by the local hospital laboratory.
- See Appendix 2 for the list of clinical laboratory tests to be performed.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3 (Appendix 3).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs (serious and non-serious) will be collected and registered by the investigator in the CRF, from the start of study treatment until the last follow up visit at the time points specified in the SoA (Section 1.3). SAEs will be collected starting from Informed Consent signature (see 8.3.2).

Investigators are not obligated to actively seek AEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Monitoring of AEs

Patients will be monitored throughout the study for AEs to the study treatment. AEs will be documented and collected on an on-going basis during the treatment period and the relevant follow up period. The Investigator will instruct the patient how to communicate any AEs occurred in this period. Medical events fulfilling one or more criteria of seriousness and occurring after the informed consent has been signed, must be immediately (within maximum 24 hours) reported to the Sponsor using an SAE form (separate paper forms will be supplied to the investigators), even if the study treatment administration has not been started yet.

Serious adverse events occurring before the initiation of the study treatment, must also be recorded on the “Medical History/Current Medical Conditions” pages of the CRF (but not in the AE page),

The Investigator has to follow all AEs until resolution, stabilization, further investigation results are obtained, or the participant is lost to follow-up.

SAEs still present at the end of the study period and for the subsequent 30 days must be followed until a final outcome (that is any outcome different from “on-going”) is determined.

An AE that is initially reported as non-serious and later on meets the criteria for an SAE must be reported as an SAE as soon as the information regarding the presence of one or more seriousness criteria become known to the investigator.

8.3.3. Clinical Laboratory Abnormalities

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study

will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with a disease reported in the medical history, unless judged by the Investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The Investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.3.4. Recording of AEs and SAEs

During the study, site personnel will evaluate and record any change in the pre-existing condition(s) and/or the occurrence of any AEs.

Subjects will be questioned for the occurrence of any new or worsening sign or symptom at each study visit. The Investigator or designee will enquire about AEs by asking non-leading questions, such as in the following examples:

At the first scheduled AE enquiry on Day 0 (pre-dose) subjects will be asked:

"How are you feeling?"

At subsequent scheduled intervals subjects will be asked:

"Since you were last asked, have you felt unwell or different from usual?"

Out of range laboratory results arising once study treatment has begun, will be reviewed by the Investigator. The Investigator will determine whether the signs and symptoms represent clinically significant changes from the subject's baseline, and if so, they should be recorded as an AE.

The Investigator will evaluate all AEs as to:

- Seriousness: See definition in Appendix 3
- Severity: See definition in Appendix 3.
- Causal Relationship to study drug: See definition in Appendix 3.
- Outcome.

All AEs, serious and non-serious, must be recorded in the AE section of the CRF. SAEs must also be reported to the Sponsor in 24 hours though the SAE form.

After the end of study period, including follow-ups, only if a SAE is believed to be related to the study drug administration should it be reported to the Sponsor.

Adverse Events causing treatment discontinuation

If a subject is withdrawn from the study as a consequence of an AE, this must be recorded and reasoned in the CRF, and the subject must be followed up until the AE outcome resolution.

8.3.5. Prompt Reporting of SAEs to Sponsor

Once an Investigator becomes aware that an SAE has occurred in a study subject, he/she will immediately (within 24 hours from being aware of an SAE) notify the Sponsor:

-- by phone (TEL: 0532/236835)

- or by e-mail (a.marra@ospfe.it) to notify and transmit SAEs.

In case of Serious Adverse Events, the Investigator will transmit electronically if applicable or fill in an SAE form and will transmit it within 24 hours since becoming aware of the event, to Sponsor.

The SAE form must be completed as thoroughly as possible with all details available at that time point and signed by the Investigator (or appropriately qualified designee).

If the Investigator does not have all information regarding an SAE he/she will not wait to receive additional information before notifying the Sponsor of the event and completing the form. The form will be updated when additional information is received (follow up reports).

The Investigator will always provide an assessment of causality at the time of the initial report.

If follow up data obtained after having already reported an SAE indicates that the assessment of causality is incorrect, then a follow up SAE form will be filled in with the amended information, signed and dated, and resubmitted to the Sponsor.

In accordance with local Independent Ethics Committee (IEC) requirements, the Investigator must also notify IEC of any SAEs according the guidelines of the Ethics Committee.

The Investigator, and others responsible for subject care, should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors. This may include seeking further opinion from a specialist in the field of the AE. The Sponsor may also request extra tests. If a subject dies, any post-mortem findings, including histopathology will be provided to the Sponsor if available. No medical help, diagnosis, or advice should be withheld from the subject due to an inability to contact the Sponsor

8.3.6. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts, in order to collect all relevant information. Particularly, all SAEs will be followed until resolution, stabilization, further investigation results are obtained, or the participant is lost to follow-up. Further information on follow-up procedures is given in Appendix 3.

8.3.7. Expeditable Events

Expeditable events are those AEs that are causally related to the study product, and that are both serious and unexpected (Serious Unexpected Suspected Adverse Reaction- **SUSAR**), see Appendix 3.

8.3.8. Pregnancy

Any pregnancy where the fetus may have been exposed to study drug, should be notified by the Investigator to the Sponsor, by filling in the “Pregnancy Form” and sending it, within 24 hours of its knowledge, to the Sponsor:

- by e-mail (a.marra@ospfe.it)

• Outcome of the pregnancy (normal or abnormal) must be followed up and recorded.

• Abnormal pregnancy outcome must be notified on an expedited basis (i.e. within 24 hours of the Investigator becoming aware of the abnormal pregnancy outcome) using the SAE form. This refers especially to congenital anomalies in the fetus/child, fetal death and spontaneous abortion, and adverse reactions in the neonate that are classified as serious.

• Pregnancy will be recorded as an AE in all cases. It will be qualified as an SAE only if it fulfils SAE criteria (see above).

8.3.9. Disease Related Events and/or Disease Related Outcomes not Qualifying as AEs or SAEs

Not applicable

8.4. Treatment of Overdose

The investigator should consult the product label of the licensed study medication for advice on treatment of overdose.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The superiority of the LABD(s)+ICS group vs. LABD(s) group in terms of time to first re-hospitalization and/or death will be tested. The following hypotheses scheme will be considered:

H_0: there is no difference in the time to first re-hospitalization and/or death between the two treatment groups.

H_1: there is a difference in the time to first re-hospitalization and/or death between the two treatment groups

9.2. Sample Size Determination

The sample size calculation is based on the superiority criteria of the LABD+ICS group vs. LABD alone group in terms of re-hospitalization and/or death. With 464 patients in each group, the percentage of patients experiencing the composite event (re-hospitalization and/or death) is expected to be 9% in the LABD+ICS group and 15% in the LABD alone group. A log-rank test (two-sided 5% significance level) will have 80% power to detect a difference between treatment groups in terms of time to first re-hospitalization and/or death (primary efficacy endpoint). Adjusting for an expected 10% dropout rate, a total of 516 patients per group will need to be randomized.

9.3. Populations for Analyses

The following populations will be considered for the analysis:

- **Randomized population**: all randomized patients.
- **Safety population**: all randomized patients who receive at least one administration of the study treatment in a given treatment period.
- **Intention-to-Treat population (ITT)**: all randomized patients from the safety population with at least one available post-baseline efficacy evaluation during the treatment period.
- **Per-protocol population (PP)**: all randomized patients from the ITT population without any major protocol deviations (e.g., wrong inclusions, forbidden concomitant medications, etc.). The exact definition of major protocol deviations will be discussed with the clinical team case by case during the review of the data and will be described in the Data Review Report.

The statistical analysis will be performed after database lock.

The primary efficacy variable will be analysed both in the ITT and in the PP populations. As this is a superiority study, the primary analysis population will be the ITT. All the other efficacy variables will be analysed in the ITT population only.

Analysis of safety variables will be performed on the safety population.

9.4. Statistical Analyses

All statistical analyses will be undertaken by CROS NT S.r.l. (Verona, Italy) using SAS software, release 9.4 or higher (SAS Institute, Cary, NC, USA).

The following describes the statistical analysis as it is foreseen at the time of planning the trial.

A detailed Statistical Analysis Plan (SAP) will be described in a separate document to be completed after the protocol is finalised and before database lock.

9.4.1. Descriptive Statistics

Descriptive statistics will be provided in summary tables by treatment group according to the type of variable summarized:

- Quantitative variables will be summarized using n (sample size), arithmetic mean, standard deviation (SD), median, minimum and maximum;
- Categorical variables will be summarized using frequency count and percent distribution.

9.4.2. Participant Accountability

Disposition of patients, patient status and patients excluded from analysis sets will be summarized by treatment group.

9.4.3. Description of Baseline Characteristics

The baseline demographic characteristics will be summarized by treatment group by means of descriptive statistics for the ITT population.

The following parameters will be presented:

- demographics;
- medical history (including CV diseases);
- previous and concomitant medications (including CV medications);
- physical examination;
- vital signs;
- efficacy parameters.

9.4.4. Missing Data

The number of patients with missing data will be presented under the "Missing" category, if present. Missing values will be included in the denominator count when computing percentages. When continuous data are being summarized, only the non-missing values will be evaluated for computing summary statistics. Further details on dealing with missing data, along with the handling of possible outliers, will be described in the SAP.

Other critical missing data will be discussed prior to database lock, if any. Decisions will be taken during the data review of the data and will be fully documented in the Data Review Report

9.4.5. Principles of Statistical Analysis

For all inferential analyses, p-values will be rounded to three decimal places. Statistical significance will be declared if the rounded p-value is ≤ 0.05. No adjustment for multiple testing is planned.

9.4.6. Efficacy Analyses

Primary Efficacy Variable

The primary efficacy variable is the time from baseline (Visit 2) to first re-hospitalization and/or death. If the patient discontinues/completes the treatment period and no re-hospitalization and/or death is observed, then the time to first re-hospitalization and/or death is treated as right censored at the end of treatment period (i.e. date of Visit 6) or at the time of the withdrawal during the treatment period (i.e. the date of discontinuation).

The primary efficacy variable will be analyzed using the Kaplan-Meier estimator. Comparison between treatment groups will be performed using the log-rank test stratified by center. A Kaplan-Meier plot for time to first re-hospitalization and/or death will also be presented by treatment group.

The LABD(s)+ICS group will be declared to prolong time to first re-hospitalization and/or death, compared to the LABD(s) group, if the difference between the two treatments is significantly in favour of LABD(s)+ICS (i.e. the p-value from the log-rank test is ≤ 0.050).

In addition, a Cox proportional hazards regression analysis will be performed as well, presenting the treatment effect as a hazard ratio with the associated 95% confidence interval with center, age and treatment group as factors. The inclusion of any other potential confounding factors in the model will be evaluated during the Data Review, verifying the homogeneity of factors distributions among treatment groups.

A sensitivity analysis will be also carried out excluding efficacy data (i.e. hospitalization and death) collected after the crossover occurrence (i.e. patients that switch from one treatment group to the other adding or stopping ICS). The crossover patients that do not experience any hospitalization or death will be considered as censored at the time of cross-over start. Kaplan-Meier, log-rank test and Cox model will be repeated on this modified analysis dataset.

Secondary Efficacy Variables

The number of re-hospitalizations and deaths (all cause) will be analysed using a Poisson regression model. The model will include the number of events as dependent variable and treatment group, age and center as factors. Log-time on study will be used as an offset. The over dispersion parameter based on the deviance will be considered in order to account for between-patient variability in the events rate and standard errors will be estimated allowing for extra-Poisson variation.

All the other counting variables will be analysed with the same model.

All the continuous variables will be summarized at each visit by means of descriptive statistics. Mean change from baseline value and the 95% confidence intervals will be calculated. P-values of paired t-tests will be provided for mean changes from baseline.

Change in continuous variables will also be analysed using an ANCOVA model, with treatment group, centre and age as factors and baseline as covariate.

9.4.7. Safety Analyses

The number and the percentage of patients experiencing adverse events, adverse drug reactions, serious adverse events, severe adverse events and adverse events leading to study withdrawal will

be summarized by treatment group. Adverse events will also be summarized by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and comparison between treatments will be performed using a Chi-square test or Fisher's exact test, as appropriate.

Any other safety variables to be summarized by treatment group using descriptive statistics will be detailed in the SAP.

9.4.8. Other Analyses

A subgroup analysis will be performed by considering the patients randomized with Triple Therapy (LAMA+LABA+ICS) or LAMA+LABA. The analysis of primary endpoint and the number of re-hospitalizations and deaths (all cause) secondary analysis will be performed on this subset of patients.

Other subgroup analyses may be performed for efficacy and safety endpoints based on baseline disease characteristics which could provide evidence to assess effectiveness, adherence levels and the true value of adding ICS treatment to LABD.

9.5. Interim Analyses

Not foreseen.

9.5.1. Data Monitoring Committee (DMC)

The Data Monitoring Committee will periodically review and evaluate the accumulated study data for safety, study conduct and progress, scientific validity and integrity.

The DMC will monitor the progress of the study, enrollment, study performance in terms of data management metrics and will undertake a review of the safety data including adverse events.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health

Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

The study will be coordinated by a Scientific Steering Committee composed of highly qualified and experienced clinical investigators.

The study will be monitored by a Data Monitoring Committee, which will monitor the following:

1. Participant safety, burden, confidentiality
2. Study performance and all aspects of quality control
3. Study productivity

The DMC will monitor the progress of the study, enrolment, study performance in terms of data management metrics and review of safety data like adverse events.

The Committees will have regular teleconferences and will meet at least twice a year in person with the Principal Investigators.

10.1.6. Dissemination of Clinical Study Data

A clinical study report describing the results of this study will be written by CROS NT S.r.l. (Verona, Italy). The study report will be written within one year after the end of the study.

The investigators plan to write a paper describing the results of this study for publication in an appropriate peer reviewed medical journal.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 7 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF 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.

10.1.9. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The following blood tests will be performed for screening purposes only at the local hospital laboratory.

- full blood count (to include hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell (RBC) count, white blood cell (WBC) count and differential (platelets, neutrophils, lymphocytes, monocytes, eosinophils and basophils)
- fibrinogen
- NT-BNP or B-type natriuretic peptide (BNP)
- lipid profile (to include total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides)
- creatinine
- sodium
- potassium
- calcium
- glucose
- C- reactive protein (CRP)
- alanine amino transferase (ALT)
- gamma glutamyl transferase

*

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Adverse event (AE) definition

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Serious adverse event (SAE) definition

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Important medical event

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

SAE not requiring immediate reporting

The following reasons for hospitalisations will not to be managed as SAEs but just recorded in the CRF:

- Hospitalization planned before entry into the clinical study which is part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition;
- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
- Hospitalization for treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen.

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor's representative in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor's representative In this case, all participant identifiers, with

the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor's representative.

- The investigator will attempt to establish a **diagnosis** of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

  The term "severe" is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator must assess the relationship between study treatment and each AE/SAE. He/she will use the following definitions for any adverse event being collected in the study and for all serious adverse events, to assess the relationship of the adverse event to the use of study treatment:

- "Reasonable possibility" that the AE is related to the study drug. For example, when an adverse event has a strong temporal relationship to study drug or recurs on re-challenge and another etiology is unlikely or significantly less likely or a more likely alternative etiology does not exists.
- "Not reasonable possibility" that the AE is related to the study drug. For example, when an adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology), or an adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.

The investigator will use clinical judgment to determine the relationship.

The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor's representative. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor's representative.**

The investigator may change his/her opinion of causality in light of follow-up information and in this case will send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Assessment of Expectedness

The expectedness is assessed by the Sponsor versus the Reference Safety Information identified for the study treatment (IB or SmPC).

An adverse event should be assessed as "expected" from the perspective of events previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product.

An "unexpected" adverse event is an AE, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's brochure or summary of product characteristics).

Follow-up of AEs and SAEs

- The investigator must perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the

sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide upon request the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE form to the sponsor within 24 hours of being aware of the new information.

SAE Reporting by the investigator to the sponsors via Paper SAE form

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor.
- Notification by email is also acceptable.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in section 8.3.

SUSAR reporting by the sponsor

SUSAR Reporting to Competent Authorities/Ethic Committees

SUSARs are subject to expedited electronic reporting by the Sponsor to EudraVigilance Clinical Trial Module (EVCTM) and to the concerned Ethics Committees. SUSARs must be reported, within the timelines reported below, by the Sponsor or a suitably qualified designee.

The **clock for expedited initial reporting (day 0)** starts as soon as the information containing the minimum reporting criteria has been received by the sponsor.

The minimum information includes, at least, all of the following:

— valid EudraCT number (where applicable),

— sponsor study number,

— one identifiable coded subject ,

— one identifiable reporter,

— one SUSAR,

— one suspect IMP (including active substance name- code),

— a causality assessment.

Reporting Timelines:

Adverse event type	**EU Regulatory Deadlines (within)**
Related, unexpected serious reports of death or life-threatening	**7 calendar days** from day 0 for initial safety reports **15 calendar days** from the day 0 for follow-up safety reports
Any other serious related unexpected reports	**15 calendar days** from day 0

SUSAR reporting to Investigators

Periodically, the Sponsor will distribute to all Investigators involved in the study, line listings and or individual safety reports in order to inform all of them about the suspected unexpected serious adverse reactions (SUSARs) which have occurred in the study.

10.4. Appendix 4: Abbreviations

AECOPD	acute exacerbation of chronic obstructive pulmonary disease
AE	adverse event
AF	atrial fibrillation
ATS	American Thoracic Society (ATS)
CAT	COPD Assessment Test
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CRP	C reactive proteine
CV	cardiovascular
DRG	diagnosis related group
eCRF	electronic case report form
ERS	European Respiratory Society
ESC	European Society of Cardiology
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GCP	Good Clinical Practice
HDL	high density lipoprotein
HF	heart failure
HIPPA	Health Insurance Portability and Accountability Act
IB	investigators brochure
ICF	informed consent form
ICH	International Conference on Harmonization
ICS	inhaled glucocorticosteroids
IEC	Independent Ethics Committee
IHD	ischaemic heart disease
IRB	Institutional Review Board
LABA	long-acting beta2-agonist

LABD	long acting bronchodilators
LAMA	long acting antimuscarinic
LDL	low density lipoprotein
MCV	mean corpuscular volume
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
mMRC	modified Medical Research Council
PDTA	Percorsi Diagnostico Terapeutici Assistenziali (best medical practice)
PT	preferred term
QoL	quality of life
RBC	red blood cell
SABA	short acting beta agonist
SABD	short acting bronchodilator
SAE	serious adverse event
SoA	schedule of activities
SOC	system order class
RCT	Randomised controlled trial
WBC	white blood cell
WHO	World Health Organisation

10.5. Appendix 5: List of Cardiovascular Drugs

To be eligible for recruitment into the study the participant must be receiving at least one of the CV treatments listed below given alone or in combination.

Treatments for atrial fibrillation

Calcium channel blockers (such as diltiazem, verapamil)

Beta-blockers

Cardiac glycosides

Anti-arrhythmics (such as amiodarone, dronedarone, sotalol, dofetilide)

Anti-arrhythmics (such as flecainide, propafenone)

Anti-arrhythmics (such as quinidine, disopyramide)

Drugs for pharmacological cardioversion (such as flecainide, amiodarone or propafenone)

Treatments for heart failure

Angiotensin-converting enzyme inhibitors (ACE-inhibitors)

Angiotensin receptor blockers (ARBs)

Angiotensin receptor-nephrilysin inhibitors (ARNIs) (such as valsartan/sacubitril)

Ivabradine

Beta blockers

Aldosterone antagonists

Isosorbide dinitrate or hydralazine

Nitrates

Phosphodiesterase-3 inhibitors (such as milrinone, inamrinone (formerly amrinone), cilostazol)

Diuretics (thiazide, loop, or natriuretic peptides)

Cardio-stimulatory or inotropic drugs which stimulate contractility (such as digitalis, beta-agonists, sympathomimetic drugs)

Treatments for ischemic heart disease

Alpha-adrenoceptor antagonists (alpha-blockers) (such as prazosin, terazosin, etc)

Angiotensin converting enzyme (ACE) inhibitors (such as benazepril; captopril; enalapril; fosinopril; lisinopril; moexipril; quinapril; ramipril, etc)

Angiotensin receptor blockers (ARBs) (such as candesartan, eprosartan, irbesartan, losartan; olmesartan, telmisartan, azilsartan, valsartan)

Beta-2-adrenoceptor agonists (β2-agonists)

Calcium-channel blockers (CCBs)

Centrally acting sympatholytics (such as clonidine, α-methyldopa)

Direct acting vasodilators (such as hydralazine)

Endothelin receptor antagonists (such as bosentan)

Nitrodilators (such as isosorbide dinitrate, isosorbide mononitrate, nitroglycerine, etc)

Phosphodiesterase inhibitors

Potassium-channel openers (such as minoxidil)

Renin inhibitors (such as aliskiren)

11. References

Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med. 1987 Feb;106(2):196-204.

Calverley et al, Salmeterol and fluticasone propionate and survival in COPD. N Eng J Med 2007; 356(8): 775-89.

European Medicines Agency Guideline EMA/CHMP/483572/2012. Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD) 21 June 2012.

Fried TR et al. Caring for the older person with chronic obstructive pulmonary disease. JAMA 2012; 308(12): 1254.

Gershon A, Croxford R, Calzavara A, To T, Stanbrook MB, Upshur R, Stukel TA. Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. JAMA Intern Med. 2013 Jul 8;173(13):1175-85

Gershon et al. Combination long-acting beta-agonists and inhaled corticosteroids compared with long-acting beta-agonists alone in older adults with COPD. JAMA 2014; 312(11): 1114.

Global initiative for chronic Obstructive Lung Disease (GOLD) 2018, www.goldcopd.org

Gupta et al. The COPD Assessment Test: Can It Discriminate Across COPD Subpopulations? Chest 2016; 150(5): 1069-79.

Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, et al. 2014 ACC/AHA Key data elements and definitions for cardiovascular endpoint events in clinical trials. Circulation 2015;132:302-361

Iannella H et al. Inhaled corticosteroids and the increased risk of pneumonia: what's new? A 2015 updated review. Therapeutic advances in respiratory disease. 2016; 10(3): 235-55.

Lipson et al. Single Inhaler Triple Therapy versus Dual Therapy in COPD: Results of the IMPACT Trial. N Engl J Med 2018 (published online).

Lisspers K, Larsson K, Johansson G, Janson C, Costa-Scharplatz M, Gruenberger JB, Uhde M, Jorgensen L, Gutzwiller FS, Stallberg B.et al, Economic burden of COPD in a Swedish cohort: the ARCTIC study. Int J Chron Obstruct Pulmon Dis 2018; 13:275-285

Macie C, Wooldrage K, Manfreda J, Anthonisen NR. Inhaled corticosteroids and mortality in COPD, Chest 2006;130(3):640-6

Magnussen et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. N Eng J Med 2014; 371(14): 1285.

Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988; 93(3): 580-6.

May SM, Li JT. Burden of COPD: healthcare costs and beyond. Allergy and asthma proceedings. 2015; 36(1): 4.

Miller MR et al. Standardisation of spirometry. Eur Resp J 2005; 26(2):319-38.

Ministero della Salute. www.salute.gov.it/portale/temi/p2_4.jsp?lingua=italiano&tema=Assistenza,%20ospedale%20e%20territorio&area=ricoveriOspedalieri

NICE Guideline. Multimorbidity: clinical assessment and management. [NG56] September 2016. https://www.nice.org.uk/guidance/ng56

Papi et al. Regular versus as-needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial. Lancet Resp Med 2015; 3(2):109-19.

Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, Guasconi A, Montagna I, Vezzoli S, Petruzzelli S, Scuri M, Roche N, Singh D. Extra-fine inhaled triple therapy versus dual bronchodilator therapy in COPD (TRIBUTE): a double-blind, parallel group, randomised controlled trial. The Lancet. Published online 8 February 2018 (https://doi.org/10.1016/S0140-6736(18)30206-X)

Roca et al. Mechanisms of acute exacerbation of respiratory symptoms in COPD. Eur J Clin Invest 2013; 43 (5): 510

Roversi S, Fabbri LM et al. COPD and Cardiac Diseases. An Urgent Need for Integrated Care. Am J Respir Crit Care Med 2016; 194(11): 1319

Serra-Picamal XS, Roman R, Escarrabill J, Garcia-Altes A, Argimon JM, Soler N, Faner R, Martinez Carbonell E, Trilla A, Agusti A.. Hospitalizations due to exacerbations of COPD: A big data perspective. Respir Med. Published online 16 Jan 2018 (http://dx.doi.org/10.1016/j.rmed.2018.01.008)

Shah et al. COPD Readmissions: Addressing COPD in the Era of Value-based Health Care. Chest 2016; 150(4): 916

Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation 2003;107:1514–1519

Sin DD et al. Inhaled corticosteroids and mortality in COPD. Thorax 2005; 60(12): 992

Singh et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting beta2-agonist therapy for COPD (TRILOGY): a double-blind, parallel group, randomised controlled trial. Lancet 2016; 388(10048): 963

Tinetti ME et al. Designing health care for the most common chronic condition--multimorbidity. JAMA 2012; 307(23): 2493

Tokgoz et al. Patient Outcome after COPD Exacerbations Requiring Non-invasive Ventilation during Hospitalization. Archivos de bronconeumologia. 2016; 52(9): 470

Vanfleteren LEGW, Spruit MA, Wouters EFM, Franssen FME. Management of chronic obstructive pulmonary disease beyond the lungs. Lancet Respir Med. 2016 Nov;4(11):911-924

Vestbo et al. Fluticasone furoate and vilanterol and survival in COPD with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. Lancet 2016(a); 387(10030): 1817-26

Vestbo J et al. Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice. N Eng J Med 2016(b); 375(13): 1253-60

Vestbo J, Papi A, et al. Single inhaler extrafine triple therapy versus long acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. Lancet 2017; 389:1919-1929

Wang MT, Liou JT, Lin CW, Tsai CL, Wang YH, Hsu YJ, Lai JH. Association of Cardiovascular Risk with Inhaled Long-Acting Bronchodilators in Patients with Chronic Obstructive Pulmonary Disease: A Nested Case-Control Study. JAMA Intern Med. 2018 Feb 1;178(2):229-238.

Wedzicha JA, Singh R, Mackay AJ. Acute COPD exacerbations. Clin Chest Med. 2014; 35(1): 157

Wedzicha et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Eng J Med 2016; 374(23): 2222.

World Health Organization. Projections of mortality and causes of death, 2015 and 2030. http://www.who.int/healthinfo/global_burden_disease/projections/en/

