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Note for guidance on clinical investigation of medicinal products for treatment of asthma

Draft

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Note for guidance on clinical investigation of medicinal products for treatment of asthma

Table of contents

Executive summary

This document is a revision of the earlier Note for Guidance (CPMP/EWP/2922/01) which came into effect in May 2003. It should be considered as general guidance on the development of medicinal products for the treatment of asthma and should be read in conjunction with other European and ICH guidelines which may apply to this disease area and patient population. The current revision has taken into account the updated international clinical recommendations for asthma, focused on a control-based management in order to include revised concepts of the disease and new variables developed to assess the effect of medicines for asthma treatment. A detailed chapter for the development of medicinal products for the treatment of asthma in children has been included. Some considerations for the development of immunotherapy are also included. However, since limited experience exists regarding clinical trials of specific immunotherapy for the treatment of allergic asthma, scientific advice from the national competent authorities or EMA is highly recommended.

1. Introduction (background)

Asthma affects a large percentage of the European population and the incidence has increased in recent years. The duration and intensity of treatment depend 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 authorised or are in development for the treatment of asthma in Europe. Diagnosis and treatment of adults and children normally follows the stepwise schedules described in clinical guidelines, which are remarkably similar across 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 'References' at the end of this document. However, these guidelines have evolved with time and important concepts such as 'asthma severity' and 'asthma control' have been reviewed and redefined and a different classification of asthma severity has been discussed. These differences in terms, definitions and classification compared with those in earlier use should be taken into account in the development of new medicinal products for the treatment of asthma.

Asthma is a chronic inflammatory disorder of the airways caused by the interaction of genetic and environmental factors. It is characterised by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness and an underlying inflammation. Asthma is a heterogeneous disease in its manifestations and also in its response to treatment.

Previous versions of clinical guidelines for asthma classified 'asthma severity' as intermittent, mild persistent, moderate persistent and severe persistent asthma based on clinical characteristics and medication required to maintain disease control. However, the definition of asthma severity has been subject to modification in the different versions of these guidelines and now this concept is defined as the difficulty in controlling asthma with treatment. Therefore, severity is based on the intensity of treatment required to control the patient's asthma (NHLBI, 2007; GINA, 2011).

The main objective in asthma treatment is to maintain asthma control. The concept of 'asthma control' is not synonymous with 'asthma severity' and is defined as 'the extent to which the various manifestations of asthma have been reduced or removed by treatment'. This concept encompasses two components, the patient's recent clinical status/current disease impact (symptoms, night awakenings, use of reliever medication and lung function) and future risk (exacerbations, decline in lung function or treatment related side effects). According to the GINA Guidelines asthma is controlled when a patient

has daytime symptoms only twice or less per week, has no limitation of daily activities, has no nocturnal symptoms and no exacerbations, has normal or near normal lung function and uses reliever medication twice or less per week. GINA proposes a classification of asthma by level of control in three categories (controlled, partly controlled and uncontrolled). A proposal of different severity grades based on the intensity of treatment needed to maintain asthma control is also mentioned. Five steps are distinguished representing each step a treatment option for controlling asthma.

The GINA Workshop Report classifies drug treatments as controllers or relievers. In addition allergen-specific immunotherapy is available for allergic asthma although its specific role is not completely established yet. Controllers are taken daily and long-term and include both anti-inflammatory drugs and drugs which control symptoms (inhaled corticosteroids, leukotriene modifiers, anti-IgE treatment, oral corticosteroids). Relievers are medications used on an as-needed basis to reverse bronchoconstriction and relieve symptoms. Examples of relievers include rapid-acting bronchodilators (e.g. short- and some long-acting β_2 agonists). Some chronic treatments are of little immediate benefit in the acute attack, for example anti-inflammatory prophylactic treatment.

European and US guidelines recommend a stepped management approach to treatment based on disease control. The goal of treatment is to achieve and maintain control. The level of asthma control obtained with treatment determines the need to step up or step down to the next treatment step in order to achieve optimum control with the minimum level of medication. The majority of asthma patients can achieve and maintain clinical control with standard treatment. Those patients who do not achieve adequate control with the highest level of medication (reliever plus two or more controller treatments) are considered to have difficult-to-treat asthma.

2. Scope

This document is intended to provide guidance for the clinical evaluation of new medicinal products for the treatment of asthma.

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles 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:

- General Considerations for Clinical Trials (ICH 8)
- Statistical Principles for Clinical Trials (ICH E9)
- Dose Response Information to Support Drug Registration (ICH E4)
- Guideline on Clinical Investigation of Medicinal Products in the Chronic Treatment of Patients with Chronic Obstructive Pulmonary Disease (COPD) (EMA/CHMP/483572/2012)
- Note for Guidance on Population Exposure: The Extent of Population Exposure to assess Clinical Safety (ICH E1)
- Replacement of Chloroflurocarbons (CFCs) in Metered Dose Inhalation Products - EudraLex vol. 3BR3a (III/5378/93-Final)
- Pharmacokinetic Studies in Man - EudraLex vol. 3C C3A
- Notes for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (ICH E11)

- 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) (CPMP/EWP/4151/00)
- Studies in Support of Special Populations: Geriatrics (ICH E7 CHMP/ICH/379/95) and related Q&A document (EMA/CHMP/ICH/604661/2009)
- 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)
- Points to Consider on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99)
- Guideline on Missing Data in Confirmatory Clinical Trials (CPMP/EWP/1776/99)
- Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases (CHMP/EWP/18504/2006)
- Guideline on the investigation of drug interactions (CPMP/EWP/560/95)

4. Efficacy

4.1. Selection of patients

When considering the eligibility of patients for clinical studies, asthma should be pre-defined using existing clinical guidelines for its diagnosis. The diagnosis of asthma is usually based on clinical symptoms and assessment of airflow limitation. The diagnosis should be made on the basis of both parameters within a pre-specified time before enrolment. Spirometry, performed under standardised recommendations to measure forced expiratory volume in one second (FEV1) and forced vital capacity (FCV), is the preferred method to assess airflow limitation, its reversibility and variability. The reversibility of FEV1 after inhalation of a short-acting β2 adrenergic agonist should normally be greater than 12-15 % and 200 ml. However, in patients on controller therapy this figure may be difficult to attain. In this case, the reversibility criteria for diagnosis could be provided by the patient's medical history. Peak expiratory flow (PEF) measurements can also be used to diagnose asthma but their value can underestimate the airflow limitation. In patients with clinical symptoms and normal lung function measurement of airway hyperresponsiveness (direct or indirect) could be useful to establish the diagnosis although the specificity of the test is limited. A lack of airway hyperresponsiveness can exclude a diagnosis of asthma if no controller medication is being used.

Depending on the objective of the study controlled patients, partially controlled or uncontrolled patients could be selected. Whatever the status of the patients finally selected, treatment should be standardized as much as possible in order to establish a baseline that is appropriate for the interpretation of the study results. Patients randomised to study treatments should be free from respiratory infection.

For clinical studies to investigate the efficacy of specific immunotherapy the patients' history of allergy and the causal allergen should be well-documented before study entry (according to the CHMP Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Disease- CHMP/EWP/18504/2006).

The inflammatory airway profile should be characterised if this is relevant to the mechanism of action of the test drug; for example, baseline eosinophilia, IgE production or cytokines if that aspect of the immune system is targeted by the investigational product.

When selecting patients for a clinical study it is important to consider and record obesity, body weight and body mass index.

The risk posed by asthma depends upon its severity. In principle for a new product it is expected that separate studies are carried out for each grade of asthma severity for which the new product is intended to be used. The criteria used to classify severity of asthma should be clearly established in the protocol as the current clinical classification differs from that stated previously in treatment guidelines. Patient population should be adequately characterised indicating whether they are treatment-naïve or not. For patients already receiving treatment for asthma, description in terms of minimum treatment received to maintain control is an important issue to be considered. Medication should be recorded during a sufficient period of time to provide adequate characterisation. Patients' baseline characteristics of lung function, daytime and night-time symptoms and use of rescue medication should be recorded. Previous history of exacerbations should be well documented, specifying the use of oral/systemic corticosteroids and emergency department visits/hospitalizations. Co-morbidities and concomitant therapies should be documented. When using inhalers, inhaler technique and adherence to treatment and time of dosing should be optimised. This is particularly important for children. The claimed indication should only include those grades of asthma severity in which the new drug has been studied and found to have a favourable risk/benefit balance.

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, see the CHMP Guideline on Clinical Investigation of Medicinal Products in the Treatment of Chronic Obstructive Pulmonary Disease (COPD) EMA/CHMP/483572/2012. The differentiation between COPD and asthma may be difficult as these two conditions may overlap. Patients with predominantly COPD should be excluded from studies in asthma.

Patients with asthma who are current smokers may be included in the study population provided they meet the asthma entry criteria. Smoking history should be recorded and a subgroup analysis carried out to determine any effect of smoking on trial outcome. Any subgroup should be sufficiently large to be statistically relevant. 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.

It should be ensured that treatment arms are balanced according to important predictors of outcome. Stratification according to relevant baseline characteristics, for example, number of exacerbations, use or no use of long-acting β_2 agonist could be considered. Depending on the mechanism of action of the medicinal products, other relevant factors might be considered.

Relevant identified sub-populations should be justified and defined a priori in the study protocol. The following examples could be considered: e.g. age, , frequency of exacerbations, smoking status, known sensitivity to NSAIDs status, eosinophilia, and co-sensitisations to different allergens. 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.

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 sections 6 and 7, respectively.

4.2. Methods to assess efficacy

Lung Function: Both FEV_1 and PEF reflect airway obstruction and are accepted as spirometric evaluations of the effect of anti-asthma drugs. Pre-bronchodilator FEV_1 is considered the most suitable variable and has been considered as a measure of asthma control as it is influenced by short-term fluctuations in airflow limitation. Its relationship with symptoms experienced by the patient is poor but a low FEV_1 is described as an independent predictor of asthma exacerbations. Peak expiratory flow evaluation is a variable considered more appropriate for ambulatory monitoring of lung function.

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 the test drug 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. The analysis used should be adequately justified.

Other spirometric measures, such as vital capacity (VC) and flow rates at lower lung volumes, such as the flow at 75% and 25% of VC above residual volume (RV) and post-bronchodilator FEV_1 and FVC can be used as complementary endpoints in asthma studies. Additional tests of lung function may be useful in Phase II trials.

Airway hyperresponsiveness and challenge testing: Challenge testing with 'direct' (methacholine, histamine) and 'indirect' (mannitol, adenosine monophosphate, hypertonic saline) agents is a measure of the tendency of airways to narrow in response to a stimulus that has little or no impact in normal individuals. Challenge testing with an appropriate allergen can be considered in clinical studies for specific immunotherapy. The objective of these tests is to assess the provocative concentration or provocative dose of the challenge/stimulus that causes a certain degree of airway narrowing (usually a 20% fall in FEV_1). A weak correlation with symptoms, lung function and markers of airway inflammation is described but an increase in hyperresponsiveness appears to predict loss of asthma control. The selected test should be justified, the study should include some determination of repeatability and an adequate washout-period with short- and long-acting bronchodilators should be assured.

Asthma Exacerbations: Exacerbation rate is a clinically relevant endpoint to assess controller treatment in asthma patients. The prevalence of asthma exacerbations is identified in clinical guidelines as an important component in the achievement of asthma control. The definition of exacerbation and the severity of the exacerbation should be pre-defined in the study protocol. The following definitions for exacerbations should be considered:

Severe exacerbations of asthma are usually defined as a requirement for systemic corticosteroids or an increase from the maintenance dose of corticosteroids for at least three days and/or a need for an emergency visit, or hospitalization due to asthma.

Moderate exacerbations are usually considered as events that require a change in treatment to avoid progression of worsening asthma to a severe exacerbation and the occurrence of one or more of the following – deterioration of symptoms of asthma, increased use of "rescue" inhaled bronchodilators, deterioration in lung function, which last for two days or more but usually not severe enough to warrant systemic corticosteroids or hospitalization.

Mild exacerbations – the definition of "mild exacerbation" is difficult and should be avoided as its characteristics are similar to the normal variation seen in asthma control.

The methods used to capture (as percentage of patients, annualized rate, time to event) and analyse this endpoint should be justified as should the change in the number of exacerbations thought to be clinically relevant. The length of the study should be of sufficient duration to capture these events (at least 12 months) and as recruitment should continue throughout all four seasons a twelve-month follow-up is a minimum requirement. During the trial it is necessary to document in what season the wheezing episodes/exacerbations occur.

Symptom scores: Assessment of symptoms is an acceptable clinical variable although there are no validated scales. Both daytime and night-time symptoms should be recorded. The use of diaries is encouraged, preferably electronic diaries to enhance accuracy of recording. 'Symptom free days' and 'Number of night awakenings' are considered relevant variables to be measured. Problems of sensitivity should be taken into account in mildly or very severely affected populations.

Reliever use: The increased use of reliever medication is an acceptable clinical endpoint that reflects lack of asthma control, i.e. frequency and intensity of symptoms. However, it can also be a measure of a patient's symptom tolerance or, if used to prevent exercise-induced asthma, the level of physical activity. The use of β_2 agonists for the relief of symptoms should be recorded and reported separately from prophylactic use. It is considered important to record the frequency with which the β_2 agonist is required and the number of actuations required during both the day and the night.

Composite scores: Different composite scores have been developed to measure "asthma control", using categorical or numerical variables. These instruments provide information about clinical symptoms and limitation of daily activities from a patient's perspective. Composite scores are composed of individual variables that are considered of value in the assessment of the impact of treatment on different aspects of asthma control. Examples of categorical composite variables are 'asthma control days' or 'well-controlled'/'total control' asthma weeks. Numerical composite variables score different clinical symptoms or signs on a scale and give a numerical score to represent control. Lung function or markers of airway inflammation are part of the variable in some of them. Examples of these scores are the Asthma Control Test (ACT) or the Asthma Control Scoring System (ACSS), the Asthma Control Questionaire (ACQ) and the Asthma Therapy Assessment Questionaire (ATAQ). Measures to enhance patients' compliance with questionnaire completion should be considered. When constructing this kind of variable/score both the individual and the composite variables should be validated and the appropriateness of the cut-point values to distinguish "control" versus "no control'" and the weight of each component should be adequately justified. The analysis of the composite variable should be provided in absolute terms and as a proportion of patients achieving a defined target level of control. The components of the composite variable should also be individually analyzed in order to know if the overall effect is driven by a single variable.

Reduction of controller medication: Reduction of controller medication as a consequence of the therapy is a clinically relevant endpoint.

Biomarkers of airway inflammation: Some measures have been developed for the assessment of airway inflammation and provide supportive information. Eosinophil counts and fractional concentration of exhaled nitric oxide (FE_{NO}) provides information about the underlying disease activity in eosinophilic asthma.

Health related quality of life: Patient perception of asthma may differ from that of clinicians and should be assessed by health related quality of life (HRQoL) questionnaires, generic or disease-specific. Some asthma related Quality of Life Questionnaires are validated. The use of a specific questionnaire and the defined difference considered clinically relevant should be justified.

4.3. Study design

4.3.1. Pharmacodynamic studies

Initial human studies should provide preliminary safety data and an estimation of the dose range to be investigated in therapeutic studies. The mechanism of action should be investigated and discussed in relation to other relevant drugs that are available.

Formal pharmacodynamic studies are not possible for allergen products. However, to show the effect of specific immunotherapy on the immune system immunological changes (e.g. changes in allergenspecific IgG levels, T-cell responses, and/or cytokine production) and/or modifications of the endorgan specific response (e.g. provocation tests) should be measured. These parameters can be followed in other studies on specific immunotherapy.

4.3.2. Pharmacokinetic studies

The pharmacokinetics of the product should be described and absorption, bioavailability, metabolism and elimination characterised. An assessment of the extent of systemic absorption of inhaled drugs and their fate is expected.

Pharmocokinetic studies are not possible for products for specific immunotherapy. During specific immunotherapy usually plasma concentrations of the active substance are not measurable, due to the nature of the product.

4.3.3. Therapeutic exploratory guidelines

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. These studies should characterise the crucial part of the dose response curve. It may be useful to include one or more doses of an active control drug. Alternatively, to enhance the assay sensitivity the inclusion of a placebo and an active control would be needed. Study designs depend upon the pharmacology of the test drug and the response to treatment may follow a very different time course not only dependent on the drug but also on the outcome measure.

For β2 adrenergic agonists, a cumulative dose response may be performed preferably using FEV1 (or peak expiratory flow) as a pharmacodynamic endpoint; for anti-inflammatory drugs parallel group comparative studies are likely to be necessary comparing at least two, if not, more doses of the test drug with two doses of the comparator drug. Alternatively the bronchoprotection/bronchial reactivity model may be used for both β2 adrenergic agonists and anti-inflammatory drugs – for anti-inflammatory drugs this must follow chronic dosing. See the CHMP Guideline on orally inhaled products – (CPMP/EWP/4151/00).

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 long-acting bronchodilators 6-12 week studies are recommended, whilst shorter treatment duration might be accepted for short-acting bronchodilators. If an anti-inflammatory effect and/or an effect on exacerbations is being explored a longer duration of study will be needed.

For specific immunotherapy a bronchial provocation test or reduction of controller medication may be considered for efficacy analysis.

Additional investigations may also be necessary, such as the measurement of biomarkers of airway inflammation, or pharmacodynamic measures related to the proposed mechanism of action.

4.3.4. Main efficacy studies

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 and its intended mechanism of action. The design of the efficacy studies will depend on whether a new product will be a reliever or a controller treatment. Products for specific immunotherapy are neither reliever nor controller medication and have to be addressed separately.

4.3.4.1. Design

Reliever medication

Clinical trials of reliever drugs are expected to be parallel group, double blind, randomised and controlled. Efficacy may be shown in short-term trials of four-week duration. It should be justified that efficacy is maintained without tolerance.

Controller medication

Claims for chronic treatment with controller medication should be supported by the results from randomised, double blind, parallel group, controlled clinical trials of at least six months duration, although a longer duration may be necessary depending on the endpoint selected (for example, exacerbations). The established use of inhaled corticosteroids as first choice controller treatment for most patients makes these drugs the comparator of choice.

Specific Immunotherapy

Clinical trials of products for specific immunotherapy are expected to be parallel group, double blind, randomised, and controlled. Normally the investigational medicinal product should be supplied as add on treatment to needed controller and/or reliever medication. The evaluation period should cover the period of high allergen exposure (e.g. pollen season for seasonal allergens or seasonal variations for perennial allergens). The study duration has a strong influence regarding the approvable indication (see also CHMP/EWP/18504/2006).

4.3.4.2. Comparators and concomitant treatments

Reliever medication

The preferred option is a three-arm study where the new drug is compared with placebo and with a short-acting β2 agonist. Reliever medication is expected to be administered in addition to adequate background treatment according to the degree of severity. Appropriate rescue measures should be established.

Controller medication

With the exception of milder patients, for whom no controller treatment is currently recommended, a controller therapy is the treatment of choice for the management of persistent asthma. For a drug that is intended as a first-line controller treatment, an active comparator trial should be performed comparing with a standard treatment for a specific treatment step. An inhaled corticosteroid is usually involved in all steps. For this comparison, the inhaled corticosteroid should be given in an adequate dose and for an adequate duration.

A three-arm study including a comparison with placebo is strongly recommended in at least one pivotal clinical study, in order to ensure assay sensitivity. These studies are normally carried out in patients

with milder asthma. Although study treatment duration is expected to be at least six months, a shorter duration for the placebo arm may be acceptable.

If the drug is not intended to be substituted for inhaled corticosteroids, add-on designs where the new drug is compared with placebo are required. A third arm with a standard upgrading comparator(s) (the next medication step according to treatment guidelines) should be considered.

Concomitant treatments

It should be established that the patients' 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 and documented to avoid compromising the interpretation of the data.

The use of all concomitant treatments including bronchodilators, oral corticosteroids, inhaled corticosteroids, antibiotics and mucolytic antioxidants should be accurately recorded and balanced among treatment groups at baseline. A run-in to standardise concomitant medication is recommended. The use of rescue medication should be standardized whenever possible and potential bias should be detected and considered in the evaluation.

4.3.4.3. Blinding / masking

Double-blinding is preferred whenever possible. When masking is not feasible (for example, some inhalers), a three arm study comparing the new drug with placebo (blinded comparison) and with an active comparator (unblinded control group comparison) is preferred. In this case, efforts should be made to assure that the personnel involved in the performance of efficacy tests and collection of efficacy data (i.e. spirometry, exacerbations, quality of life, etc.) remain blind to treatment allocation. In all cases it is recommended that the assessment of the main efficacy and safety outcomes is performed blind by an independent adjudicating committee (see section 4.3.4.4. "Selection of the primary endpoints").

4.3.4.4. Selection of the primary endpoints

Asthma is a multidimensional disease. The use of different endpoints is encouraged as different measures assess different manifestations of the disease and may not correlate with each other. The selection of the most appropriate primary endpoint will depend on whether the drug is a reliever or controller medication and the drug's mechanism of action, and the grade of asthma severity/level of asthma control.

For any primary endpoint selected, the minimally important difference should be defined a priori, taking into consideration the severity of the patient population and disease characteristics, the control group, study duration and the hypothesis to be tested.

Reliever medication

For a new short-acting bronchodilator indicated as reliever medication, where the pharmacodynamics have been established clearly in earlier studies, the emphasis is on the measurement of airway obstruction. FEV1 measurements, adjusted for baseline and measured over time should be used as the primary endpoint in studies in adult patients with asthma.

Controller medication

A new treatment should demonstrate achievement or maintenance of asthma control and reduction in exacerbations. In general for a new controller treatment equal emphasis should be placed on lung

function and symptom based clinical endpoints. A significant benefit from co-primary endpoints of lung function and clinical symptoms should be demonstrated so that no multiplicity adjustment to significance levels is indicated.

For new anti-inflammatory drugs exacerbations are considered the variable of choice. However, although exacerbations are described for all grades of severity, their occurrence in mild asthma may be insufficient for their use as a variable in this population. In this case other symptomatic endpoints should be selected. Composite scores to assess asthma control can be used as co-primary endpoints. Whichever score is used should be validated. The components of a composite score should be individually analysed as secondary endpoints.

For a new bronchodilator drug to be administered as concomitant medication with inhaled corticosteroids, an effect on both lung function and exacerbations should be demonstrated. Pre-bronchodilator FEV1 and exacerbations should be considered as co-primary endpoints.

Specific immunotherapy

Products for specific immunotherapy are intended to modify the immunological mechanism underlying allergic asthma and thus require some time for onset of action. Therefore clinical trials start as add on therapy which has to be considered in the evaluation of the primary endpoint (e.g. evaluation in the context of a stepwise reduction of controller medication). Lung function, composite scores, number of exacerbations or reduced need for controller medication could be considered as primary endpoints.

4.3.4.5. 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 other secondary endpoints may provide useful information. These may measure different aspects of the disease and they should be justified through reference to published data supporting their validity.

A measure of lung function should always be included as a secondary endpoint if not considered to be a primary endpoint. Symptom scores (daytime and night-time symptoms), use of rescue medication, biomarkers, airway hyperrresponsiveness and quality of life should be considered as secondary endpoints, taking into account the drug's mechanism of action. The use of variables that are considered a target for the drug effect but are not commonly used in the development programme for drugs for use in the management of asthma are encouraged in order to validate new ways of assessing a treatment effect.

5. Clinical safety

5.1. Long-term clinical safety

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 safety a particular concern. Long-term safety data from at least 1 year of treatment should be provided.

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.

Clinically significant interactions with commonly co-prescribed medications, particularly for the elderly, and with drugs relevant to the metabolic pathways of the new drug should be studied.

5.2. Specific safety concerns

Inhaled therapy reduces systemic exposure and hence increases the margin of safety. However, specific safety concerns may arise from the use of 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 required.

Systemic safety should be assessed through both pharmacokinetic and pharmacodynamic/clinical studies and will depend on the pharmacotherapeutic group. For example the assessment of the systemic effects of inhaled corticosteroids in adults should include an appropriate sensitive measure of hypothalamic pituitary adrenocortical (HPA) axis function and the preferred pharmacodynamic method of assessing the HPA axis is the repeated assessment of the change from baseline in 24-hour plasma cortisol. Systemic effects of corticosteroids on bone mineral density and the eyes should also be assessed. The clinical assessment of systemic effects should be carried out at steady state.

6. Studies in the elderly

The elderly merit particular attention with regard to safety, see Note for Guidance on Studies in Support of Special Populations: Geriatrics (ICH Topic E 7). Separate efficacy studies are not necessary in the elderly provided there is adequate representation of elderly subjects in trials. Particular attention should be paid to the adequate utilization of inhalation delivery devices.

7. Studies in children

The high incidence of asthma in children makes this a target population of special relevance. Diagnosis of asthma in early childhood is challenging and is based mainly on clinical judgement, assessment of symptoms and physical findings. Asthma diagnosis in children has important consequences, should be used with caution and must be distinguished from other causes of persistent or recurrent wheeze. Episodic wheezing and cough is very common, even in children who do not have asthma, particularly in those under 3 years. 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 expected to be 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. Paediatric studies should be conducted as early as the development of the medicinal product allows, to avoid authorisation of the product in adults only, without an indication for use in children through lack of data. It is recommended that studies in children should commence as soon as potential benefit has been shown in adults and certainly prior to authorisation of the product in adults.

Sufficient data should be provided to allow the adequate assessment of risk/benefit for the three age ranges: under six years of age, 6-12 years of age, and over 12 years of age. A well defined population of children need to be studied in each age subset.

Specific immunotherapy in children younger than 5 years is not recommended in general. However since specific immunotherapy has an indication for treatment of the paediatric population, products for specific immunotherapy should be tested for efficacy and safety in paediatric populations. The efficacy of products for specific immunotherapy has to be evaluated in special trials in the paediatric population and not in combined trials with paediatric population and adults. Adolescents and adults can be investigated as a combined population. In general, all European regulations regarding this specific vulnerable population (e. g. ICH Topic E11, European Paediatric Board, etc.) have to be followed. In general the recommendations for studies in adults are also valid for studies in paediatric populations.

Children 6 years of age and older

Diagnosis of asthma in children 6 years and older should be based on the presence of clinical symptoms (wheezing, cough, breathlessness and chest tightness), history (recurrent symptoms, worsening in the presence of exercise, pollens, house-dust mites, worsening or occurrence of symptoms at night, atopy or family history of asthma), response to treatment and results of lung function tests (including bronchoprovocation and bronchodilatation tests). As the most frequently used inclusion criterion, i.e. >12 % improvement of FEV_1 in response to a short acting β_2 agonist is no longer seen in the majority of well-controlled asthmatic children, a more suitable inclusion criterion would be a > 10% drop of FEV_1 following induced bronchoconstriction and/or a 10% rise after inhaled short actingβ_2 agonist, particularly in children aged 6 –12 years.

Children younger than 6 years of age

In children below 6 years of age the diagnosis of asthma should be based on personal and family history of asthma, symptoms, physical examination and response to therapy with short-acting bronchodilators and inhaled glucocorticosteroids.

Lung function tests (spirometry) are not recommended to be used routinely in children below 6 years, however some tests (e.g. specific airways resistance, impulse oscillometry, FEV0.5 or FEV0.75) may be performed in specialised centres.

The most relevant diagnostic symptom should be the doctor's diagnosis of wheeze; additional symptoms should include dry cough, particularly nocturnal cough and cough and/or wheeze associated with exercise. In the differential diagnosis of recurrent wheezing the following possibilities have to be taken into consideration in this age group:

1. viral bronchitis/bronchiolitis
2. allergic rhinitis
3. obstruction involving large airways (laryngotracheomalacia, tracheal stenosis, bronchostenosis, vascular rings, enlarged lymph nodes, tumours, vocal cord dysfunction, foreign body aspiration into trachea or bronchus)
4. gastroesophageal reflux
5. cystic fibrosis
6. bronchopulmonary dysplasia
7. congenital heart diseases

Children included in clinical trials must be well characterised with regard to:

1. age at onset of symptoms

2. history of typical symptoms
3. history of exacerbations, severity of exacerbations
4. presence/absence of atopy and co-morbidities (atopic dermatitis, allergic rhino-conjunctivitis)
5. family history of atopy, particularly maternal history of atopy and IgE mediated allergic disease
6. prematurity and low birth weight
7. exposure to tobacco smoke
8. recurrent viral infections in early childhood.

The list of risk factors mentioned above is particularly important for younger children, but should be also taken into account in older children.

7.1. Inclusion criteria

Children 6 years of age and older

For children 6 years of age and older the following inclusion criteria for clinical trials are proposed

- Presence of clinical symptoms (wheezing, cough, breathlessness and chest tightness),
- Classification of asthma severity as outlined in section 4.1 (lines 180 – 191)
- History of asthma symptoms (recurrent symptoms, worsening in the presence of exercise, pollens, house-dust mites, worsening or occurrence of symptoms at night, atopy or family history of asthma) and response to treatment
- Lung function testing:
  - greater than 10% drop of FEV_1 following induced bronchoconstriction and/or a 10% rise after inhaled short acting β_2 agonist.

The inflammatory airway profile should be characterised if this is relevant to the mechanism of action of the test drug as outlined in section 4.1.

Children younger than 6 years of age

For children younger than 6 years the following inclusion criteria for clinical trials are proposed:

- lead symptom for inclusion: doctor diagnosed wheezing
- children 2 years and above:
  - history of at least 3 episodes of wheezing with or without nocturnal cough and exercise-induced wheeze/cough requiring and responding to β_2 agonist treatment

    and
  - where two of these episodes require unscheduled healthcare utilization

    and
  - where one of these episodes is doctor confirmed

    and
  - where one of these episodes needs to have occurred within the 6 months prior to enrolment.

- children 6 months to less than 2 years:
  - a minimum number of 2 episodes of wheezing requiring unscheduled healthcare utilization and each involving treatment with a β_2 agonist; one of these episodes needs to be doctor confirmed and one needs to have occurred within 3-6 months prior to enrolment.

The inclusion of infants younger than 6 months in clinical trials to evaluate drugs for the management of asthma is not recommended.

7.2. Endpoints

Children 6 years of age and older

The primary endpoint should be asthma control and change in lung function, using composite scores as outlined in section 4.2

In children, asthma control means minimal or no symptoms , minimal or no use of rescue medication and no activity limitations. Examples of composite scores validated for use in children are Asthma Control Test (ACT), Asthma Therapy Assessment Questionnaire (ATAQ or the Asthma Control Scoring System (ACSS).

In exercise-induced bronchoconstriction /asthma the primary endpoint should be fall in FEV1 after exercise using a standardised (treadmill) exercise test.

Children younger than 6 years

The primary endpoint should be asthma control, such as number of exacerbations, diary based symptom episodes, number of hospitalisations for wheeze exacerbations (a sufficient asthma trial duration of at least one year is needed), need for systemic corticosteroids. An example of composite score validated for use in children younger than 6 years is the Asthma Control Questionnaire (ACQ), also the “Test for Respiratory and Asthma Control in Kids” (TRACK) was reported with good sensitivity/specificity.

No validated and standardised endpoints are currently available for assessment of exercise-induced asthmatic symptoms in children less than 6 years of age. Children below the age of 6 years are not expected to reliably comply with the standardised (treadmill) exercise test.

7.3. Trial design

Design of the study should depend not only on the investigational product but also on severity of asthma.

Children 6 years of age and older

In children 6 years and older, in whom asthma can be reliably diagnosed, 3-arm studies (study drug – placebo – active comparator (standard of care)) are preferable. New biological treatments should be studied in comparative trials, demonstrating superiority over standard treatment or as add-on to standard treatment in those patients uncontrolled on low-dose ICS.

Children younger than 6 years of age

Due to differences in asthma pathology extrapolation of data from adults or older children is not considered appropriate. Currently there is little evidence of the efficacy of marketed drugs for the treatment of asthma in this age group; therefore placebo-controlled studies of one year duration are

needed. A pre-requisite must be clear pre-specified criteria for initiation of standardised rescue treatment and for drop-out/withdrawal from the study.

7.4. Safety

Long- term safety assessment is of particular interest in the paediatric population for whom longer treatment periods are expected. This applies mainly for controller medications but also to reliever medications depending on how frequently they are used.

The effect of corticosteroids on growth, skeletal changes, endocrinology and immune function should be addressed. Monitoring of local side effects of chronic inhaled corticosteroids such as oral candidiasis, dysphonia and cataracts should also be included in paediatric studies.

New agents that interact with the immune system deserve particular attention particularly because the immune system is under development up to the age of 12 years. Possible consequences on immune defence or immune suppression should be evaluated. The duration of action of the drug 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 safety and efficacy measures should be addressed according to potential risk identified in the RMP.

7.5. Selection of delivery devices

Particular attention should be paid to the effects of age on the adequate function of inhalation delivery devices. For children under 6 years of age with chronic asthma both corticosteroid and bronchodilator therapy should be routinely delivered via a pressurised meter dose inhaler (pMDI) and a specific named spacing device for use with the particular pMDI and with a facemask where necessary. The choice of device within the range of pMDIs and spacers available should be governed by individual need and the likelihood of compliance. Where this combination is not effective, depending upon the child's condition, nebulised therapy may be considered.

For children aged 6 years and older a dry powder inhaler (DPI) may also be considered. In contrast to pressurized and non-pressurized MDIs, some DPIs show a variable flow dependency in their deposition characteristics. Therefore characterisation of flow rate dependency in the patient populations in whom the DPI is to be used should be presented. The CHMP Guidance referred to in section 3 and which discusses the requirements for clinical documentation for orally inhaled products (CPMP/EWP/4151/00) needs to be taken into consideration for a proper characterisation of drug and device combination.

Overall, the design of any clinical trial in children with asthma with an inhalation device should take the following into account:

- it is important to use an inhaler device which is appropriate for the age group concerned. This applies to both the test and reference treatment groups. All medications delivered via pMDI should always be administered with an age appropriate spacer device attached.
- The concomitant use of inhaler devices which necessitate different inhalation manoeuvres is not recommended as this might be confusing and can lead to poor inhalation technique with at least one of the devices.
- Both the child and the caregiver should be trained to use the inhalation device correctly. A correct inhalation technique is often lost over time and therefore inhalation instructions should be given repeatedly to achieve and maintain correct inhalation technique in children with asthma. Patients

should demonstrate their inhalation technique, and relevant instructions and corrections should be provided at every visit.

- Compliance has to be objectively checked, dose counters or weighing of canisters are acceptable methods in this regard. Inhaler devices intended for the paediatric population should include a dose counter and feedback should be provided to patients/caregivers on the correct use of the inhaler.

Definitions

Asthma: chronic inflammatory disorder of the airways caused by the interaction of genetic and environmental factors and characterised by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation.

Asthma severity: the difficulty in controlling asthma with treatment. Severity is based on the intensity of treatment required to control the patient's asthma.

Asthma control: the extent to which the various manifestations of asthma have been reduced or removed by treatment. According to GINA guidelines, asthma is controlled when a patient have daytime symptoms only twice or less per week, have no limitations of their daily activities, have no nocturnal symptoms, no exacerbations, normal or near normal lung function and use of reliever medication twice or less per week.

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