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Respiratory Drafting Group

## Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD)

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<sup>1</sup> correction related to a change on p. 4



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## Executive summary

This guideline is a revision of the CPMP Points to Consider on Clinical Investigation of Medicinal Products in the Chronic Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD) (CPMP/EWP562/98). It is intended to update this previous guidance with new scientific knowledge of the disease as stated in new and updated clinical guidelines and to revise the requirements for the clinical investigation of medicinal products for the treatment of COPD accordingly. The requirements for pivotal studies, consideration of the need for reversibility testing of pulmonary function in patients with COPD, primary and secondary efficacy variables in clinical studies and the potential role of biomarkers have been updated.

### 1. Introduction

COPD is a preventable respiratory disorder characterised by airflow limitation, which is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response in the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs it is also associated with significant systemic consequences.

It is estimated that approximately eight percent of the population have COPD and approximately ten percent of those over 40 years of age. However the true prevalence of the disease is likely to be higher than this due to under-diagnosis and diagnosis delayed until the disease becomes clinically apparent and is then moderately advanced. COPD is the fourth leading cause of death in Europe and is expected to rise to third by 2020. Worldwide, cigarette smoking (both current and past smoking) is the most commonly encountered risk factor for COPD.

COPD is characterised by chronic inflammation associated with remodelling of the airway, lung parenchyma and pulmonary arteries, which in turn, give rise to the pathophysiological findings in COPD – mucus hypersecretion and ciliary dysfunction, airflow limitation and hyperinflation, gas exchange abnormalities, pulmonary hypertension and systemic effects. The chronic airflow limitation seen in COPD is caused by a mixture of small airway disease (chronic obstructive bronchitis) and parenchymal destruction (emphysema), with the relative contribution of each varying from person to person.

COPD is a heterogeneous disease in terms of its clinical presentation, disease severity and rate of disease progression. Some patients have few complaints but an extremely sedentary lifestyle; others describe chronic respiratory symptoms (e.g. dyspnoea on exertion and cough); some patients present with an acute exacerbation (e.g. wheezing, cough and dyspnoea). Intermittent exacerbations of COPD, which represent an exacerbation of the inflammatory response, can be caused by exposure to infection (viral, bacterial) or to environmental pollutants.

Weight loss, nutritional abnormalities, skeletal muscle dysfunction, cardiovascular effects, anaemia, systemic inflammation, mental dysfunction are well-recognised extrapulmonary symptoms and signs of COPD. Patients with COPD are at increased risk of myocardial infarction, angina, respiratory infections, osteoporosis, bone fractures, diabetes, depression, sleep disorders, glaucoma and anaemia.

COPD and its comorbidities cannot be cured and therefore must be treated on a chronic basis. The ultimate goal of treatment in COPD is to improve overall survival. Although much of the damage is irreversible at the time of clinical presentation, early diagnosis and appropriate management can prevent and improve symptoms (particularly dyspnoea), reduce the frequency and severity of exacerbations, improve health status and improve exercise capacity. At present no treatment has been shown to modify the rate of decline in lung function or to improve overall survival apart from smoking cessation.

Since the disease is usually progressive, the overall approach to managing stable COPD involves a stepwise increase in treatment, depending on the severity of the disease. The most important step in treating COPD is to encourage smoking cessation. Pharmacological therapies and non-pharmacological therapies should be added in a stepwise fashion depending on the severity of the disease and the clinical status of the patient. The mainstays of drug therapy for symptomatic relief in stable COPD are bronchodilators (primarily  $\beta_2$  agonists, anticholinergics and less often theophylline) and mucolytics and in more severe cases, long-acting  $\beta_2$  agonists (LABA) or long-acting muscarinic antagonists (LAMA)<sup>2</sup> with or without inhaled corticosteroids (ICS) concomitantly or in combination. Recently, anti-inflammatory drugs with a new mechanism of action e.g. PDE-4 inhibitors, have been shown to have a role in severe COPD. Triple therapy (i.e. LABA + ICS + an anticholinergic) might also be considered for certain patients.

Supplemental therapies, such as oxygen, pulmonary rehabilitation and physiotherapy, immunisations, nutrition and exercise also play an important role in the management of COPD.

## 2. Scope

This document is intended to provide guidance for the clinical evaluation of new medicinal products for the treatment of COPD, new products which may provide symptomatic relief through improvement of airway obstruction, which may modify or prevent exacerbations or which may modify the course of the disease or modify disease progression. However specifically, this guideline will focus on the maintenance treatment of COPD. This guideline will not focus on treatment of exacerbations.

## 3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles (4) and parts I and II of the Annex I to Directive 2001/83/EC as amended. Applicants should also refer to other relevant European and ICH guidelines (in their current version) on the conduct of clinical development, especially those on:

- Dose-Response Information to Support Drug Registration – CPMP/ICH/378/95 (ICH E4);
- Note for Guidance on Studies in Support of Special Populations: Geriatrics (ICH Topic E 7) and the Questions and Answers – EMEA/CHMP/ICH/604661/2009;
- Statistical Principles for Clinical Trials – CPMP/ICH/363/96 (ICH E9);
- Choice of Control Group in Clinical Trials – CPMP/ICH/364/96 (ICH E10);
- Population exposure: The Extent of Population Exposure to Assess Clinical Safety for Drugs – CPMP/ICH/375/95 (ICH E1A);
- Guideline on the investigation of drug interactions – CHMP/EWP/125211/2010
- Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) Including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and For Use in the Treatment of Asthma in Children and Adolescents – CPMP/EWP/4151/00 Rev. 1;
- CPMP Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Asthma – CPMP/EWP/2922/01;

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<sup>2</sup> corr: a reference to LAMA has been included under the Introduction section as an alternative to LABA in combination with ICS for the most severe patients to make it consistent with the rest of the guideline.

- Guideline on Missing Data in Confirmatory Clinical Trials - CPMP/EWP/1776/99 Rev.1-;
- Guideline on Clinical Development of Fixed Combination Medicinal Products - CPMP/EWP/240/05 Rev.1.

This Guideline is intended to assist applicants during the clinical development of medicinal products.

## 4. Main text

### 4.1. Patient characteristics and selection of patients

Diagnosis of COPD should be considered in any patient who has symptoms of cough, sputum production or dyspnoea or a history of exposure to risk factors for the disease, particularly tobacco smoking.

COPD is confirmed when a patient who has persistent or recurrent symptoms that are compatible with COPD (i.e. chronic cough, chronic sputum production, dyspnoea) is found to have airflow obstruction that is not fully reversible (i.e. post-bronchodilator forced expiratory volume in one second to forced vital capacity ratio (FEV<sub>1</sub>/FVC) less than 0.70 (according to The Global Initiative for Chronic Obstructive Lung Disease (GOLD) or below the lower limit of normal (LLN) in patients over 60 years of age (according to ATS/ERS guidelines) and there is no alternative explanation for the symptoms and airflow obstruction. Alternatively, the FEV<sub>1</sub> to FEV<sub>6</sub> ratio below 0.73, or the LLN, can be used for diagnosis. Spirometry should be performed after the administration of an adequate dose of an inhaled bronchodilator in order to minimise variability.

The following key aspects should be considered when selecting the target population:

- Characterisation of the population based on reversibility of chronic airflow limitation.

Generally, patients with other causes of chronic airflow limitation should be excluded from clinical studies in COPD. Chest radiography can be of value in the differential diagnosis in suspected COPD. Patients with asthma or predominantly asthma, cystic fibrosis, bronchiolitis obliterans and fibrosis due to tuberculosis or very rarely  $\alpha$ 1-antitrypsin deficiency should not be recruited to, and should be excluded from, clinical studies in COPD.

Diagnosis should not rely on the presence or absence of reversibility of airflow obstruction. Nevertheless, the study population should be characterised with respect to the presence of airflow reversibility.

Ideally the aim should be to study a homogenous population of patients with COPD and mainly irreversible airway function, which would allow for better characterisation of the effect of the drug. However it is accepted that up to 50% of patients with COPD do have some degree of reversibility of airflow obstruction and therefore some degree of freedom in respect of the inclusion of patients with differing degrees of airway reversibility, and the resultant need for sub-group analyses in respect of these differing degrees of airway reversibility, will be required. Consistency of effect across such sub-groups should be demonstrated.

If patients with reversibility are to be included, consideration should be given to the mechanism of action of the test drug and it must be ensured that the results are not driven by this subset of patients particularly when testing drugs with a bronchodilator mechanism of action.

- Disease severity

The severity of the target COPD population should be defined a priori. Severity is classified on the basis of airflow limitation, symptoms, risk of exacerbation and presence of comorbidities (GOLD 2011). The most widely accepted classification of the spirometric severity of COPD is according to the Global Initiative for Chronic Obstructive Lung disease (GOLD). The GOLD classification is based on the degree of impairment of lung function and recognises four stages: Stage I: mild, Stage II: moderate, Stage III: severe and Stage IV: very severe. Furthermore, a combined COPD assessment based on GOLD-staging of airflow limitation, risk of exacerbation and current symptoms has been proposed (GOLD 2011). Alternative approaches to evaluate and stage disease severity can be used if validated, justified and generally accepted in clinical practice.

Patients with mild COPD are generally treated with short-acting bronchodilators on demand with a firm recommendation for smoking cessation. Unless there is a specific need to study patients with mild disease, such patients would not normally be recruited into clinical studies assessing maintenance treatments for COPD. Clinical studies of medicinal products for maintenance treatment of COPD should see recruitment of patients with moderate to very severe disease.

- Baseline characteristics

Patient and disease characteristics at baseline (i.e., demographic data, including age, sex, body mass index, pre- and post-bronchodilator FEV<sub>1</sub>, reversibility of airflow limitation, dyspnoea scale, duration of disease, frequency, duration, severity and management of acute exacerbations in the last year prior to study inclusion, previous and concomitant therapies, and concomitant diseases including those specifically related to COPD such as weight loss and peripheral muscle wasting and dysfunction) should be well documented. Efforts to include a population representative of the target population should be made, including patients with relevant comorbidities.

If possible patients are expected to remain clinically stable and free of exacerbations over a pre-specified period prior to randomisation to study treatments. Criteria for defining stability should be stated in the study protocol.

It should be ensured that treatment arms are balanced according to important predictors of outcome. Stratification according to relevant baseline characteristics, for example disease severity, number of exacerbations, could be considered. If the study includes a measure of exercise capacity or health status in the efficacy assessment, the documentation of baseline exercise capacity/health status is mandatory.

- Smoking history

Special attention should be paid to current and/or past history of tobacco smoking (i.e.  $\geq$  X pack years). In efficacy studies formal stratification of patients according to smoking status (non-smokers, current smokers, ex-smokers) could be carried out.

Tobacco exposure should be monitored carefully throughout clinical studies in all patients and changes in smoking status documented and reported. The influence of this exposure on the estimates of efficacy should be evaluated by quantifying and illustrating any differences in tobacco exposure between the treatment groups and discussing the possible quantitative effect of these differences on outcome. Smoking cessation programmes and nicotine replacement therapy offered to smokers as aids to smoking cessation prior to randomisation should be carefully documented, as they may be confounders and may modify the treatment effect. Any effect of these aids on study outcome measures should be examined and documented and the possibility of pharmacokinetic interactions between the proposed new product and any replacement therapies should be investigated.

- Sub-populations

Relevant identified sub-populations should be justified and defined *a priori* in the study protocol. The following examples could be considered of interest: e.g. severity, degree of airflow obstruction reversibility, phenotype (i.e. chronic bronchitis versus emphysema), frequency of exacerbations (i.e. >2-3/year), degree of dyspnoea (e.g. MRC $\geq$ 2), requirement for oxygen therapy, exercise capacity, BMI (e.g. <21) and/or smoking status. The selection of the most relevant subpopulations should be made on a case by case basis. Consistent effects in relevant sub-populations should be shown.

## **4.2. Methods to assess efficacy**

Different types of drugs may be developed for COPD which may provide symptomatic relief through improvement of airway obstruction, which may modify or prevent exacerbations or which may modify the course of the disease or modify disease progression.

The selection of endpoints will depend on the objective(s) of the clinical programme/clinical study. See further details in Section 4.3.

Depending on the mechanism of action of the drug substance under evaluation, a complete characterisation of the effect of any therapy in COPD would require the inclusion of a number of different variables belonging to those domains expected to be affected by the study drug, because most treatments will produce benefits in more than one area.

Comorbidities commonly present in patients with COPD, particularly heart failure, may impact on the clinical endpoints used in the assessment of medicinal products for the treatment of patients with COPD (e.g. symptom questionnaires, exercise capacity, specific disease index). The effect of comorbidities on some of these endpoints will need to be considered.

### **4.2.1. Efficacy endpoints**

#### **Lung function**

Changes in spirometric parameters should be measured as a relevant part of the overall effect of any new therapy in the treatment of patients with COPD. Spirometry should be undertaken by trained healthcare professionals according to standardised methods.

FEV<sub>1</sub> is the most extensively used parameter for adopting treatment strategies in COPD. FEV<sub>1</sub> is one of the most repeatable lung function parameters and in COPD is a measure of the obstructive element of the disease.

If FEV<sub>1</sub> is the primary endpoint, the pre-bronchodilator FEV<sub>1</sub> is the preferred measure in the development of a new product for maintenance treatment, although depending on the mode of action other lung function parameters (e.g. post-bronchodilator FEV<sub>1</sub>) could be the parameter of choice. Whether the preferred parameter is the pre-bronchodilator FEV<sub>1</sub> or the post-bronchodilator FEV<sub>1</sub> or other lung function parameters, this should be justified.

It is recommended that FEV<sub>1</sub> is measured both pre- and post-bronchodilator, both at baseline and at repeated visits during each study treatment period. For a bronchodilator serial post-dose FEV<sub>1</sub> measurements should be carried out to characterise the time profile in order to determine time to effect and duration of effect, particularly in Phase II studies. The maintenance of the effect over time for any drug with an effect on lung function should also be assessed.

A central quality assurance system is highly encouraged. The classification of lung function values as "valid" or "invalid" should be pre-specified and scientifically justified in the protocol according to

acceptable standards. It should be stated and justified how valid or invalid measurements will be used in the study analysis. A description of the quality achieved during spirometric testing should be provided in the study report by means of generally accepted parameters.

Other measures of lung function which could also be recorded to characterise the effect of a new active substance include inspiratory capacity (IC), functional residual capacity (FRC), residual volume/total lung capacity (RV/TLC), forced vital capacity (FVC) and slow VC and the diffusing capacity of the lung for carbon monoxide (DLCO). Some of these measures of lung function may correlate better with improvements in symptoms and exercise tolerance than does FEV<sub>1</sub>. They might be considered as appropriate alternative physiological endpoints if validated for use in COPD. Slow VC is preferred to FVC in some cases of severe airflow obstruction, particularly emphysema.

## **Exacerbations**

Definitions of exacerbation and severity of the exacerbation need to be standardised to allow comparisons between different interventions in different settings.

The proposed definition of an exacerbation of COPD is an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication (GOLD 2011). Although criteria for medical interventions might be subject to local differences, the following classification of the severity of exacerbations is recommended for stable COPD patients:

- Mild: exacerbations described as an increase in respiratory symptoms that can be controlled by the patient with an increase in usual medication;
- Moderate: exacerbations that require treatment with systemic corticosteroids and/or antibiotics;
- Severe: exacerbations that require hospitalisation or result in death.

The rate of moderate or severe exacerbations is a clinically relevant endpoint related to the associated morbidity and mortality and the usually significantly increased health-care requirement.

The frequency and/or severity of exacerbations are important outcome measures that should be considered in clinical studies in COPD. Such measures can include reduction in the number of exacerbations, annual rate and severity of exacerbations. Time to first exacerbation might also be considered. If one of these measures is chosen as the primary efficacy endpoint, the others should be assessed also to ensure that improvement in one endpoint does not result in worsening in another.

An evaluation of the frequency of exacerbations should normally be made over a period of at least one year due to seasonal variation in exacerbation rates. The timing of the study treatment may prove important (e.g. capturing the winter cold season in the majority of patients).

There should be an established minimum time interval between exacerbations to consider them as different episodes. The end of an exacerbation has to be defined clearly so that a difference between the existing exacerbation and a new exacerbation can be measured. Evaluation by an external adjudication committee is encouraged.

## **Patients' and investigators' reported outcomes**

The development of COPD may affect several aspects of a patient's health manifest by symptoms and physical limitations, and ultimately affecting general well-being and health perception. Disease-specific



questionnaires, dyspnoea and symptom scales are considered relevant outcomes for the characterisation of response to treatment.

#### *Health status and Health Related Quality of Life (HRQoL)*

The impact of disease on a patient's daily life, activity and well-being should be assessed at regular intervals. There is a wide range of questionnaires available. Disease-specific questionnaires (e.g. the Chronic Respiratory Questionnaire (CRQ) and the St George's Respiratory Questionnaire (SGRQ)) cover different health related domains. Disease-specific instruments tend to be more sensitive to changes and therefore better suited to measure treatment effects in COPD than generic instruments.

More recently new tools have been introduced into clinical trials. Among them, the COPD Assessment Test (CAT), a patient and clinician rating scale, deserves some consideration for its easy management and its good correlation with the SGRQ.

General questionnaires (e.g. SF-36) and questionnaires with a narrower perspective such as the activity of daily living questionnaires (Nottingham Extended Activity of Daily Living (EADL) or London EADL) or the functional status questionnaires can also provide relevant information, focusing on the number of activities that a patient can perform.

Other health-related questionnaires, specific or generic, can be utilised if sufficiently validated and extensively used.

#### *Dyspnoea*

Instruments used to measure dyspnoea should rely on patient-reported outcomes and be multidimensional whenever possible. Dyspnoea can be measured using clinical ratings based on activities of daily living and ratings during an exercise task. The Baseline and Transition Dyspnoea Indices (clinician rated scales, BDI and TDI, respectively) and the dyspnoea component of the CRQ (patient rated scale) are examples of clinical ratings extensively used in randomised controlled trials. The BDI/TDI is a validated instrument developed to measure the impact of dyspnoea on three domains – functional impairment, magnitude of task and magnitude of effort.

Alternatively, there are a number of methods for patients with COPD to rate their dyspnoea during an exercise test such as cycle ergometry or treadmill walking. The two more commonly used methods are the Borg Category Rating Dysnea Score (CR10), which is preferred, and visual analogue scales (VAS).

#### *COPD symptom scales*

According to widely accepted COPD treatment guidelines, (ERS, ATS, GOLD), the three cardinal symptoms of COPD are dyspnoea, sputum production and cough. The symptoms can be evaluated over the course of the clinical study by use of patient diaries. Improvements in these symptoms are to be expected with most drugs, but the magnitude of improvement is difficult to estimate and a clinically relevant standard for improvement has not yet been established. This needs to be discussed on a study by study basis.

Symptoms to be recorded should include – night-time symptoms, night-time awakening, daytime symptoms, cough, wheezing, dyspnoea, sputum production, etc.

#### *Patients' questionnaires or diary cards*

Questionnaires or diary cards should be provided, one for the patient to capture the unreported exacerbations (mild exacerbations) and another for the investigator to collect the reported (moderate-

severe) exacerbations. Diary entries may be entered into an electronic diary which, in addition to recording exacerbation data, may also capture symptoms

### **Exercise capacity**

In patients with COPD exercise testing is useful in the clinical setting to assess the degree of impairment, prognosis and the effects of interventions. Several methods for evaluating exercise capacity have been developed.

The severity and cause of exercise intolerance are best assessed by conducting standardised laboratory exercise testing in which detailed physiological respiratory/ metabolic measurements are made while patients perform cycle ergometry or walk at a specific speed on the treadmill. Laboratory test protocols can be either constant ("endurance") or incremental work rate tests. Endurance tests rather than incremental testing have been more extensively used in COPD. Cycle and treadmill exercise have been used interchangeably although the former has been used more commonly in clinical studies in COPD, as the work rate for endurance and incremental tests is easier to quantify.

Simpler tests can also be used, although the information gathered is more limited. The six-minute walking distance (6-MWD) is a relatively simple test that has been used extensively in studies to evaluate possible benefits of pharmacological intervention; the shuttle walking test, a better standardised and simpler field test, is also widely used.

### **Rescue medication**

The use of *rescue* medication (e.g.  $\beta_2$  agonist, reliever inhaler) reflects effects on symptoms and therefore can be considered as a clinical endpoint. Both the number of times that rescue medication is required during the day and at night and the number of puffs used on each occasion should be recorded; the number of times that *rescue* medication is used is the more relevant measure.

### **Composite scores**

Changes in the BODE-Index are considered of interest. The BODE-Index is a composite index based on body mass index, airflow obstruction as measured by FEV<sub>1</sub>, dyspnoea assessed by the Medical Research Council (MRC) Dyspnoea Scale, and exercise capacity measured by the 6-minute walking distance.

Other composite scores might be used if validated and generally accepted.

### **Imaging**

Computed tomography (CT) imaging can accurately characterise lung parenchymal changes and facilitate quantitative assessment. Although in clinical practice plain radiography still has an important role in the evaluation of COPD, CT densitometric evaluation might have a role in the assessment of the progression of emphysema and the evaluation of airway wall thickening. As yet the use of CT imaging is not fully validated and therefore is not appropriate for use in clinical studies as a primary or important secondary endpoint. However to explore the possible role that CT imaging might have in clinical studies in COPD, its inclusion as a secondary endpoint should be considered.

Other important considerations when using CT imaging concern the total exposure to radiation.

If changes in lung structure are to be assessed it should be demonstrated that the observed changes in lung tissue are linked to functional changes which provide clinically meaningful benefit to the patient.

### **Other potential endpoints**

Physical activity should be considered as a potential secondary endpoint.

The value of biomarkers of systemic inflammation in COPD is not yet established. To explore the possible role that they might have in clinical studies in COPD, their inclusion as secondary endpoints should be considered.

### **4.3. Strategy and design of clinical trials**

#### **4.3.1. Early studies**

When a new chemical entity is being developed full pharmacokinetic/pharmacodynamic documentation is required.

##### **Pharmacodynamic studies**

The mechanism of action should be characterised and the selection of the relevant pharmacodynamic endpoints justified. First studies in man should provide preliminary safety data and should determine the dose range to be studied in the therapeutic programme.

##### **Pharmacokinetic studies**

The pharmacokinetics of the product should be described and absorption, bioavailability, distribution, metabolism and elimination characterised.

For orally inhaled drugs the extent of systemic absorption due to pulmonary absorption and gastrointestinal absorption should be distinguished (e.g. in studies utilising an active charcoal blockade).

Pressurised and non-pressurised metered dose inhalers, dry powder inhalers and nebulisers have different flow-dependent pulmonary deposition patterns and pulmonary deposition of drug following inhalation from these different inhalation devices may also be dependent on the severity of the disease/inhalation capacity of the patient (e.g. dry powder inhalers) and/or the patient's ability to co-ordinate actuation of the inhalation device with inspiration of breath (e.g. pressurised metered dose inhalers). Consequently, variability in performance should be investigated through pharmacokinetic studies, possibly supported by scintigraphic lung deposition studies, in order to select the patient population able to use the device appropriately or select the dose for each patient group to achieve the required pulmonary deposition.

The use of spacing devices to improve a patient's ability to co-ordinate actuation of the pressurised metered dose inhaler with inspiration of breath has to be supported by appropriate *in vitro* data, pulmonary deposition data and/or clinical data.

##### **Therapeutic exploratory studies**

Specific dose response studies should be performed. Extrapolation from previous dose finding studies in related diseases such as asthma are only of limited value as there is no certainty that both asthma and COPD would respond in a similar way to the same dose.

The choice of the population will depend mainly on the mechanism of action of the products and on the intended target population.

The dose related benefit and adverse effects should be characterised in double blind, randomised, parallel group, placebo controlled studies. The aim of dose response studies is to define the dose with the best benefit/risk balance and dosing schedule for confirmatory studies. The final study design will depend on the pharmacology of the test product.

Studies of short duration, the duration depending on the mechanism of action of the drug and the selected endpoints, may be sufficient, for example, for bronchodilators 6-12-week studies may be acceptable. If an anti-inflammatory effect and/or an effect on exacerbations is being explored a longer duration of study will be needed.

The effect on lung function and patient reported outcomes such as symptoms and health status are appropriate measures for exploratory studies.

### **4.3.2. Therapeutic confirmatory trials**

The selection of patients for confirmatory studies will depend on the type of drug and its intended place in the treatment of COPD. Patients should always be treated in line with international clinical management recommendations.

#### **Choice of comparator**

Selecting an appropriate comparator is difficult as drugs with differing modes of action and combinations of treatments are used in the management and treatment of COPD.

For symptomatic treatment, the most useful comparators are either a placebo and an active comparator or an active comparator alone depending on the type of drug being studied and its place in the therapeutic armamentarium. Placebo-controlled studies might be acceptable but only in certain circumstances. The use of placebo might raise ethical issues especially in patients with moderate to severe disease unless it is added to the best standard of care.

In all studies adequate *rescue* measures must be available.

The choice of the comparator will depend also on the severity of COPD and the type of study design (i.e. substitution of standard therapy, add-on therapy or combination therapy). Conventional pharmacological treatment of COPD depends on the severity of the disease. Ultimately, in the selection of the comparator consideration must be given to current clinical treatment recommendations.

#### **Choice of minimal important difference**

The minimally important difference should be defined in the protocol and needs to be related to the stage of disease and the characteristics of the population and be justified through literature.

#### **Blinding/Masking**

Double blinding is preferred whenever possible. When a double blind study is not possible (e.g. some inhalers are difficult to blind), a three-arm study comparing the new drug with placebo (blinded comparison), and including an active comparator in the third arm of the study (unblinded comparison) as another control arm, would be preferred. If an unblinded trial is conducted, a blinded evaluation is necessary.

#### **Study design**

The therapeutic management of COPD is concerned with either the provision of symptomatic relief which may modify or prevent exacerbations or modification of the course of the disease and disease progression.

## **Symptomatic treatment of COPD**

### *Population*

Clinical studies of medicinal products for maintenance treatment of COPD should recruit patients with moderate to very severe disease.

### *Primary endpoint*

Efficacy in the symptomatic treatment of COPD can be demonstrated either through a single primary endpoint or through co-primary endpoints, depending on the endpoints selected. The choice of endpoint might be influenced by the mechanism of action of the test product. Whichever endpoints are chosen must be thoroughly justified.

Measurement of lung function parameters alone is considered to be insufficient in the assessment of therapeutic effect. If lung function is selected as a primary endpoint (FEV<sub>1</sub> would be the parameter of choice), additional evidence of efficacy must be demonstrated through the use of a co-primary endpoint, which should either be a symptom-based endpoint or a patient-related endpoint. In moderate/severe COPD this might be the number of exacerbations and/or symptoms such as dyspnoea on exertion, or health status assessed through the use of a disease-specific questionnaire such as the St George's Respiratory Questionnaire (SGRQ) and/or assessment of exercise capacity. Efficacy should be demonstrated convincingly for both co-primary endpoints and improvements seen in these endpoints must be statistically significant and clinically relevant.

In certain circumstances clinically relevant and patient-relevant endpoints of efficacy (rather than physiological measures of lung function) may be acceptable as the single primary endpoint in the assessment of efficacy provided that the chosen endpoint is valid and is a generally accepted tool with which to monitor treatment effect, e.g. exacerbations. In such cases, further support from relevant/key secondary endpoints of function and symptoms or health status, will be required.

### *New drugs intended as alternatives to well known and well-accepted therapies such as bronchodilators or inhaled glucocorticosteroids*

All patients entered into clinical studies should receive adequate background/maintenance therapy according to the severity of their disease. The appropriate study design would be either a study in which patients receive the new drug (the test product) in one arm, an established comparator in the second arm and placebo in the third (preferred option), or would be a study comparing the new drug with the established active comparator only. The three-arm placebo- and active-controlled study would aim to demonstrate that the test product is superior to placebo and allow putting results into perspective; the two-arm study would aim to demonstrate that the test product is at least non-inferior to the active comparator.

Active control non-inferiority studies must be sensitive enough to be able to discriminate between the new product and the active control product and to be able to pick up clinically relevant differences, which might exist between the two active products. A clinically relevant response to treatment must be demonstrated. Such comparative studies must have assay sensitivity.

If only a comparison with placebo is available or appropriate, the effect of the new drug must demonstrate clear statistically significant and clinically relevant benefit over placebo and the safety profile must be examined and described carefully to ensure that the benefit/risk balance is acceptable.

### *Add-on therapy*

Most patients with moderate to severe COPD are treated with bronchodilators alone or bronchodilators plus inhaled corticosteroids. For drugs to be used as add-on therapy, a placebo comparison must be carried out providing that all patients receive optimised background therapy (for example, a long-acting  $\beta_2$  agonist alone or a long-acting  $\beta_2$  agonist plus an inhaled corticosteroid).

### *Study duration*

Study duration will depend on the primary endpoints chosen. The effect on lung function parameters and symptoms might be demonstrated in 12 to 24 weeks; demonstration of efficacy through reduction in exacerbations will require studies of longer duration, at least one year.

COPD is a chronic disease and symptomatic benefit is expected to be maintained long-term. Therefore, although efficacy may be demonstrated in controlled clinical studies over 12 to 24 weeks, demonstration of maintenance of effect in longer extension studies to at least one year, blinded whenever possible, is required.

### **Medicinal products aimed to modify the course of the disease and/or disease progression.**

To date, no treatment has demonstrated an effect on disease progression apart from smoking cessation.

There is limited experience in these types of studies. In principle, clinical studies of medicinal products that might modify the course of the disease or might slow or prevent disease progression in COPD should preferentially recruit early-stage patients.

Studies to demonstrate the effect of the new drug on prevention of disease progression, potential disease modification, etc should be parallel group and controlled (and if possible double blind) studies.

Prevention of the disease progression in COPD should be demonstrated by modifying the long-term decline in lung function. A possible effect of any treatment in the prevention of disease progression may be assessed by means of periodical measurements of FEV<sub>1</sub> over time, comparing the difference in the decline in FEV<sub>1</sub> as measured by the slope of the FEV<sub>1</sub> curve between treatment groups. Alternative parameters might be used if justified and properly validated. Because of the variability shown in longitudinal studies, confident assessment of the rate of decline in an individual patient requires a sufficiently long period of study, at least 3-5 years.

### **Concomitant therapy**

Medications that are permitted during clinical studies, including *rescue* medication, should be pre-specified in the protocol and their use recorded accurately.

The possible influence of non-pharmaceutical management of COPD on pharmaceutical intervention, e.g. smoking cessation, surgical treatment, oxygen, physiotherapy, exercise, etc, should be assessed. Nutritional status and nutrient supply during the pharmaceutical intervention should also be controlled.

The use of all concomitant therapies should be accurately recorded and balanced across treatment groups at baseline. A run-in period to standardise concomitant medications is recommended. The use of *rescue* medication (short-acting bronchodilators) should be standardised wherever possible to minimise confounding of the results, should be recorded carefully and should be analysed.

## Handling of withdrawals

Handling of missing data should be in line with the Guideline on Missing data in Confirmatory Clinical Trials (CPMP/EWP/1776/99 Rev1). Additional statistical methods should be implemented to take into account the potential for over dispersion due to the variability in exacerbation rates between subjects.

## 4.4. Safety

### 4.4.1. Specific safety concerns

In COPD reduction of therapy once symptom control has been achieved is not normally possible. Moreover, continuing deterioration of lung function usually requires the progressive introduction of more treatments to limit the impact of such deterioration. Therefore a complete safety evaluation, as the primary safety assessment, is required for any treatment for COPD and requires focus on the occurrence of adverse events for each individual component and adverse events known to occur with the particular combination of active drugs. This means that the assessment of adverse events related to a specific treatment or therapeutic group, for example inhaled corticosteroids, would require assessment of both local effects, such as oropharyngeal examination, and systemic effects, such as assessment of hypothalamic pituitary adrenocortical (HPA) axis function, assessment of bone mineral density and ophthalmological assessments for determination of new onset lens opacities and/or increased ocular pressure; the assessment of adverse events related to a particular combination of active drugs, for example long-acting  $\beta_2$  agonist and inhaled corticosteroid combinations, would require assessment of any increased incidence of pneumonia or lower respiratory tract infections.

A particular safety concern for any immuno-modulatory compound is the long-term effect on host defence, cancer defence, wound healing or response to vaccination. Any dossier submitted should address such concerns. The incidence of upper respiratory tract infections, sinusitis, bronchitis, pneumonia and tuberculosis in controlled trials is of particular interest.

Cardiovascular adverse effects (myocardial infarction, angina, hypertension, atrial fibrillation, cardiac failure, cardiovascular death, QT prolongation, systemic embolism, stroke, etc.) are of particular concern and should be closely monitored, assessed and described, particularly when using combinations of long-acting  $\beta_2$  agonists + anticholinergics. Indications of increased risk of cardiovascular adverse events are an important concern and may trigger the need for additional studies to exclude an unacceptable increase in cardiovascular risk associated with the new drug substance.

Weight loss and any other potentially relevant identified AEs should be addressed during clinical development. Special attention should be paid to any potential deleterious effect on body mass index. Any other safety concern, potential or identified during pre-clinical or clinical development should be adequately addressed in subsequent studies. Specific safety studies to address potential or identified risks may be needed.

All cause-mortality should be considered a relevant safety endpoint. This should always be linked to an assessment of the potential relationship with COPD. A causality assessment of all deaths should be made.

Changes in the BODE Index might be predictive of mortality in patients with severe COPD; its assessment is highly recommended.

#### **4.4.2. Extent of exposure and long-term safety data**

Chronic obstructive pulmonary disease is a chronic disease and therefore robust prospective safety data from at least 1 year of treatment are required.

An adequate representation of patients with COPD with common characteristics and/or common concomitant diseases (i.e., the elderly, patients with renal or hepatic impairment or patients with heart failure) is required in such studies.



## LIST OF ABBREVIATIONS

ATS/ERS	American Thoracic Society/European Respiratory Society
BDI/TDI	Baseline and Transition Dyspnoea Indices
COPD	Chronic Obstructive Pulmonary Disease
CRQ	Chronic Respiratory Questionnaire
CR10	Borg Category Rating Dyspnoea Score
CT	Computed Tomography
DLCO	Diffusing capacity of the Lung for Carbon Monoxide
FEV <sub>1</sub>	Forced Expiratory Volume in one second
FEV <sub>6</sub>	Forced Expiratory Volume in six seconds
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQoL	Health Related Quality of Life
IC	Inspiratory Capacity
LABA	Long-acting $\beta_2$ Agonist
LLN	Lower Limit of Normal
MRC	Medical Research Council
SGRQ	St George 's Respiratory Questionnaire
RV/TLC	Residual Volume / Total Lung Capacity
6MWD	Six Minute Walking Distance
VAS	Visual Analogue Scale
VC	Vital Capacity