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Guideline on clinical investigation of medicinal products in the treatment of Chronic Obstructive Pulmonary Disease (COPD)

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Guideline on Clinical Investigation of Medicinal Products in the Treatment of Chronic Obstructive Pulmonary Disease (COPD)

Table of contents

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 the guidance with new scientific knowledge of the disease and to revise the requirements for the clinical investigation of medicinal products for the treatment of COPD.

1. Introduction (background)

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable respiratory disorder, characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences (ATS/ERS).

COPD is a common condition with a high and continually increasing morbidity and mortality throughout the world. It results in an enormous economic and social burden both of which are increasing. It is estimated that approximately 8 percent of the population have COPD and approximately 10 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 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 – mucous hypersecretion and cilliary 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 (obstructive bronchitis) and parenchymal destruction (emphysema), the relative contribution of each varies 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 effects of COPD.

COPD and its comorbidities cannot be cured and therefore must be treated on a chronic basis. 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, improve exercise capacity and prolong survival. At present no treatment is shown to modify the rate of decline in lung function.

Since the disease is usually progressive the step-down therapeutic approach used for asthma is not applicable for drugs which relieve symptoms in COPD. One of the most important aspects of management of COPD is the avoidance of and cessation of tobacco smoking. 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 β2 agonists, anticholinergics and less often theophylline) and in more severe disease, inhaled glucocorticoids used in combination with long-acting β2 agonists (LABA). Supplemental therapies, such as oxygen, pulmonary rehabilitation and physiotherapy, 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.

3. Legal basis

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 (ICH E4);
- Statistical Principles for Clinical Trials (ICH E9);
- Choice of Control Group in Clinical Trials (ICH E10);
- The Extent of Population Exposure to Assess Clinical Safety for Drugs (ICH E1A).
- Requirements for Clinical Documentation for Orally Inhaled Products for Use in the Treatment of Asthma and COPD (CPMP/EWP/4151/00 Rev1 and /48501/08).
- Guideline on the clinical development of medicinal products in the treatment of asthma (CHMP/EWP/2922/01 Rev1
- Guideline on Missing Data in Confirmatory Clinical Trials (CPMP/EWP/1776/99 Rev1

- 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).

This Guideline is intended to assist applicants during the clinical development of medicinal products. It is only guidance; any deviation from guidelines should be explained and discussed in the Clinical Overview.

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 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 (FEV1/FVC) less than 0.70 (according to GOLD initiative) or below the lower limit of normal in patients over 60 years of age (according to ERS/ATS and the BOLD group) and there is no alternative explanation for the symptoms and airflow obstruction. Alternatively, the FEV1 to FEV6 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.

Chest radiography helps in differential diagnosis.

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

- Characterisation of 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. Such patients include those with asthma, cystic fibrosis, bronchiectasis, bronchiolitis obliterans and fibrosis due to tuberculosis or α1-antyripsin deficiency, such patients should not be recruited to, and should be excluded from, clinical studies in COPD whenever possible.

Up to 50% of patients with COPD have some degree of reversibility. In principle, patients with predominantly asthma should be excluded from clinical trials in COPD. Although this may affect external validity, it will allow for an assessment of a homogeneous population. However, if finally patients with different degrees of reversibility are enrolled, the consistency of the effect depending on the degree of reversibility should be shown.

- Disease severity

The severity of the target COPD population should be defined a priori. Severity is classified on the basis of the post bronchodilator FEV1 value. The most widely accepted classification of the 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.

Figure 1-2. Spirometric Classification of COPD Severity Based on Post-Bronchodilator FEV_1

Stage I: Mild	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted
Stage II: Moderate	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted
Stage III: Severe	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted
Stage IV: Very Severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO_2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.

Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Updated 2009

According to this classification patients with post bronchodilator FEV1/FVC ratio reduced but with normal FEV1, i.e. ≥80% predicted, have mild COPD. These patients are routinely treated with short-acting bronchodilators on demand, plus a recommendation for smoking cessation and are not normally included in clinical studies aimed to assess the symptomatic and functional effect of new therapies. Therefore, clinical studies of medicinal products for the maintenance treatment of COPD should typically include patients with moderate to very severe disease.

Patient and disease characteristics at baseline (i.e., demographic data, including age, sex, body mass index, pre- and post-bronchodilator FEV1, disease reversibility, dyspnoea scale, duration of the 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. If the study includes a measure of exercise capacity in the efficacy assessment, the documentation of baseline exercise capacity is mandatory.

Special attention should be paid to the current or past history of tobacco smoking (i.e. ≥ X pack years). In efficacy studies formal stratification of patients according to smoking status (non-smokers, current smokers, ex-smokers) should be carried out prior to randomisation. 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 confounding factors during the

study. The possibility of pharmacokinetic interactions between the proposed new product and any replacement therapies should be investigated.

The possible influence of other non-pharmaceutical management on pharmaceutical intervention , e.g., surgical treatment, oxygen, physiotherapy, exercise, etc, should be investigated.

Medications that are permitted during the trials, including rescue medication, should be pre-specified in the protocol and justified.

Definition of exacerbation and severity (of the exacerbation) need to be standardised to allow comparisons between different interventions in different settings (See also Section 4.3).

Relevant identified sub-populations should be limited, justified and defined a priori in the study protocol. The following examples could be considered: e.g. according to the severity, phenotype (i.e. chronic bronchitis versus emphysema), to the frequency of exacerbations (i.e. >2-3/year), degree of dyspnoea (e.g. MRC≥2), requirement for oxygen therapy, exercise capacity, BMI (e.g. <21) and/or smoking status.

4.2. Methods to assess efficacy

Different types of drugs may be developed for COPD based on whether the drug is intended for one or more of the following- improve airflow obstruction, provide symptom relief, modify or prevent exacerbations, alter the disease progression, or modify lung structure.

The selection of endpoints will depend on the objective(s) of the clinical programme/clinical study.

Efficacy should be demonstrated in two endpoints (co-primary). Lung function measurements combined with instruments that encompass symptomatic-based end-points (e.g. in moderate/severe COPD –exacerbations, Saint George's Respiratory Questionnaire, symptoms, etc) are recommended for the demonstration of efficacy.

4.2.1. Relevant 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 physicians according to standardised methods.

FEV1 is the most extensively used parameter for adopting treatment strategies in COPD. FEV1 has the advantage of being the most repeatable lung function parameter and one that measures changes in both obstructive and restrictive types of lung disease.

If FEV1 is the primary endpoint, the pre-bronchodilator FEV1 is the preferred measure.

However it is recommended that FEV1 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 FEV1 measurements should be carried out to characterise the time profile curve that will help in the estimation of 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.

To date no treatment has been shown to modify 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 serial measurements of FEV1 over time, comparing the difference in the decline in FEV1 as measured by the slope of the FEV1 curve between treatment groups. Because of the variability shown in longitudinal studies, confident assessment of the rate of decline in an individual patient requires a sufficient period of time, of at least several years.

Other measures of lung function which should also be recorded to characterise the effect of a new active substance include inspiratory capacity, FRC, RV/TLC, vital capacity, DLCO. These measures of pulmonary function may correlate better with improvements in symptoms and exercise tolerance than does FEV1 and should be considered as possibly appropriate alternatives.

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 explicitly how this approach will be used to assign patients to the intention-to-treat and per protocol populations. A description of the quality achieved during spirometric testing should be provided in the study report by means of generally accepted parameters.

Exacerbations:

The proposed definition of an exacerbation of COPD is a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication (GOLD 2009). Although criteria for medical interventions might be subjected to local differences, the following classification 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 requires treatment with systemic steroids and/or antibiotics;
- Severe: exacerbations that require hospitalisation or result in death.

The rate of moderate to severe exacerbations is a clinically relevant endpoint owing 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 severity of exacerbations or reduction in the frequency of

exacerbations. If one of these measures is chosen as the primary efficacy endpoint, the other also should be assessed to ensure that improvement in one endpoint does not result in a worsening on the other.

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. In any case, 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. 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.

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 Indexes (BDI and TDI, respectively) and the dyspnoea component of the CRQ are examples of clinical ratings extensively used in randomised controlled trials. The BDI/TDI is a validated instrument developed to measure the impact of dyspnea on three domains – functional impairment, magnitude of task and magnitude of effort.
Alternatively; there are two common methods for patients with COPD to rate their dyspnoea during an exercise test such as cycle ergometry or treadmill walking: 0-10 category ratio (CR10) scale and VAS, CR10 is preferred.

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 case by case basis.

Symptoms to be recorded should include – night-time symptoms, night-time awakening, daytime symptoms, cough, wheezing, dyspnoea, sputum production ….
Rescue medication – the use of rescue medication is considered a relevant endpoint to assess effect on symptoms.

Patient's 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.

4.2.2. Secondary efficacy endpoints

Depending on the mechanism of action of the drug 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. This is justified as most treatments will produce benefits in more than one area.

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 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.
More standardised tests have patients walking at a specific speed on the treadmill or performing cycle ergometry. Exercise duration, power output and peak oxygen consumption are also standardized measures of exercise capacity.

General health related questionnaires: 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 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 HR questionnaires, specific or generic, can be utilised if sufficiently validated and extensively used.

Imaging: CT imaging can accurately characterise lung parenchyma 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. However CT imaging is not yet appropriate for use in clinical studies as currently it is not fully validated. Other important considerations relate to the total exposure to irradiation. To explore the possible role that CT imaging might have in clinical studies in COPD, its inclusion as a secondary endpoint could be considered.
If changes in lung structure are assessed, it should be demonstrated that the observed changes in lung tissue are functional and that the treatment provides clinically meaningful benefit to patients

Composite scores. Changes in the BODE-Index might also be of interest. It is a composite index based on body mass index, airflow obstruction as measured by FEV1, dyspnoea assessed by the MRC dyspnoea scale, and exercise capacity measured by the 6-minute walk test.

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

Initial human studies should provide preliminary safety data and an estimation of the dose range to be tested in therapeutic studies. The mechanism of action and resulting relevant pharmacodynamic endpoints should be investigated and discussed, i.e. if FEV1 is a suitable endpoint for the clinical studies, it seems logical to use this as a pharmacodynamic endpoint in PK/PD studies.

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. using 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 inhalation device(s) 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 (pressurised metered dose inhalers). Consequently, variability in performance should be investigated by pharmacokinetic studies, possibly supported through 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 device with inspiration of breath should be supported by appropriate in vitro data, pulmonary deposition data and/or clinical data.

Dose finding studies

Specific dose response studies should be performed. Extrapolation from previous dose finding studies in related diseases such as asthma may only be 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 studies. The aim of dose-response studies is to define the most effective dose and dosing schedule for confirmatory studies. The study design will depend on the pharmacology of the test product.

Double blind, randomised, parallel group, placebo controlled studies are required. The effect on lung function and patient reported outcomes such as symptoms and health status are appropriate measures for exploratory studies. The use of exhaled biomarkers in exploratory studies may be considered, but as their role in COPD remains to be clarified and clinical experience is limited, their use should be justified through the literature

Studies of short duration, the duration variable depending on the mechanism of action of the drug, may be sufficient (e.g. 8-12 weeks for bronchodilators). A longer duration of study may be needed if an anti-inflammatory effect and/or an effect on exacerbations is being explored.

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 several modes of action and combinations of treatment are possible in the management and treatment of COPD. The most useful comparator is a placebo and/or an active comparator, depending on the type of drug and its place in the therapeutic armamentarium. The use of placebo might raise ethical issues especially in moderate to severe patients unless this is added to the best standard of care. In all cases, adequate rescue measures must be implemented.

Conventional pharmacological treatment of COPD depends on the severity of the disease. In patients with mild COPD an as-required approach is usually sufficient. Chronic treatment of COPD with bronchodilators as monotherapy is usually restricted to symptomatic patients with moderate disease, since the combination of bronchodilators has shown a good benefit/risk balance. The addition of regular treatment with inhaled corticosteroids (ICS) to bronchodilator treatment is appropriate for symptomatic patients with a FEV1 < 50% predicted (Stage III and IV COPD) and repeated exacerbations who have significant symptoms despite regular therapy with long-acting bronchodilators. Ultimately, the choice of comparator will depend on the degree of COPD severity and the type of study design (i.e.: substitution of standard therapy, add-on therapy, combination therapy, second line therapy in patients intolerant to established therapies).

Choice of minimal important difference:

Although some learned societies have proposed different definitions of minimal

important differences, there is no general agreement on the degree of change in lung function or decrease in exacerbations considered to be clinically relevant. Minimal clinically important difference may be helpful to estimate the sample size for a specific trial, but its role for considering the clinical trial results as 'compelling' exclusively based on a pre-specified magnitude of that outcome is considered controversial. A detailed justification of the potential clinical relevance of these limits in the light of the scientific literature available at the time of submission together with the obtained results of other outcomes with the characteristics of the included population will need to be considered.

Blinding/Masking:

Double blinding is preferred whenever possible. When masking is not feasible (e.g. some inhalers are difficult to blind), a three-arm study comparing the new drug with placebo (blinded comparison), and the inclusion of an active comparator (unblinded comparison) as a control group would be preferred. Efforts should be made to ensure that the personnel involved in the performance of efficacy tests and the collection of efficacy data (i.e. spirometry measurements, collection of data on exacerbations, quality of life measures, etc.) are not aware of treatment allocation. In all cases it is recommended that the assessment of the main efficacy and safety outcomes is carried out blind by an independent adjudicating committee.

Study design:

The benefit on lung function alone is considered of lesser clinical importance to patients themselves; therefore, lung function measurements are insufficient as the only primary endpoint in confirmatory studies unless combined with instruments that encompass symptomatic-based end-points (e.g. in moderate/severe COPD – exacerbations, Saint George's Respiratory Questionnaire, symptoms, etc). Efficacy in both endpoints (co-primary endpoints) should be demonstrated so that no multiplicity adjustment to significant levels would be indicated.

New drugs intended to replace well known and well accepted therapies – 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 three-arm study where 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 a two-arm study comparing the new drug with the established active comparator. The three-arm study would aim to demonstrate that the test product is superior to placebo and at least non-inferior to the active comparator; the two-arm study would aim to demonstrate that the test product is at least non-inferior to the active comparator.

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

Add-on therapy:

Most patients with moderate to severe COPD are treated with bronchodilators alone or bronchodilators plus ICSs. For drugs to be used as add-on therapy, a placebo comparison is acceptable, providing that all patients receive optimised background therapy (i.e. LABA in moderate disease or LABA plus ICSs in severe disease).

Substitution therapy in patients intolerant of or unable to receive standard therapies:

If the new drug is intended for use in those patients intolerant of standard treatment, a placebo controlled study is acceptable, providing that all patients receive adequate background therapy according to the severity of their disease (e.g. a new anti-inflammatory drug plus bronchodilator versus placebo plus bronchodilator in cases of intolerance to previously used ICS in patients with severe COPD).

Concomitant therapy:

The use of all concomitant therapies should be accurately recorded and balanced among treatment groups. 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, and should be recorded carefully and should be analysed.

Study duration:

COPD is a chronic disease and symptomatic benefit is expected to be maintained in the long term. Therefore, although efficacy may be demonstrated in 12-24 weeks in controlled clinical studies, maintenance of the effect in longer extension studies (e.g. 1 year studies) should be assessed.

In addition, data following cessation of therapy should be provided (e.g. randomised withdrawal of test product versus placebo).

Studies to demonstrate the effect of the new drug on prevention of disease progression, potential disease modification, etc should be parallel group, controlled studies of sufficient very long duration. It is acknowledged that such a long duration of a placebo controlled trial may raise feasibility and ethical concerns.

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 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 these changes. Therefore a complete safety evaluation of any treatment for COPD requires focus on the occurrence of events of interest for either each individual component or known to occur with the particular combination of active drugs, as the

primary safety assessment. The assessment of adverse events related to a specific treatment or therapeutic group, for example, inhaled corticosteroids, would require oropharyngeal examination, assessment of hypothalamic pituitary adrenocortical (HPA) axis function, assessment of bone mineral density, ophthalmological assessments of new onset of lens opacities and/or increased ocular pressure, or monitoring of any increased incidence of pneumonia or lower respiratory tract infections related to long-acting β_2 agonist/inhaled corticosteroid combinations.

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 are of particular interest.

Cardiovascular adverse effects (myocardial infarction, angina, stroke, systemic embolism, hypertension, atrial fibrillation, etc.), renal or hepatic adverse events, weight loss or psychiatric effects should be addressed during clinical development. 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 specific potential or identified risks may be needed.
All cause-mortality might be considered a relevant safety endpoint. This should always be linked to an assessment of the potential relationship with COPD. Causality assessment of deaths by an independent adjudication committee is recommended.

4.4.2. Extent of exposure and long-term safety data

Given that COPD is a chronic disease, robust prospective safety data from at least 6 months (usually at least 300-600 patients) and at least 1 year (usually at least 100 patients) is required. Adequate follow-up of patients after treatment withdrawal is required to assess any possible rebound effect or any other adverse effect.

Patients with COPD usually receive combination therapies. Drug-drug interaction studies with common drugs used for treating COPD and also with those relevant to the metabolic pathways of the new drug are required. An adequate representation of patients with COPD with common characteristics or common concomitant diseases (i.e., the elderly, patients with renal or hepatic impairment or heart failure) is required.

LIST OF ABBREVIATIONS

ATS/ERS	American Thoracic Society/European Respiratory Society
BDI/TDI	Baseline and Transition Dyspnoea Indices
BMI	Body Mass Index
BOLD	Burden of Obstructive Lung Disease Initiative
COPD	Chronic Obstructive Pulmonary Disease
CRQ	Canadian Respiratory Disease Questionnaire
CR10	Borg Category Rating Dyspnoea Score
CT	Computed Tomography
DL,CO	Diffusing capacity of the Lung for Carbon Monoxide
FEV_1	Forced Expiratory Volume in one second
FEV_6	Forced Expiratory Volume in six seconds
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQoL	Heath Related Quality of Life
LABA	Long-acting β_2 Agonist
LA-BD	Long-Acting Bronchodilators
MRC	Medical Research Council Dyspnoea Scale
SGRQ	St George´s Respiratory Questionnaire
RV/TLC	Residual Volume / Total Lung Capacity
6MWD	Six Minute Walking Distance
VAS	Visual Analogue Scale