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# COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

# NOTE FOR GUIDANCE ON THE CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF ASTHMA

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# NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR TREATMENT OF ASTHMA

## 1. BACKGROUND

Asthma affects a large percentage of the European population and the incidence has increased in recent years. The duration and intensity of treatment depends upon the severity of the disease. Therapy is often started at a young age and given over many years. This makes long-term safety a particular concern.

Many medicinal products are licensed or are in development for the treatment of asthma in Europe. Treatment of adults and children normally follows the stepwise schedules of professional guidelines, which are remarkably similar in different countries. Detailed guidelines on diagnosis and treatment of asthma from several EU countries and the US agree on major issues. These guidelines provide background information for the clinical investigation of medicinal products in the treatment of asthma and are listed in Section 3.2 below.

The regulatory assessment of any new product is determined by the evaluation of risk benefit. In the case of asthma, this evaluation will depend partly upon the role the product is expected to play in reducing the risk posed by the condition. The risk in turn depends upon the severity of asthma for which the product is intended to be marketed.

## 2. EXISTING REGULATORY GUIDELINES

This document is intended to be read in conjunction with existing regulatory guidelines that already cover aspects of asthma. These include:

General Considerations for Clinical Trials (ICH E8)

Statistical Principles for Clinical Trials (ICH E9)

CPMP Points to Consider on Clinical Investigation of Medicinal Products in the Chronic Treatment of Patients with Chronic Obstructive Pulmonary Disease (CPMP/EWP/562/98)

The Extent of Population Exposure to Assess Clinical Safety of Medicines Intended for Long-term Treatment of Non-Life Threatening Conditions (ICH E1A)

CPMP Note for Guidance - Replacement of Chloroflurocarbons (CFC's) in metered dose inhalation products

Notes for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (ICH E11)

Clinical Investigation of Medicinal Products in Geriatrics, (ICH E7)

Notes for Guidance on Choice of Control Group in Clinical Trials (ICH, E10)

Guideline for PMS studies for Metered Dose Inhalers with new propellants (CPMP/180/95)

CPMP Points to Consider on Multiplicity issues in Clinical Trials (CPMP/EWP/908/99).

## 3. DEFINITION AND DIAGNOSIS

### 3.1 Definition

Asthma is a chronic inflammatory disorder of the airways caused by the interaction of genetic and environmental factors. It is characterised by widespread, variable and reversible airflow

obstruction, associated with spontaneous or pharmacologically induced airway hyper-responsiveness. Acceptable definitions are given in the guidelines listed in 3.2 below.

Additional features such as the link with atopy, increased IGE Production and peripheral blood eosinophilia may be associated with Asthma, but are not necessary for the diagnosis.

### 3.2 Existing Guidelines on Diagnosis

Acceptable definitions are given in existing European and US guidelines listed below:

Global Initiative for Asthma, GINA Workshop Report, NHLBI/WHO, 2002.

Guideline for the diagnosis and management of asthma, National Institute of Health and National Heart, Lung and Blood Institute, 1997.

British Asthma Guidelines, Thorax 1997;52:S1-21.

Asthma therapy in children and adults. Recommendations of the German Respiratory League of the German Society of Pneumology, Medizinische Klinik, 1998;93:639-50.

### 3.3 Severity of asthma

The system described in the GINA Workshop Report, referenced in the previous paragraph, is acceptable for the grading of the severity of asthma.

Severity may be classified as intermittent, mild persistent, moderate persistent and severe persistent asthma. It is acknowledged that this classification, derived from the GINA guidelines, is more relevant to patients at presentation, rather than those for whom treatment has been optimised. For those patients on optimised treatment, classification may be based on treatment requirement.

### 3.4 Differentiation of asthma from chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) and asthma have different aetiologies, but may coexist in the same patient. For the definition of COPD and its separation from asthma for patient recruitment into clinical trials, please refer to Points to Consider on Clinical Investigation of Medicinal Products in the Chronic Treatment of Patients with Chronic Obstructive Pulmonary Disease (EWP 562/98).

The differentiation between COPD and asthma may be difficult as these two conditions may overlap. Patients with predominant COPD should be excluded from trials of asthma.

Current smokers may be included in the trial population, provided they met the asthma entry criteria. Smoking history should be recorded and a subset analysis carried out to determine any effect of smoking on trial outcome.

## 4. CURRENT TREATMENT OF ASTHMA

European and US guidelines recommend a stepped approach to treatment, which is linked to a categorisation of the severity of the condition. The GINA Workshop Report classification of asthma severity is widely accepted in which the level of therapy is stepped up or down depending upon the grade of severity. The goal of this approach is to control asthma with the minimum of medication.

The stepped approach to asthma can be used to grade the severity of the disease and is used to guide treatment in clinical practice. It appears reasonable to allow these principles to guide drug development as regards patients to be studied, suitable comparators and appropriate endpoints.

The GINA Workshop Report classifies drug treatments as controllers or relievers. Controllers are taken daily long term and include both symptomatic and anti-inflammatory drugs. Examples of relievers include short acting bronchodilators.

Most pharmacological agents that are used for acute attacks have also been used chronically. Some chronic treatments are of little immediate benefit in the acute attack, for example anti-inflammatory prophylactic treatment.

An applicant should make clear how a new product relates to current treatment; whether it is primary therapy or add on therapy, whether it is reliever or controller treatment.

## 5. SELECTION OF PATIENTS

When considering the eligibility of patients for clinical trials, asthma should be pre-defined using existing guidelines for its diagnosis. This is normally based on clinical symptoms and proof of reversibility. The diagnosis should be made on the basis of both parameters within a pre-specified time before enrolment. The reversibility of $FEV_1$ after inhalation of a short acting beta adrenergic agonist should normally be greater than 15 %. In patients on controller therapy this figure may be difficult to attain. In this case, an alternative reversibility threshold may be acceptable if it is justified. The patient's asthma should be stable clinically over a pre-specified period before entering randomisation, sufficient to establish a baseline that is adequate for the design of the trial, and the patient should be free from infection. The criteria for defining asthma stability should be stated in the study protocol.

The patient's atopic immune status should be characterised, if this is relevant to the test product's mechanism of action; for example, baseline eosinophilia and IgE production if that aspect of the immune system is targeted by an anti-inflammatory agent.

When assessing the risk benefit of treatment, the risk posed by asthma depends upon its severity. In principle, it is expected that separate trials for a new product are carried out for each grade of asthma severity: intermittent, mild persistent, moderate persistent and severe asthma for which the new product is intended to be used. The claimed indication should only include those grades of asthma severity in which the new drug has been tested and found to have a favourable risk/benefit ratio.

Standardisation of clinical methodology is important. Patients should be adequately trained in respiratory function testing, inhaler technique, compliance and the use of diary cards.

The elderly and children merit additional consideration and are discussed below in Section 10.

## 6. STUDY DESIGN

### 6.1 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 should be investigated and discussed in relation to other relevant drugs that are available.

Both primary and secondary pharmacodynamic studies are required and these should be double blind and placebo controlled. They may involve patients and healthy volunteers, although the effect of asthma severity on the distribution, and hence pharmacodynamics, of inhaled drugs may limit the interpretation of data from non-asthmatic subjects.

### 6.2 Pharmacokinetic studies

The pharmacokinetics of the product should be described and absorption, bioavailability and elimination characterised. An assessment of the extent of systemic absorption of inhaled drugs and their fate is expected; for further guidance, see the separate proposed document on Inhalational Devices.

### 6.3 Dose response relationship

The dose related benefit and adverse effects should be characterised in randomised, double blind, placebo controlled studies as suggested in ICH E-4, Dose Response Information to Support Drug Registration. This guideline also states that it may be useful to include one or more doses of an active control drug, as the inclusion of a placebo and active control allows the assessment of assay sensitivity. These studies should characterise the crucial part of the dose response curve and define the lowest effective dose. The design depends upon the pharmacology of the test agent. For beta adrenergic agonists, an accumulative dose response may be performed using $FEV_1$ or peak expiratory flow as a pharmacodynamic endpoint. For an anti-inflammatory agent, fixed dose parallel studies will be necessary. Additional tests may be necessary, such as the measurement of bronchial reactivity, or pharmacodynamic measures related to the proposed mechanism of action.

### 6.4 Main efficacy studies

The design of the efficacy studies will depend whether a new product will be reliever or controller treatment.

#### 6.4.1 Reliever Medication

Clinical trials of reliever drugs are expected to be parallel, double blind, randomised, and controlled. Efficacy may be shown in short term trials of four weeks duration, but longer trials are necessary to establish that efficacy is maintained without tolerance.

#### 6.4.2 Controller Medication

The established use of inhaled corticosteroids as first choice controller treatment for most patients makes these drugs the comparator of choice. Claims for chronic treatment should be supported by the results from randomised, double blind, parallel, controlled clinical trials of at least six months duration.

## 7. COMPARATORS AND CONCOMITANT TREATMENTS

### 7.1 Comparators

#### 7.1.1 Reliever drugs

The choice of a control will depend on the grade of asthma severity. For patients with intermittent asthma, the preferred option is a three-arm study where the new drug is compared with placebo and with a short acting beta-agonist. For higher grades of severity, active comparator trials are preferred, with short acting beta-agonist as the preferred comparator. In this case, reliever medication is expected to be administered in addition to adequate background treatment.

#### 7.1.2 Controller drugs

With the exception of mild intermittent asthma, for which no controller treatment is currently recommended, inhaled corticosteroids are considered the treatment of choice for asthma control. For a drug that is intended as a first-line controller treatment, an active comparator trial should be performed where the severity grade of asthma is specified and the new drug is compared to an inhaled corticosteroid. For this comparison, the inhaled corticosteroid should

have been given in an adequate dose and for an adequate duration according to the severity of the asthma.

In patients with mild persistent asthma, a three-arm study including placebo is strongly recommended. Although study treatment duration is expected to be at least six months, a shorter duration for the placebo arm may be acceptable. In patients with more severe asthma, the new drug may be compared to inhaled corticosteroids adequately dosed. Alternatively, if the drug is not intended to be substituted for inhaled corticosteroids, add-on designs where the new drug is compared to placebo are required.A third arm with a standard upgrading comparator(s) should be considered.

### 7.2 Concomitant Treatments

It should be established that the patient's existing therapy is appropriate for the severity of their asthma. Although concomitant rescue therapy should never be denied, concomitant therapy should be simplified where possible to avoid compromising the interpretation of the data.

The use of all concomitant treatments including bronchodilators, oral corticosteroids, inhaled corticosteroids, antibiotics as well as mucolytic antioxidants should be documented fully. An imbalance in the use of these medications between treatment groups may affect the outcome and appropriate analysis plans should be made beforehand to account for this possibility. This analysis should quantify the possible extent of the bias arising from the imbalance and evaluate the amount of the treatment effect attributable to the randomised treatments.

## 8. RECOMMENDED PRIMARY AND SECONDARY ENDPOINTS

### 8.1 Lung Function

Both $FEV_1$ and peak expiratory flow (PEP) reflect airway obstruction and are accepted as spirometric evaluations of the effect of anti-asthma drugs.

Whichever measure of airway obstruction is chosen, the reproducibility and sensitivity of the method should be assessed. The timing of the measurement of lung function should be standardised and recorded in relation to the last dose of trial and concomitant medication. The effect on spirometry of any diurnal variation in airway obstruction should be taken into account. If home recording equipment is used, reproducibility is particularly important and an electronic diary record should be considered to validate the timing of measurements.

Other spirometric measures, such as determining vital capacity and flow rates at lower lung volumes, such as the flow at 25% of the vital capacity above residual volume can be used as complementary endpoints in asthma trials. Additional tests of lung function may be useful in Phase II trials.

### 8.2 Clinical Endpoint

Acceptable symptom based clinical endpoints include symptom scores and the use of reliever medication.

Exacerbation rates may be useful to assess controller treatment in more severe asthma. There is no universal definition of exacerbation rate, but the most useful parameters are symptom scores, the need for rescue medication and an objective worsening of airway obstruction. Exacerbations and their severity should be pre-defined in the study protocol, as should the change in the number of exacerbations that is thought to be clinically relevant. Severe exacerbations have been defined as a need for oral corticosteroids, asthma related unscheduled medicinal visits, asthma related visits to the emergency department, more than a 30% fall in peak expiratory flow on two successive days, or the need for admission to hospital

for asthma. Asthma control is a concept that combines the clinical endpoints mentioned above that may provide a useful long-term clinical endpoint assessment. As defined by the GINA Workshop Report, control may be defined as no, or minimal symptoms, no emergency visits, minimal need for short acting beta-agonists, no limitation on activities, PEF variability <20%, and no adverse effects from drugs. Alternative definitions may be possible if justified as clinically relevant.

### 8.3 Selection of the Primary Endpoints

The selection of the most appropriate primary endpoint will depend upon whether the drug is proposed as reliever or controlled medication, and the grade of asthma severity.

#### 8.3.1 Reliever Medication

For a new short acting bronchodilator indicated as reliever medication, where the pharmacodynamics have been established clearly by earlier trials, the emphasis is on the measurement of airway obstruction.

#### 8.3.2 Controller Medication

For a new controller treatment for mild persistent asthma, equal emphasis should be placed on lung function and the symptom based clinical endpoint. A significant benefit for both primary end points, lung function and the symptom based clinical end point, should be demonstrated so that no multiplicity adjustment to significance levels is indicated.

For moderate and severe persistent asthma, symptom based endpoints are particularly important. These may include the frequency of exacerbations and an assessment of asthma control.

### 8.4 Selection of Secondary Endpoints

When endpoints listed above are not specified as primary they may be chosen as secondary endpoints. In addition, a number of secondary endpoints may provide useful information. These measure different aspects of the condition and they should be justified by referencing published data that support their validity. Examples in chronic asthma include symptom scores, use of rescue medication, nocturnal symptoms, exercise tolerance, exacerbation rates and quality of life.

## 9. CLINICAL SAFETY

### 9.1 Long term clinical safety

The duration and intensity of treatment depends upon the severity of the disease, but therapy is often started at a young age and given over many years. This makes safety a particular concern. Long-term safety data should be provided. This should be in line with the ICH E1A guideline - The extent of population exposure to assess clinical safety of drugs intended for long-term treatment in non-life threatening conditions (ICH E1A).

New agents that interact with the immune system deserve particular attention. An application for an agent that suppresses immune function should document the consequences for immune defence of immune suppression. For example, an agent that impairs leucocyte function, or inflammatory mediator function, should be investigated for its effect on the host response to infection. The possibility that an immunosuppressive agent might induce malignancy should be investigated. The duration of action of the agent on the immune system should be documented and the duration of the clinical assessment of safety adjusted accordingly. Depending on the product, the assessment of antibody formation may be necessary.

Post marketing commitments may be required.

### 9.2 Local and systemic adverse events

Inhaled therapy usually allows a reduction in systemic exposure and hence an increase in the margin of safety. However, specific safety concerns may arise from the inhaled route, such as vocal cord myopathy, oral fungal infection or cataract formation associated with inhaled corticosteroid use. The assessment of the effect on ciliary function may be necessary. An assessment of the extent of systemic absorption of inhaled drugs is expected.

For inhaled corticosteroids, an appropriate sensitive measure of hypothalamic pituitary adrenal axis function should be used. In children, the effects on long-term growth and bone density should be evaluated.

### 9.3 Interaction Studies

Interaction studies should be designed after the adequate investigation of the pharmacodynamics, pharmacokinetics, metabolism and excretion of the medicinal agent. Clinically significant interactions with commonly co-prescribed medication, particularly for the elderly, should be excluded, or documented with appropriate advice in the SPC, see CPMP Notes for Guidance on the Investigation of Drug Interactions, EWP/560/95.

## 10. STUDIES IN THE ELDERLY AND CHILDREN

### 10.1 The Elderly

The elderly merit particular attention with regard to safety, see Clinical Investigation of Medicinal Products in Geriatrics, ICH E7. Separate efficacy studies are not necessary in the elderly, but pharmacokinetic studies should compare the elderly with younger adults. Safety studies should include the assessment of pulmonary and systemic adverse events.

### 10.2 Children

The high incidence of asthma in children makes this a target population of special relevance.

The pathology and pharmacology of childhood asthma differs in many respects from that in adults and extrapolation from studies in adults to children is limited. Unless the medicinal product is contraindicated in children, the applicant should follow the advice laid out in the ICH Notes for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99). If the medicinal product is a major therapeutic advance for the paediatric population, studies in children should begin early in development when sufficient safety data are available to adequately justify the use in children. The justification to start a paediatric programme should take into account that there are established treatments approved for use in children. The submission of paediatric data in the application would be expected. Sufficient trial data should be provided to allow the adequate assessment of risk benefit for the three age ranges of under five years of age, 5-12 years, and over 12 years of age. The difficulty of measuring lung function in young children is acknowledged. In young children any evaluation parameter used as a primary endpoint should be validated for the appropriate age group studied.

Paediatric studies should be conducted as early as the development of the medicinal product allows, to avoid excluding children in the authorised indication because of lack of data. It is recommended to implement the paediatric studies after potential benefit has been shown in adults and before registration of the product in adults. A specific dossier is recommended to register use in children. This should be submitted with the main application and include kinetic, exploratory and controlled studies.

Long-term safety, such as the effect of corticosteroids on growth, skeletal changes, endocrinology, and immune function should be addressed. Post marketing surveillance

measures and the possibility of instituting an active reporting system for adverse events in children should be addressed.

Particular attention should be paid to the effect of age on the adequate function of inhalation delivery devices, although a separate guideline will be released covering these. For children under five with chronic asthma both corticosteroid and bronchodilator therapy should be routinely delivered by pressurised meter dose inhaler and a spacer system, with a facemask where necessary. Where this combination is not effective, depending upon the child's condition, nebulised therapy may be considered. In the case of children aged three to five years a dry powder inhaler may also be considered. The choice of device within the pressurised metered dose inhaler and spacer range should be governed by individual need and the likelihood of compliance. The design of any trial with a delivery device should take this advice into account.

## 11. INHALATION DEVICES

A separate Note will address this issue for Guidance or Points to Consider document.

This document will be revised in accordance with the scientific advances made in this area. The issue of use in pregnancy and lactation will be addressed in a separate document.