Guideline on the clinical investigation of medicinal products for the treatment of asthma

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Executive summary

This document is a revision of the 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 section on 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 allergen immunotherapy for the treatment of allergic asthma, scientific advice from the national competent authorities or CHMP is highly recommended.

1. Introduction (background)

Asthma affects 3% to 9% of the European population. Its prevalence increased in the latter part of the 20th century, but in Western Europe appears to have remained stable in the last decade. 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 practice guidelines. 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. 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 underlying inflammation. Asthma is a heterogeneous disease in its manifestations and also in its response to treatment. Several clinical and inflammatory asthma phenotypes have been described recently including e.g. early-onset mild allergic asthma, later-onset asthma associated with obesity, and severe non-atopic asthma with frequent exacerbations. The elucidation of asthma phenotypes is being further refined by identifying endotypes based on pathophysiologic mechanisms present in different groups, e.g. aspirin-exacerbated respiratory disease, and neutrophilic asthma. Recently attention is given to the overlap of asthma and COPD syndrome (ACOS). Further investigations are ongoing to characterise asthma populations and validate different phenotypes. 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 Guideline 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. Five treatment steps are distinguished, each step representing a treatment option for controlling asthma in patients 5 years of age and older. GINA proposes a classification of asthma severity by the type and intensity of controller medication required for the control of the disease (Step 1-5) for investigational purposes. GINA also proposes a classification in three categories (mild, moderate and severe asthma) assessed retrospectively once the patient is on regular controller treatment for several months.

The GINA Workshop Report classifies drug treatments as controllers or relievers. Controllers are taken daily and long-term and include both anti-inflammatory drugs (inhaled corticosteroids, leukotriene modifiers, anti-IgE treatment, oral corticosteroids) and long-acting beta agonists. 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 one long-acting β_2 agonists). A new category has recently been included, i.e. add-on therapies for patients with severe asthma, which include additional therapeutic options that may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high dose controller medications and treatment of modifiable risk factors. In addition allergen immunotherapy is available for allergic asthma although its specific role is not established yet.

European and US treatment 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 development and 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:

- 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)

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

- Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMA/CHMP/EWP/147013/04)

- 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)

- 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;

- Guideline on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)

- Guideline on the Choice of control group in clinical trials (CPMP/ICH/364/96)

- 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 Rev.1)

- 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. Rev. 1)

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 (FEV_1) and forced vital capacity (FVC), is the preferred method to assess airflow limitation, its reversibility and variability. The reversibility of FEV_1 after inhalation of a short-acting β2 adrenergic agonist should normally be greater than 12% 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 records. Peak expiratory flow (PEF) measurements can also be used to diagnose asthma but may 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.

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 symptomatic chronic or acute respiratory infection. Criteria for defining stability should be stated in the study protocol.

For clinical studies to investigate the efficacy of allergen 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 and systemic profile should be characterised if this is relevant to the mechanism of action of the test drug; for example, baseline eosinophilia (e.g. sputum), fractional concentration of exhaled nitric oxide (FENO), IgE production or cytokines if that aspect of the immune system is targeted by the investigational product. The usefulness of FENO as a biomarker is not yet determined.

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. If the expected target of a given medicinal product is only patients with a certain degree of asthma severity, the studies should focus on that population. The criteria used to classify severity of asthma should be clearly established in the protocol and be in line with 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 treatment required to maintain control is an important issue to be considered. Patients' compliance to medication should also be evaluated before the start of the study. 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. The term Asthma COPD Overlap Syndrome has recently been proposed for a patient population with a similar number of features of both asthma and COPD. However, the clinical experience with this new defined group is fairly limited and will be achieved the coming years. Ideally the aim should be to study a homogenous population of patients with asthma. For the definition of COPD and its separation from asthma for patient recruitment into clinical trials, see also the CHMP Guideline on Clinical Investigation of Medicinal Products in the Treatment of Chronic Obstructive Pulmonary Disease (COPD) EMA/CHMP/483572/2012. Patients with predominantly COPD should be excluded from studies in asthma.

It is recommended that stratified randomisation is used to reduce the chance of imbalances in important prognostic factors such as prior number of exacerbations, smoking history, or prior use of beta 2 agonists. Depending on the mechanism of action of the medicinal products, other relevant factors might be considered.

Subgroup analyses of known prognostic factors (some of which will be stratification factors in the randomisation) should be predefined in the study protocol, according to the recommendations made in the relevant guidelines. Examples of relevant subgroups to consider are age, frequency of exacerbations, smoking status, known hypersensitivity to NSAIDs status, eosinophilia, sensitisations to different allergens, presence of allergic comorbid conditions, and obesity. The selection of the most relevant subgroups should be made on a case by case basis. It is expected that consistent effects in the relevant subgroups are shown to provide clear evidence of efficacy in the requested study population.

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. Sufficient numbers of smokers should be included in the studies to explore whether the size of clinical benefit in smokers is consistent with that seen in non-smokers. 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.

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

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. It can also be used to monitor the anti-inflammatory effect of inhaled corticosteroids, provided that the FEV_1 is not influenced by the concomitant use of bronchodilators. Therefore a sufficient washout period is needed i.e. the time that the FEV_1 returns to baseline. The relationship between FEV_1 and symptoms experienced by patients 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 home monitoring of lung function.

Whichever measure of airway obstruction is chosen the reproducibility and sensitivity of the method should have been validated. 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. 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.

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 treatment guidelines as an important component in the achievement of asthma control. The definition of exacerbation and the severity of the exacerbation should be specified in the study protocol. The

definition should be in line with generally accepted treatment guidelines. The following definitions for exacerbations may be considered:

Severe exacerbations of asthma are usually defined as a requirement for systemic corticosteroids or an increase of the maintenance dose of oral corticosteroids for at least three days and/or a need for an emergency visit, hospitalization or death due to asthma. The protocol should establish the requirements to consider changes in disease activity as a new exacerbation and not part of the previous episode, e.g. two courses of systemic corticosteroids separated by at least 1 week are regarded as separate exacerbations.

Moderate exacerbations are usually defined 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 reliever medication, deterioration in lung function, which last for two days or more but 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.

Regardless of the definition finally used, exacerbations should be confirmed with objective evidence of asthma deterioration by the investigators.

Patients with a history of frequent exacerbations should be recruited. The methods used to analyse this endpoint (as percentage of patients, annualized rate, time to event) should be justified as should the change in exacerbations thought to be clinically relevant. The length of the study should be of sufficient duration to capture these events and dependent on the agent under study and the severity of asthma in the patient population. During the trial it is useful 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.

Reliever use: The increased use of reliever (rescue) 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 short-acting 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 short-acting β_2 agonist is required and the number of actuations required during both the day and the night.

Composite scores: 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 based on individual variables that are considered of value in the assessment of the impact of treatment on several aspects of asthma control. Examples of categorical composite variables are 'asthma control days' or 'well-controlled'/'total control' asthma weeks. Numerical composite variables score several clinical symptoms or signs on a scale and give a numerical score to represent control. In some composite scores lung function or markers of airway inflammation are part of the variable. Examples of composite scores are the Asthma Control Test (ACT) or the Asthma Control Scoring System (ACSS), the Asthma Control Questionnaire (ACQ) and the Asthma Therapy Assessment Questionnaire (ATAQ). Measures to enhance

patients' compliance with questionnaire completion should be considered. When constructing composite scores both the individual and the composite variables should be validated and the appropriateness of the cut-point values to distinguish "control" versus "lack of control'" and the weight of each component should be justified. The analysis of the composite variable could be provided in absolute terms and as a proportion of patients achieving a defined target level of control, i.e. a responder analysis. The components of the composite variable should also be individually analysed in order to know if the overall effect is driven by a single or a small number of variables.

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

Airway hyperresponsiveness and challenge testing: Challenge testing with 'direct' (methacholine, histamine) and 'indirect' (mannitol, adenosine monophosphate, hypertonic saline) agents are a measure of the tendency of airways to narrow in response to a stimulus that has little or no impact in normal individuals. In the case of clinical studies for allergen specific immunotherapy, challenge testing with an appropriate allergen can be considered. The objective of challenge testing 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. Challenge testing is difficult to perform and particularly to standardise. Therefore, it might well be included as an exploratory variable for single/a few centres and for small numbers of patients considered to be representative of the overall population to be studied. 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.

Biomarkers of airway inflammation: Some measures have been developed for the assessment of airway inflammation and provide supportive information. For example, eosinophil counts and fractional concentration of exhaled nitric oxide (FE_{NO}) provides information about the underlying disease activity in eosinophilic asthma, although their value to guide treatment remains to be established. Thus, at present these are only considered exploratory endpoints.

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, such as AQLQ-S and Mini-AQLQ, have been validated. The use of a specific questionnaire and the differences 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. Pharmacodynamic studies might need to be double blind and placebo controlled. They may involve patients or healthy volunteers although the effect of asthma severity on the pulmonary deposition, and thus on pharmacodynamics, of inhaled drugs may limit interpretation of data from non-asthmatic subjects'.

For dose selections and pharmacodynamics studies: please refer also to guideline on the clinical development products for specific immunotherapy for the treatment of allergic diseases (Doc. Ref. CHMP/EWP/04/2006).

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 subsequent metabolism and elimination is expected.

The absence of pharmacokinetic studies for allergen immunotherapy or certain immunomodulators is accepted as long as it is not possible to measure the active substance. However, if possible, plasma concentrations should be measured

4.3.3. Therapeutic exploratory studies

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

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

The dose related benefit and adverse effects should be characterised in randomised, double blind, placebo controlled studies. These studies should characterise the dose response curve. It may be useful to include one or more doses of an active control drug. 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.

The final study design will depend on the pharmacology of the test product. Studies of short duration, the duration depending on the mechanism of action of the drug and the selected endpoints, may be sufficient. For example, for long-acting bronchodilators 6-12 week studies may be acceptable, 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.

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.

For allergen immunotherapy provocation tests, using either a bronchial allergen challenge or allergen challenge in an environmental exposure chamber (measurement of symptoms and lung function), 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 allergen 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. Evidence of lack of tolerance with repeated courses should be provided.

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. The established use of inhaled corticosteroids as first choice controller treatment for most patients makes them the comparator of choice.

Allergen immunotherapy

Clinical trials of products for allergen immunotherapy are expected to be parallel group, double blind, randomised, and placebo controlled. Alternative study designs should be explained and justified by the sponsor. Normally the investigational medicinal product should be studied 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 autumn/winter 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 widely used 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 patients with milder asthma, 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 where patients are randomised to receive either the test treatment or the standard treatment for the 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, particularly if a non-inferiority hypothesis is being tested in order to ensure assay sensitivity. These studies are normally carried out in patients with less severe forms of persistent 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 on top of standard background medication are required. A third arm should be considered. In this case, the comparator(s) should correspond to the next treatment step according to guidelines (i.e. increase in inhaled corticosteroid dose or adding a long acting bronchodilator to inhaled corticoids). However, in patients already receiving optimal dose of inhaled corticosteroid associated with a long acting bronchodilator, placebo controlled studies in add-on to optimal background medication might suffice.

Concomitant treatments

It should be established that the patients' existing therapy is appropriate for the severity of their asthma. Concomitant rescue medication should never be denied. Concomitant and rescue 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, and mucolytic antioxidants should be accurately recorded and balanced, at least for those critical, among treatment groups at baseline. A run-in phase 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 a double blind study is not feasible (for example, some inhalers are difficult to blind), 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. 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 clinical relevance of the findings should be contextualised in relation to the severity of the patient population and disease characteristics, the control group, study duration and the hypothesis to be tested. A predefined responder analysis, or a range of analyses, might be used to facilitate the interpretation of outcome data

Reliever medication

For a new bronchodilator indicated as reliever medication, where the pharmacodynamics has been established clearly in earlier studies, the emphasis is on the measurement of airway obstruction. FEV_1

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

In general for a new controller treatment the preferred endpoint is exacerbations. Measurement of lung function parameters alone is considered to be insufficient in the assessment of therapeutic effect. Lung function should be measured either as a co-primary or a key secondary endpoint.

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 less severe persistent 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.

In principle, for a new long-acting bronchodilator drug to be administered as concomitant medication with inhaled corticosteroids, an effect on both lung function and exacerbations should be demonstrated. In case LABD were to be investigated in less severe forms, the previous considerations made for anti-inflammatory drugs could also apply.

Allergen immunotherapy

Products for allergen 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. Regardless of the choice of the primary efficacy parameter, the applicant should provide a definition of a clinically meaningful effect in the primary efficacy endpoint and the basis for choosing this value.

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 various 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. 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 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.

5.2. Long-term clinical safety

The duration and intensity of asthma 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 for controller treatments 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 leukocyte 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.

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 patients 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. 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).

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. It is recommended that studies in children should commence as soon as potential benefit has been shown 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 13-17 years of age. A well-defined population of children need to be studied in each of these age groups unless a waiver can be justified. Extrapolation from adult data in children of six years of age and older is not generally acceptable, unless justified and discussed on a case by case basis as reflected in section 7.3. However data on PK and/or PD in children will be needed in all age groups. In general, European regulations regarding this specific vulnerable population (e. g. ICH Topic E11, European Paediatric Board, etc.) have to be followed. The recommendations for studies in adults are also valid for studies in paediatric populations.

Allergen immunotherapy in younger pre-school children is not recommended in general. However since allergen immunotherapy can be used for treatment of the paediatric population, such products should be tested for efficacy and safety in paediatric populations. The efficacy of products for allergen immunotherapy should be evaluated in special trials in the paediatric population and not in combined trials including children and adults. Adolescents and adults can be investigated as a combined population.

7.1. Selection of patients

Diagnosis of asthma in early childhood is challenging due to difficulties in performing lung function tests and therefore it is mainly based on clinical judgement, assessment of symptoms and physical findings. A diagnosis of asthma in children has important consequences and therefore should be made with caution and must be distinguished from other causes of persistent or recurrent wheeze. Episodic wheezing and cough is very common, particularly in those under 3 years.

Children ≥6 years of age and adolescents

Diagnosis of asthma in children 6 years and older should follow the recommendations stated in the relevant clinical guidelines and be based on the presence of respiratory symptoms, history, response to treatment and results of lung function tests (including reversibility tests). Spirometry is the best lung function test for diagnosing asthma and for measuring lung function when assessing asthma control. In children, an obstructive pattern on spirometry is defined as a FEV_1/FVC ratio <80-85%. Assessment of absolute improvement in FEV_1 following a short-acting bronchodilator might also be considered in diagnosis. 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, the reversibility criteria for diagnosis could be provided by the patient's medical records. In some cases, bronchial provocation tests to assess airway hyperresponsiveness (direct or indirect) may help to establish diagnosis.

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

In children younger than 6 years of age the diagnosis of asthma should be based on personal and family history of asthma and atopy, symptoms, physical examination and response to therapy with short-acting bronchodilators and inhaled glucocorticosteroids. No accurate screening tests have yet been developed to determine which young children with recurrent wheezing will develop asthma.

The most relevant diagnostic symptom is the physician´s diagnosis of wheeze; additional symptoms should include dry cough, particularly nocturnal cough and cough and/or wheeze associated with exercise, or intercostal retractions. In the differential diagnosis of recurrent wheeze causes other than asthma should be considered and excluded.

Lung function testing, bronchial provocation testing and other physiological tests do not have a major role in the diagnosis of asthma in children younger than 6 years due to the inability of most children to perform expiratory manoeuvres; however some tests (e.g. specific airways resistance, impulse oscillometry, $FEV_{0.5}$ or $FEV_{0.75}$) may be carried out in specialised centres. The type of lung function tests should match age-related capacities of the cohort to be investigated.

Children included in clinical trials should be well characterised with regard to: age at onset of symptoms, history of typical symptoms, asthma severity, history of exacerbations, severity of exacerbations, presence/absence of atopy and co-morbidities, family history of atopy, particularly maternal history of atopy and IgE mediated allergic disease, prematurity and low birth weight, exposure to tobacco smoke, recurrent viral infections in early childhood.

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

7.2. Methods to assess efficacy

As for the adult population, exacerbations, symptom scores, lung function, use of rescue medication and composite scores developed to measure asthma control are considered relevant efficacy endpoints.

The use of core outcome sets (COS) is recommended to allow comparisons of the results across clinical trials when investigating controller medications. COS should include asthma control (symptom scores, exacerbations and change in lung function).

Children ≥6 years of age and adolescents

The considerations made in Section 4.2 for the adult population can be followed for this subset of patients.

The goal of treatment is to achieve good control of symptoms and to reduce the risk of exacerbations. In children, asthma control means minimal or no symptoms, minimal or no use of rescue medication and no activity limitations. Thus, for a controller medication the effect on exacerbations and other symptomatic endpoints remain relevant endpoints for this subset of patients.

In general, lung function tests are not enough for the demonstration of efficacy for a controller medication. Lung function tests (e.g. FEV1) might be valid endpoints for a reliever medication. In exercise-induced bronchoconstriction /asthma the relevant endpoint should be the prevention of a fall in FEV1 following exercise using a standardised (treadmill) exercise test.

A number of composite scores for the assessment of asthma control have been developed and specifically validated for use in children above 6 years of age. Examples of composite scores validated for use in children are "Childhood Asthma Control Test" (C-ACT), "Asthma Therapy Assessment Questionnaire" (ATAQ) or the "Asthma Control Scoring System" (ACSS).

Children younger than 6 years

As for older children, the goal of treatment is to achieve good control of symptoms and to reduce the risk of exacerbations. In children, asthma control means minimal or no symptoms, minimal or no use of rescue medication and no activity limitations. Thus, for a controller medication the effect on exacerbations and other symptomatic endpoints remain relevant endpoints for this subset of patients.

Lung function tests (spirometry) cannot reliably be performed in children younger than 6 years, so their role in the assessment of efficacy of medicinal products is limited in this subset of patients, particularly in the youngest children.

Composites endpoints have been validated for use in children younger than 6 years. Examples include the "Paediatric Asthma Control Diary (PACD)" and the "Test for Respiratory and Asthma Control in Kids" (TRACK).

No validated and standardised endpoints are currently available for the assessment of exercise-induced asthmatic symptoms in children younger 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

7.3.1. PK/PD Studies

Data on PK and PD in children will be needed in order to establish the optimal dose in this population. Population PK modelling may help supporting the dosing used in the paediatric asthma Phase III studies. In the case of adolescents, if the PK results demonstrate similar exposure to that seen in adults, this age group could be enrolled in the adult asthma Phase III studies. In the younger age groups, 6 to <12 and then 2 to <6 years of age, PK studies could be used to confirm the dose. However, safety and efficacy studies need to be conducted according to their ages.

PK assessment should take into account restrictions on number and volume of PK samples. Reference can be made to the guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population.

7.3.2. Confirmatory studies

As for the adult population, design of the study should depend not only on the investigational product but also on severity of asthma.

Reliever medication

For a reliever medication extrapolation of the clinical data from adults may be acceptable depending on the mechanism of action of the medicinal product and based on similar PK/PD and known safety profile of the medicinal product. If confirmatory data were deemed necessary, the considerations made for the assessment of efficacy of reliever medications in adults would apply for children ⩾6 years of age and adolescents. Children below 6 years are not expected to be included in confirmatory trials for reliever medications, although PK data should be generated.

Controller medication

Children ≥6 years of age and adolescents

Extrapolation of efficacy from adult data to children of six years of age and older is not generally acceptable unless justified and that could usefully be the subject of scientific advice discussions. Paediatric efficacy/safety studies will be needed for new drugs or medications with a new mode of action.

Adolescents can be included in the adult population studies based on similar PK exposure and on the known safety profile of the medicinal product.

Children from 6-11 years of age should be studied separately, as the treatment stepwise approach may differ from those followed in adults/adolescents.

Double blind, randomised, parallel group trials are recommended. Active controls are especially valuable in the lower grades of severity, as there are established treatment regimens (e.g. addition of LABAs if patient is uncontrolled on ICS).

Three arm studies (study drug – placebo – active comparator (standard of care)) are preferable, particularly if the purpose is establishing non-inferiority of new therapy over the standard therapy. Placebo controlled trials are possible in mild grades of severity if adequate rescue medication is available.

In higher grades of severity, study drugs are added to standard therapy and not administered as mono-therapy. In this case a placebo-controlled trial with add-on design (standard therapy +study drug versus standard therapy +placebo) with adequate rescue medication would be the preferred design.

Selection of the primary endpoint for confirmatory studies will depend on the whether the test drug is a reliever or a controller medication, the drug mechanism of action and the grade of asthma severity. The considerations made in Section 4.3.4.4 for the selection of the primary endpoints apply for this subset of patients.

Study duration will depend on the selected endpoints. For a controller medication at least 6 month duration may be required. Longer duration (e.g. one year) will be needed for the assessment of exacerbations. A pre-requisite must be clear pre-specified criteria for initiation of standardised rescue treatment and for drop-out/withdrawal from the study.

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. Depending on the availability of authorised comparators, placebo-controlled studies on top of SOC or a comparison with approved standard of care are needed. The duration of the efficacy studies depends on the chosen design and end-points and may therefore be variable, provided that it can be justified. If evaluation of the number of exacerbations is chosen, study duration is suggested to be one year. Studies must be long enough in order that it is possible to draw conclusions in respect of the chosen endpoint. As for the older age groups, clear pre specified criteria for initiation of standardised rescue treatment and for drop-out/withdrawal from the study should be established.

Allergen immunotherapy

The recommendations for studies in adults in Section 4.3.4. are also valid for studies in paediatric populations.

7.4. Safety

Long-term safety assessment of at least one year duration is required in children when longer treatment with a new drug is intended. This applies mainly for controller medications but also to reliever medications depending on how frequently they are to be used.

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

New agents that interact with the immune system deserve particular attention 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 Risk Management Plan (RMP).

7.5. Selection of inhalation delivery devices

Particular attention should be paid to the effects of age on the adequate function of inhalation delivery devices. 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. For children under 4 years of age both corticosteroid and bronchodilator therapy should be routinely delivered via a pressurised metered-dose inhaler (pMDI) and an age appropriate 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 spacing devices 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 4 years and older a dry powder inhaler (DPI) may be considered although special attention should be paid as to whether children aged 4 to 6 years have the ability to use such a device correctly. In comparison to pressurized and non-pressurized MDIs, the deposition characteristics of DPIs are more flow dependant. Therefore characterisation of flow rate dependency in the range of flows/pressure drops 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. Rev1) needs to be taken into consideration for a proper characterisation of drug and device combination. Unless otherwise justified (e.g. rescue medication), 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. Patients should demonstrate their inhalation technique, and relevant instructions and corrections to use should be provided at every visit.

Compliance should be objectively checked, dose counters or weighing of canisters are acceptable methods in this regard.

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 has 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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