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# COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

# GUIDELINE ON THE CLINICAL DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF ALLERGIC RHINO-CONJUNCTIVITIS

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# GUIDELINE ON THE CLINICAL DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF ALLERGIC RHINO-CONJUNCTIVITIS

This Guideline is intended to address issues of study design, efficacy and safety for new drugs being developed for the symptomatic treatment and overall pharmacological management of allergic rhino-conjunctivitis. The Guideline should be read in conjunction with Directive 2001/83/EC, as amended, and all other pertinent elements outlined in EU and ICH guidelines:

CPMP/EWP/908/99 CPMP Points to Consider on Multiplicity issues in Clinical Trials (CPMP Adopted September 2002)

CPMP/EWP/482/99 Points to Consider on Switching between Superiority and Non-inferiority (Adopted July 2000)

CPMP/EWP/1776/99 Points to Consider on Missing Data (Adopted November 2001)
CPMP/2330/99 Points to Consider on Application with 1.) Meta-analyses and 2.) One Pivotal study (adopted by CPMP May 2001)
CPMP/EWP/2863/99 Points to Consider on Adjustment for Baseline Covariates

CPMP/EWP/2922/00 Note for Guidance on the Clinical Investigation of Medicinal Products in the treatment of Asthma (CPMP adopted November 2002)

Topic E11 Step 4 Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population. (CPMP/ICH/2711/99 - adopted July 2000)
Topic E9 Step 4 Note for Guidance on Statistical Principles for Clinical Trials. (CPMP/ICH/363/96 - adopted Mar.98)

Topic E10 Step 4 Note for Guidance on Choice of Control Group for Clinical Trials (CPMP/ICH/364/96 - adopted July 2000).

## INTRODUCTION

Allergic rhino-conjunctivitis is an allergen-induced inflammatory response. The non-infective, seasonal (SAR) and perennial allergic rhino-conjunctivitis (PAR) are the most common types and result from an immunological response mediated by IgE. There is also a Th2 cell component - accounting for chronic symptoms. Histamine is a well-known mediator responsible for the signs and symptoms of SAR but many other mediators including leukotrienes and prostaglandin $D_2$ are involved. SAR is caused by allergens released by tree, grass or weed pollination (and spores and moulds), whereas PAR results from allergens such as animal dander, dust mites and less frequently from allergens such as cockroaches or mould spores. Asthma and allergic rhino-conjunctivitis are common co-morbidities. Symptoms are both nasal and non-nasal. The most prominent nasal symptoms are itching, sneezing, rhinorrhoea and congestion. Non-nasal symptoms commonly associated with allergic rhinitis include tearing, eye itching and redness. Allergic rhino-conjunctivitis is most prevalent during school age years. Allergic rhino-conjunctivitis is rare before 5 years of age.

In the evaluation of SAR and PAR, there is a wide variety of study designs in terms of study duration, end-points chosen, analysis of data etc. Assessment and comparison of results between studies are difficult. In both, there are particular problems associated with the evaluation of products because it is difficult to control the environmental variables.

The developmental programme for drugs for the treatment of allergic rhino-conjunctivitis may frequently fail to show effectiveness, due in part to the subjective nature of the

assessments, variability in allergen exposure and spontaneous variability of the disease. This makes the use of randomisation, placebo control and blinding of crucial importance.

Although SAR/PAR can alter school performance and work productivity it is not a serious life-threatening disease. It is imperative therefore that the agents used in this condition are safe, given their repeated and often long-term use.

SAR and PAR are alike in terms of disease mediators and manifestations, with differences between the two entities primarily based on the duration of the disease. Many patients with PAR may have concomitant SAR therefore PAR trials should be conducted during autumn and winter. Given that these products are given over a whole season in SAR and over a long time period in PAR, safety over an adequate time period should be established. SAR and PAR are discussed simultaneously in the note for guidance.

Developmental programmes for oral, parenteral and topical (intranasal/ocular) drug products for the treatment of intermittent and persistent allergic rhino-conjunctivitis in children and adults will be discussed. Symptomatic agents include antihistamines, decongestants, anticholinergics, chromones and anti-leukotrienes. Chromones are also used in a preventive capacity. Intranasal cortiosteroids are the mainstay for persistent symptoms and are used in a preventive capacity. This NfG does not cover the use of specific immunotherapy and anti-IgE agents.

In this NfG a distinction is made between products used to treat acute symptoms and products used to prevent symptoms.

## I PATIENT CHARACTERISTICS AND SELECTION OF PATIENTS

### Diagnosis

It is difficult to ensure that a subject has a single allergy and more often, subjects have a combined allergic diathesis.

For SAR efficacy trials patients should have a well-documented history of SAR before study entry. Although allergic rhino-conjunctivitis remains a clinical diagnosis, there should be documentation of sensitivity by positive skin testing and/or validated IgE (RAST, Western Blot), to the relevant seasonal allergen for the geographic area.

Likewise for PAR trials, allergy to dust mites, cockroaches, cats, dogs, moulds should be documented by skin testing and/or validated IgE (RAST) before study enrolment.

Patients enrolled in acute treatment studies should be experiencing symptoms or exceeding an appropriate minimum level of symptoms at the time of enrolment.

Patients who have received anti-allergy immunotherapy (desensitising subjects with increase of allergen challenges) in the previous two years or are still receiving this kind of therapy are not eligible for study enrolment.

For products aimed to prevent symptoms, subjects should have a well-established history of allergic rhino-conjunctivitis warranting preventive treatment.

### Co-morbidity

Rhinitis and asthma frequently occur in the same patient. Patients with asthma co-morbidity might be included for obtaining safety data. A claim of efficacy in asthma however should be established according to the NfG concerning asthma.

### Co-medication

All drugs taken must be known and patients taking any that could affect their response during the study should not be enrolled. This includes co-medication used in asthma patients.

## II METHODS TO ASSESS EFFICACY

### Choice of end-points

Symptomatic relief

*Primary efficacy analyses*

In allergic rhino-conjunctivitis trials primary measures of efficacy are patient self-rated symptom scores. Symptom scores should be collected at baseline and daily over the course of the trial. The length of the baseline period should be defined and justified. It is recommended to score the symptoms at least daily. The patient should report on his status and symptoms over the previous period of 24 hours. For SAR, scoring in the evening time is recommended while in PAR, scoring on awakening might be more appropriate.

There are no standardised and generally accepted scales for scoring nasal and eye symptoms/signs in SAR/PAR studies. The symptom rating scale should be clearly defined, balanced and easily understood by both patient and physician. The development of validated scales is encouraged.

In general, the main nasal symptoms are rhinorrhoea, blocked nose, sneezing and itching. The main eye symptoms are tearing, itching and redness. These should be scored. Other symptoms/signs may be scored as well. As the use of rescue medication indicates insufficient control of symptoms the symptom score may need adjustment allowing for the use of any rescue medication.

The scores should be presented in a main symptom sum-score[1], nasal symptom sum-score and/or eye symptom sum-score, depending on the condition studied. If symptom sum-score used in- or excludes symptoms/signs other than the main ones mentioned above, this should be justified.

An appropriate primary efficacy endpoint is the change from baseline in the relevant patient symptom sumscore during the entire double-blind period. The applicant should provide a value for a clinically meaningful change in the primary efficacy endpoint and the basis for choosing this value. A merely statistical significant difference of xx points on a scale might not be sufficient. An analysis in terms of responder (e.g. patients with a 50% reduction in symptom score) might be helpful.

For an efficacy claim in allergic rhino-conjunctivitis, efficacy for the nasal and eye symptom-score should be proven separately e.g. as the symptom-score is a composite scale, the overall effect should be balanced so that e.g. i.e. the overall outcome is not driven by a large effect on a limited number of items and no effect or even worsening in the other items of the scale. The lack of effect in any symptom(s) should be discussed.

*Secondary efficacy analyses*

These may include the individual patient-rated symptoms, symptom-free days, physician-rated symptoms and signs, clinical global improvement (CGI), predefined area under curve (AUC) and validated HRQoL scales. Rescue medication should form part of secondary efficacy analysis.

[1] The main symptom sum-score is the sum of scores of the core symptoms.

Secondary efficacy analyses may be used to indicate; time to maximal effect, and onset of action.

Preventive medication

*Primary measures of efficacy*

Days of freedom from symptoms or in the event of symptoms occurring the number of days of no or minimal symptoms as predefined, is considered an appropriate endpoint. Other endpoints could be considered if justified.

Secondary efficacy analyses

These may include the individual patient-rated symptoms, use of rescue medication, symptom-free days, physician-rated symptoms, cgi, predefined AUC. These may be used to indicate time to maximal effect and onset of action.

## III STRATEGY AND DESIGN OF CLINICAL TRIALS

Given the multiple possible combinations of signs/symptoms in the primary and secondary analyses and the numerous repeated measures in individual patients there are unfortunately, opportunities in SAR/PAR studies for post hoc changes in definition of primary efficacy and in analysis set redefinition of the pollen season etc.

Therefore in SAR/PAR a detailed analytical section in the study protocol is of importance. In its absence it will not be possible to decide whether claims are data-driven or not. Further even if all is defined a priori, multiplicity has to be taken into account. Referral should be made to the PtC for Multiplicity and ICH9 on statistical principles.

**Use of rescue medication**

If rescue medication is allowed, the kind of rescue medication should be clearly stated in the protocol. This should be standardised and preferably with a short pharmacodynamic effect in order to avoid carryover effect for a prolonged period after the medication is stopped. Difference in use of rescue medication and difference in duration of use between treatment arms may bias the study results. This has to be taken into account in the analysis.

**Tachyphylaxis**

For symptomatic or preventive medication, tachyphylaxis does not usually occur with prolonged treatment. However, data are required to confirm maintenance of effect.

Interaction studies should be carried out unless the potential for systemic drug interactions is low.

### III.1 Early Studies in Man

**Pharmacodynamics (i.e. Conjunctival Allergen Challenge/ Provocation Test).**

Challenge tests are used to provide evidence of superiority over placebo and to compare local therapy with systemic therapy for allergic conjunctivitis. The Conjunctival Allergen Challenge (CAC) test also known as the Conjunctival Provocation Test is a validated model for studying allergic conjunctivitis. Clinical signs (e.g. redness) and symptoms (e.g. itching) can be quantified and are reproducible. The provoked reaction can be used to evaluate any allergic topical ocular products, with the patient acting as his/her own control. The test medication can be compared to placebo and active comparator.

Provocation Tests (e.g. the CAC) evaluating the response to an allergen challenge before and after the effect of an anti-allergic agent as compared to placebo may be used as supportive evidence for efficacy and to establish a dose effect relationship. The validity of such tests

should be thoroughly justified. For comparison of results between studies appropriate standardization of methods is needed. The use of active comparator is recommended.

The Nasal Allergen Challenge and the 'Environmental Exposure Unit (EEU)' may be considered as other potential models for pharmacodynamic studies. The use and validity of these methods requires justification.

**Pharmacokinetic data**

Pharmacokinetic data and an effective dose range should be established in supporting trials. The pharmacokinetics of the product should be described and absorption, bioavailability and elimination established. For locally applied products the extent of systemic absorption and metabolism should be stated. Refer to NfG /pharmacokinetics

**Dose-response studies**

Dose response studies are required in order to establish the effective dose range and optimum dose. These studies may be either clinical studies or validated pharmacodynamic studies. However, pharmacodynamic studies for establishing a dose response relationship should be in line with the aimed indication e.g. the CAC cannot form the basis for dose recommendation for allergic rhinitis.

### III.2 Therapeutic Confirmatory Studies

As non-inferiority trials are not possible in SAR/PAR due to lack of assay sensitivity, pivotal studies should be double-blind randomised three arm parallel group studies including a placebo and active control arm. Alternatively, the therapeutic efficacy may be tested in a superiority trial against a well-established comparator. However, if the test product is not superior to the comparator non-inferiority cannot be claimed due to the lack a placebo arm for internal validation.

The active comparator in the pivotal studies should have the same route of administration as the test product.

Pharmacodynamically SAR and PAR are considered comparable. For approval of the SAR/PAR indication for a new product at least two adequate and well controlled phase 3 clinical trials preferably one each in SAR and PAR, are recommended. For drugs of established classes (i.e. where mode of action is known) this might be two SAR or two PAR studies or one study in each condition.

If however, only 2 SAR studies are conducted, additional safety data for 12 months will be required to establish safety of chronic use of the product in patients with PAR.

**Duration of studies**

Duration of study may vary depending on the onset of action of the agent studied (e.g. on demand versus a delayed symptomatic relief), the type of indication sought (treatment versus prevention of symptoms) and the duration of allergen exposure expected.

**Symptomatic treatment**

For trials in SAR the duration of a double blind treatment period may last 2 weeks up to 4 weeks depending on the pharmacodynamic profile of the agent studied. For trials in PAR a duration of 6 up to 12 weeks is recommended.

Safety studies in PAR should have longer duration (see IV Clinical Safety Evaluation).

For SAR trials randomisation of patients within each centre into the double blind portion over a short time period is encouraged to avoid change in the environmental conditions.

**Preventive treatment**

For establishing efficacy in prevention of symptoms the trial medication should start shortly before the expected allergen exposure and be administered for as long as allergen exposure is expected. This requires a well-documented history of prior antigen exposure and response per patient. The duration of preventive trials in SAR should cover the period of exposure to the allergen e.g. should be at least 4 weeks in SAR and 12 weeks in PAR .

**Variability of pollen count in SAR environmental studies**

The daily symptom-score is influenced by the amount of pollen in the air and by the anti-allergic treatment. It might be difficult to attribute an improvement in symptom-score to treatment, spontaneous improvement or lack of sufficient allergen exposure levels.

Therefore the exposure of patients to the relevant allergens during the study period should be documented.

For SAR trials the study protocols should discuss plans for measuring pollen counts at the different study centres. Efforts may also be undertaken to develop valid methods to measure the exposure to dust mite allergens in PAR.

In order to insure a similar allergen exposure between the study arms randomisation of patients within each area specified, is obligatory. The double-blindness and placebo control should discriminate a spontaneous improvement from a treatment effect provided exposure levels are sufficient.

The degree of allergen exposure may have an impact on efficacy. However, no specific recommendations can be made how here could be adjusted for in the analysis. More data are required before any method may be accepted as validated e.g. it is unclear whether previous exposure during the season affects the responsiveness to the same pollen challenge later in the season In addition, it would require measurements of pollen exposure on an individual basis.

**Rescue medication**

If rescue medication is allowed, it might be difficult to know whether an improvement in symptom score is due to the new therapy or the rescue medication. The impact of the rescue medication on the observed effect should be taken into account. This might be achieved by a separate analysis of the symptom score on days where no rescue medication is used. Whatever method is used, it should be anticipated in advance and justified. The use of prolonged action rescue medication is not recommended because of carry-over effects.

**Specific statistical issues.**

A detailed analytical section in the study protocol is of importance to avoid post-hoc changes. In the absence of this it will not be possible to decide whether result claims in secondary analysis are data-driven or not.

Missing values have been frequently observed in SAR/PAR studies therefore a procedure for dealing with missing values should be declared in advance.

Reference must be made to the ICH9 on statistical principles, PtC concerning Multiplicity and PtC concerning missing values.

### III.3 Studies in special conditions.

**Topical products**

Recommendations with respect to study design, study duration, statistical analysis etc, are not different for topical or systemic applied agents.

For topical products the probability that a product is developed solely for allergic conjunctivitis or allergic rhinitis instead of rhinoconjunctivitis is more likely then for oral products. Hence the primary assessment may concern the nasal symptom sum-score or eye symptom sum-score only.

However, if rhinoconjunctivitis is explicitly the subject of the study and in the overall sum score an effect is seen on eye symptoms but not on nasal symptoms or visa versa the study may raise question w.r.t. study conduct e.g. right patient population.

Preferably, the active comparator in the pivotal studies should be a local applied product as well.

**Special populations: Renal/liver impairment, elderly**

Pharmacokinetic studies with orally administered drug should indicate if clinically relevant differences in the plasma concentrations or urinary recovery of unchanged product occur in patients with renal impairment or in the elderly. Depending on the method of elimination, specific pharmacokinetic studies in patients with liver impairment may be needed.

For the elderly reference should be made to the ICH7 concerning 'Studies in support of Special populations: Geriatrics'.

**Special populations: Children**

In children below 5 years of age SAR/PAR is rare. If however the diagnosis is definitely established (e.g. RAST) it is assumed that the immune response is not different from that of adolescents/adults.

For oral applied agents, PK studies are sufficient for the determination of the effective dose in children older than 2 years of age.

For topical applied agents, PK studies are needed to exclude a too large systemic absorption in doses used for adults. If so pharmacodynamic studies may be needed to establish the effective dose with a minimum of systemic absorption.

For children less than 2 years of age the immune response is considered different. Therefore below this age separate clinical studies for efficacy are needed assuming that the correct population can be defined.

Safety data are of paramount importance and 1- 3 months of paediatric safety data are required. Further, special care has to be taken to avoid the side effects including growth effects typical in this age group.

Referred is to ICH11 NfG on Clinical Investigation of Medicinal Products in the Paediatric Population.

## IV. CLINICAL SAFETY EVALUATION

### IV.1 Adverse events

Trials should address safety monitoring i.e. adverse events, routine laboratory haematology, biochemical tests and urinalysis. For some allergic rhino-conjunctivitis drugs a more thorough cardiac safety evaluation may be indicated particularly if a QT problem is suspected.

Important safety issues for intranasal corticosteroids include assessment of adrenal function. Sedation, antibody formation and immunsuppression effects must be addressed, depending on the mechanism of action.

Separate safety data are needed for SAR/PAR given the difference in long-term use. See also IV.3

For topical products, provided significant systemic exposure is excluded, local safety is more relevant.

### IV.2 Extent of population

Safety profiles must be acceptable among adult and elderly patients.

The overall patient database should include a suitable number of patients as per ICH guideline.

### IV.3 Long term safety

Data should include an appropriate number of patients evaluated for 6 months and a suitable number of patients evaluated for one year as per ICH guideline. For topical products, provided significant systemic exposure is excluded long term local safety is more relevant.