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DRAFT

GUIDELINE ON THE CLINICAL DEVELOPMENT OF PRODUCTS FOR SPECIFIC IMMUNOTHERAPY FOR THE TREATMENT OF ALLERGIC DISEASES

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Comments should be provided using this template to EWPSecretariat@emea.europa.eu
Fax +44 20 7418 86 13

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

GUIDELINE ON THE CLINICAL DEVELOPMENT OF PRODUCTS FOR SPECIFIC IMMUNOTHERAPY FOR THE TREATMENT OF ALLERGIC DISEASES

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EXECUTIVE SUMMARY

This Guideline is intended to address issues of study design, efficacy and safety for allergen extracts and allergenic proteins being developed for specific immunotherapy of allergic diseases (e.g., the long-term treatment and management of allergic conditions like rhino-conjunctivitis, mild allergic asthma and allergic reactions to insect venoms).

1. INTRODUCTION

The worldwide increase in atopic diseases such as allergic rhinoconjunctivitis, allergic asthma, and food allergy has been attributed to environmental factors, modulating genetic predisposition and the natural course of underlying allergic immune responses. Affected individuals might develop immunoglobulin E (IgE)-mediated allergic sensitisations and subsequent symptoms of different organ systems after exposure to environmental allergens, mostly proteins from plant pollen, mites, furred animals, molds and insect venoms, the latter acting independently from any atopic risk.

Long term strategies such as preventive measures and immuno-modulatory treatment play an important role besides symptomatic treatment based on pharmocotherapy. Specific immunotherapy with allergens is the repeated administration of allergen extracts or allergens to allergic individuals in order to provide sustained relief of symptoms and need for medications, and improvement in quality of life during subsequent natural allergen exposure.

Even if the mechanism of action regarding the clinical effect of specific immunotherapy is up to now not fully understood the underlying mechanisms have been studied, showing that immunotherapy has the potential to modify the course of allergic disease. Specific immunotherapy is accompanied by an increase in “blocking” IgG (e.g. IgG4 and IgA) antibodies, a constant or decreased IgE response, and a decrease in recruitment and activation of effector cells including mast cells, eosinophils, and basophils. These effects are caused by an altered T-lymphocyte response. There is immune deviation from an allergy promoting "Th2-type" response with dominant production of interleukin (IL)-4 and IL-5 in favour of “Th1-type” responses with production of interferon gamma and IL-2, and induction of “T-regulatory” cells with increases in the production of IL-10 and TGF beta.

These immunological changes are accompanied by suppression of allergen-induced T cell-dependent late responses in the skin and lung and long term disease suppression which is apparent following discontinuation. However, the mechanism is not such clear that any of the mentioned changes of the immune system is predictive for the clinical outcome.

Specific immunotherapy is an established treatment of allergic diseases caused by inhalational allergens and insect venoms with a disease modifying effect [1, 2, 3]. IgE-mediated food allergy is an important cause of acute anaphylaxis and anaphylaxis-related death but no established treatment is available so far. Clinical trials on specific immunotherapy of food allergy are ongoing and first results obtained by sublingual application have been published [4], and specific immunotherapy for food allergy has been included in 7th Framework Programme for Research and Development of the European Union.

However, up to now there is a wide variety of study designs in terms of e. g. study duration, inclusion criteria, end-points chosen, analysis of data, and control of environmental variables in the evaluation of new preparations for specific immunotherapy.

2. SCOPE

This guideline provides guidance for the development of studies of products for specific immunotherapy to enhance the assessment and comparison of results of such studies.

This guideline covers clinical studies on specific immunotherapy, regardless of the affected organ system (e.g. nose, upper and lower airways, eyes, multi organ affection (systemic reaction)), the allergen source (e.g. pollen, mites, animal dander, moulds, insect venoms, food), the allergen preparation (e.g. extracts, purified allergens, modified allergens, adsorbed allergens) or the application route (e.g. subcutaneous, sublingual).

This guideline does not cover atopic eczema/dermatitis.

3. LEGAL BASIS

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. These include, but are not limited to:

CPMP/EWP/2455/02 Guideline on the Clinical Development of Medicinal Products for the Treatment of Allergic Rhino-Conjunctivitis

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

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 March 1998)

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

CPMP/BWP/243/96 Note for Guidance on Allergen Products

EMEA/CHMP/BMWP/101695/2006 Guideline on Comparability of Biotechnology-Derived Medicinal Products after a Change in the Manufacturing Process

Topic Q5E Step 4 Note for Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (CPMP adopted December 2004)

4. MAIN GUIDELINE TEXT

4.1 Patient characteristics and selection of patients

4.1.1 Diagnosis

For specific immunotherapy trials patients should have a well-documented history of their allergic condition before study entry.

The history of atopic diseases such as allergic rhino-conjunctivitis or allergic asthma should cover at least 2 consecutive years, and diagnosis should follow current guidelines [5].

The history of insect venom allergy should be based on a detailed description of allergic symptoms after a hymenoptera sting graded by an established grading system [6].

4.1.2 Selection of patients

Subjects suffering from allergic airway diseases show varying number of allergic sensitisations. Few are mono-sensitised, the majority is sensitised to more than one allergen group and multiple sensitisations can occur at the high end of the spectrum. As a consequence specific immunotherapy studies should rather include patients with sensitisations to a limited number of allergen sources. These should be documented by positive skin testing and concordant positive IgE determinations (validated quantitative system for detecting allergen-specific IgE) to the relevant allergen to be studied with specific immunotherapy. This is important for seasonal allergic rhino-conjunctivitis, triggered by pollen or moulds, as well as perennial allergic rhino-conjunctivitis, frequently induced by dust mites or furred animals. Sensitisations to seasonal and perennial allergen sources can exist in parallel adding another level of complexity. However, not all sensitisations will be clinically relevant, defined by inducing consecutive clinical symptoms. To avoid bias of results of clinical studies, specific

immunotherapy trials on seasonal allergens should exclude subjects with clinically relevant sensitisations to other seasonal allergens with overlapping seasons and/or perennial sensitisations. Trials with perennial allergens should not include patients with clinically relevant other perennial allergies. If patients with clinically relevant seasonal allergies are included in clinical trials with perennial allergens, control periods for collection of efficacy data must not overlap with the season for the seasonal allergens.

Patients with allergic diseases due to inhalational allergens enrolled in specific immunotherapy studies should experience an appropriate minimum level of symptoms during a pre run period or observational phase. This approach will ensure at study entry a symptom level high enough to recognize relevant changes and is favourable in comparison to retrospective scoring of symptoms. Patients who have received specific immunotherapy in the previous 5 years or are still receiving this kind of therapy are not eligible for study enrolment.

Due to a higher risk of anaphylactic reactions patients with mastocytosis should be excluded from clinical trials with insect venoms.

Inclusion criteria should be defined in relation to age, gender, disease, disease severity, co-morbid conditions, previous immunotherapy, etc. Exclusion criteria should be defined, e.g. concomitant medications, other illnesses, etc. Eligibility criteria should be clearly defined in the study protocol to evaluate the general validity of the results.

4.1.3 Co-morbidity

Rhinitis and asthma frequently occur in the same patient. In studies investigating the effectiveness of specific immunotherapy on allergic rhinitis/rhino-conjunctivitis patients suffering from allergic rhinitis/rhino-conjunctivitis with allergic asthma co-morbidity may be included for obtaining safety data. However, for a claim of efficacy in asthma separate trials should be conducted and specific guidance for asthma therapy should be considered.

4.1.4 Co-medication

All drugs (including over-the-counter products) taken must be documented and drugs which could affect the results during the study must be predefined and excluded. However, the definition of rescue medication is recommended (see rescue medication).

4.2 Strategy and designs of clinical trials

4.2.1 Early studies

Classical phase I studies in healthy individuals are not appropriate for allergen extracts, since they do not provide helpful information in terms of safety and tolerability. Non-affected individuals without any hypersensitivity do not react like allergic individuals and do not carry the risk of the targeted patient population. Therefore, products for specific immunotherapy should only be tested in allergic individuals. The investigational products should be tested at different doses to provide preliminary data on safety and tolerability with regard to the maximal tolerable dose and a suitable up-dosing scheme.

If combinations of different allergens are used (e.g. mixtures of allergen extracts or of purified allergens (natural, synthetic, derived from r-DNA technology)) the applicant has to justify the dose of each allergen. Moreover, different concentrations and ratios of allergens in mixtures of purified allergens in comparison to natural extracts and the difference between natural glycosylated allergens and their recombinant/synthetic counterparts should be discussed and considered for dose selection of each ingredient.

4.2.2 Dose-finding studies

After establishing a tolerated dose range, studies should be performed to establish a dose-response relationship for clinical efficacy. Such studies may comprise a short-term treatment (e.g. 2-4 month) with different doses in several study-arms. Provocation tests (e.g. conjunctival or bronchial provocation or allergen exposure in allergen chambers) and/or clinical endpoints may be used as primary endpoints. As long as laboratory parameters such as allergen specific antibodies, T-cell

reactivity or cytokines are not validated and not correlated to the clinical outcome, they can only provide supportive information but are not feasible for determining a suitable therapeutic dose.

4.2.3 Pharmacokinetic / Pharmacodynamic studies

Pharmocokinetic studies are not possible for products of specific immunotherapy. Due to the nature of the product plasma levels are not measurable.

Pharmacodynamic aspects should be addressed using markers such as changes in allergen-specific antibody levels, T-cell responses, and/or cytokine production indicating a specific interaction with the immune system. These changes will indicate indirectly pharmacokinetic and pharmacodynamic mechanisms. These parameters can be followed in other studies on specific immunotherapy. Allergen challenge tests may be helpful also in pharmacodynamic studies thus dose-finding studies and pharmacodynamic studies may be combined.

4.2.4 Confirmatory Studies

- **Study design**

Confirmatory trials on specific immunotherapy should be performed using a randomised placebo-controlled double-blinded design. Due to the variability in individual clinical responses, unpredictability and variability of allergen exposure, and the subjective nature of symptoms assessment non-inferiority trials are not possible due to lack of assay sensitivity. Thus, in general, superiority versus placebo or any other comparator has to be shown. Since local allergic adverse events are frequent in specific immunotherapy, a placebo preparation with histamine may be considered to keep the blinding.

However, for insect venom allergy it would be considered unethical to place allergic subjects at high risks by providing placebo in the control group. Another approved product for treating insect venom allergy would be suitable as comparator in such trials. To keep the blinding the application scheme has to be the same for test and active control or other measures have to be taken to ensure a blinded study design (e.g. double-dummy design). If in such special cases a non-inferiority design is planned special attention should be drawn to the assay sensitivity of the trial. It is recommended to seek scientific advice of competent authorities for such study designs.

Since patients with allergic rhino-conjunctivitis or allergic asthma enrolled in specific immunotherapy studies should experience an appropriate minimum level of symptoms a prospective baseline period is preferred and should be included whenever possible. However, the unpredictability and variability of allergen exposure especially to pollen allergens may limit the value of information obtained from a baseline period. Retrospective scoring of symptoms might indicate that patients with a sufficient symptom level are included but suffers from memory bias and therefore should not be used further in the comparisons or analyses. Provocation tests may be useful for selecting subjects with a desired minimum level of symptoms and for matching study groups.

In case of seasonal allergies it is important to document the exposure to the relevant allergens and to define a sufficient allergen exposure level for the evaluation period as well as the baseline period.

For trials in the perennial indication it is important to minimise fluctuations in the levels of indoor allergens. Thus, sanitation measures should be finished before the start of a clinical trial and measurement of baseline symptoms should be performed after sanitation. In addition, the exposure level should be documented.

- **Study duration**

The main aim of specific immunotherapy is a persistent effect due to changes in the immune system which can only be demonstrated in long-term studies. However, significant results on efficacy of specific immunotherapy in allergic rhino-conjunctivitis/allergic asthma may be obtained after the evaluation of a single pollen season or one or two control periods for perennial allergies. Thus, depending on study duration, different claims for efficacy are possible:

1. Treatment of allergic symptoms: Short-term clinical trials conducted to show efficacy in the first pollen season after start of specific immunotherapy or to show efficacy in perennial allergies after some months of treatment.
2. Sustained clinical effect: Maintenance of significant and clinically relevant efficacy during two to three treatment years.
3. Long-term efficacy and disease modifying effect: Sustained significant and clinically relevant efficacy in post treatment years.
4. Curing allergy: Sustained absence of allergic symptoms in post treatment years.

In principle, separate studies should be considered for the different claims mentioned above. If a study is intended to serve for more than one claim, this has to be carefully pre-planned, properly accounting for possible methodological problems (e.g. the multiplicity issue). In this context the use of interim data from ongoing trials is strongly discouraged: the dissemination of study information necessary for submission purposes dangers the integrity of the ongoing trial.

Endpoints should be evaluated in each allergen season or several times during the treatment for perennial allergies and at least at end of follow-up. An enhanced efficacy during the course of the treatment would be supportive but cannot be demanded, since measurement of efficacy is influenced by allergen exposure which may vary from year to year. Moreover, a further increase may be limited by a high level of efficacy in the first treatment year(s), but continuous treatment may still be required for obtaining long term efficacy. Provocation tests performed in parallel as part of clinical studies can support the proof of efficacy, especially in years with low allergen exposure and consequently low or no clinical efficacy but maintained efficacy in provocation tests. Moreover, if the allergen concentration needed to provoke the same symptoms increases over time of the study, this is supportive for the efficacy of the treatment. However, such provocation tests are not validated as surrogate markers for efficacy.

For insect venom allergy the applicant should justify the intended treatment period. However, the need for assessment of long-term efficacy should be taken into consideration.

- **Rescue medication**

Rescue medication should generally be provided. The kind of rescue medication has to be standardised and justified by the applicant. The criteria for taking a specific rescue medication (i.e. the kind of symptom(s) and the severity of symptom(s)) should be pre-defined in the study protocol. Any intake of rescue medication has to be documented in the patients' diary.

To avoid any carry over effect after the medication has been stopped, rescue medication with a short pharmacodynamic effect should be preferred. As the use of rescue medication might impact study results, the amount and duration of rescue medication intake has to be taken into account in the analysis of efficacy.

- **Endpoints**

In general, the clinically relevant difference in the primary endpoint between test and control population should be predefined and justified by the applicant.

The appropriate endpoints for the confirmatory clinical trials are dependent on the indication sought for:

Allergic rhinitis/rhino-conjunctivitis:

Primary endpoint:

The use of rescue medication has an impact on symptom severity. Therefore, the primary endpoint has to reflect both, symptom severity as well as the intake of rescue medication.

Patient self-rated symptom scores are often used as primary measures of efficacy in clinical trials concerning patients with allergic rhinitis/rhino-conjunctivitis with or without allergic asthma. Such symptom scores should be collected on a daily basis. Up to now, no validated symptom score exists, but the measurement of symptoms on a 4-point rating scale (i.e. 0 = absent, 1 = slight, 2 = moderate,

3 = severe) is generally accepted. Favourably scored symptoms for allergic rhino-conjunctivitis are: nasal itching, sneezing, rhinorrhoea, nasal obstruction, ocular itching/grittiness/redness and ocular tearing. Likewise, no validated medication score exists. Since the different drugs used as rescue medication cause clinical effects of different magnitude and duration, and influence different organ systems, a scoring of medication should be related to their approximated relief of symptoms and to the kind of symptoms affected and requires a clinical justification.

Different approaches to combine symptom score and intake of rescue medication are possible. The method to combine both scores has to be pre-specified and justified. So far, no validated system for balancing symptom and medication score exist. Therefore, initiatives for establishing such a balanced and validated scoring system would be helpful for future assessments and should be encouraged and supported by the interested parties.

One approach is to combine both scores by a weighted sum of the symptom and medication score respectively. In such a situation the choice of the weights has to be justified.

Any analysis of such a combined score should be supported by a responder analysis (responder defined as e.g. patients with a combined score below a pre-specified level indicating a clinical benefit for the patient).

An alternative approach for combining symptom score and intake of rescue medication is the number of days with symptom control, i.e. days without intake of rescue medication and a symptom score below a pre-defined and clinically justified threshold.

Other primary endpoint definitions could be considered if clinically justified.

In case the assessment of efficacy is restricted to a specific time period the criteria defining this assessment period are part of the definition of the primary endpoint and have to be pre-specified in the study protocol.

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. A merely statistical significant effect might not be sufficient.

Secondary endpoints:

Possible secondary endpoints are: total symptom score, total medication score, individual symptom scores, health related Quality of Life (HRQoL) (validated Questionnaires), symptom load on a visual analogue scale (VAS), symptom free days, physician and patient rated clinical global improvement.

Objective measures such as spirometry (FEV1, FVC etc), paraclinical parameters (e.g. changes in IgE and IgG levels, Cytokines, other inflammatory markers) and provocation tests (skin, eye, bronchi, pollen chamber) can give additional information but are no surrogate markers and cannot replace the measurement of clinical symptoms. Provocation tests in allergen chambers deemed to be a promising tool for the evaluation of efficacy, however the results of such provocations have to be validated in comparison with clinical symptoms by natural exposure and for example the influence of measurement within or without the pollen season (influence of inflammation) has to be evaluated before such tests could be used as primary endpoints. However, the provocation in allergen chambers might be a helpful marker especially in long-term studies over several years for a pollen season in which an evaluation in regard to the natural exposure is not possible due to low pollen counts.

Insect venom allergy

The efficacy of insect venom allergy can be evaluated by a controlled sting provocation. The grading should follow an established grading system [6].

- **Methodological issues**

When planning a specific immunotherapy-study all relevant and current ICH and CHMP guidance on clinical trial methodology should be consulted.

Especially a detailed analytical section in the study protocol is of importance to avoid post-hoc changes. In the absence of such a section it will not be possible to decide whether result claims in secondary analysis are data-driven or not. Special consideration should be given to the handling of

missing values and the issue of multiplicity resulting from the use of co-primary and secondary endpoints. Procedures for dealing with such issues should be pre-defined.

In environmental studies (e.g. seasonal allergic rhino-conjunctivitis), the methods to measure the patients' exposure to e.g. pollen should be described as well as any approach to include this exposure into the analysis model.

4.2.5 Food allergy

Clinical studies regarding specific immunotherapy of IgE-mediated food allergies comprise several specific issues. For food allergy the gold standard for diagnosing and as such for evaluation of treatment efficacy is the tolerated food dose in a double-blind, placebo-controlled food challenge (DBPCFC) [7]. Due to the fact that specific allergen administration to patients with food allergies implies a high risk of provoking allergic reactions and limited experience with specific immunotherapy for food allergies is available, scientific advice should be requested by competent authorities on a case-by-case basis for such clinical studies.

4.2.6 Purified allergens (native/recombinant/synthetic peptides)

If purified allergens are used, some additional issues should be addressed. Many allergenic source materials contain several relevant allergens. Due to the sensitisation frequency in allergic subjects these different allergens are regarded as major (> 50% IgE prevalence) or minor (<50% IgE prevalence) allergens. Moreover it has to be taken into consideration, that not all allergens of a specific allergen source are known. Patients are sensitised to individual patterns of allergens which are relevant for the allergic disease in individual subjects. By using allergen extracts the patient is treated with a broad variety of allergens of the allergenic source, enhancing the chance that the patient is treated with all allergens which are relevant for her/his individual allergy. By using purified allergens the spectrum of allergens is reduced. Thus, the applicant has to justify the selected allergens and has to define and justify the selection of study population in regard to the included allergens (e.g. measurement of individual sensitisation patterns).

4.2.7 Cross-reacting allergens

The concept of cross-reacting allergens ("allergen families" or "homologous groups") of the "Note for Guidance on Allergen Products (CPMP/BWP/243/96) should be adopted for the evaluation of efficacy. Thus within one "homologous group" it is sufficient to prove the efficacy with one representative allergen. However, it is not possible to transfer efficacy results between different groups. If the concept of cross-reacting allergens should be applied on allergens which do not belong to a "homologous group", the applicant has to provide a justification for the suggested grouping. The concept of "homologous groups" is not applicable to purified allergens (native/recombinant/synthetic peptides).

4.2.8 Comparability studies

Comparability studies are needed in the case of changes in the manufacturing process which are suitable to influence the allergenic activity of the product. Depending on the change the comparability may be shown by validated in vitro assays e.g., to demonstrate similar allergen composition, potency and biological activity if the manufacturer can provide evidence of comparability through physico-chemical and biological studies. However, it may be necessary to provide evidence of the same biological potency by in vivo skin tests or even to perform tolerability or efficacy studies. In this context the appropriate guidance documents should be considered in addition. The chosen approach has to be justified by the applicant and it is recommended to seek scientific advice of competent authorities in regard to required studies on a case-by-case basis.

4.2.9 Different routes of application

The recommendations reported above remain valid for all routes of application.

It is not possible to transfer study results between different routes of application. For each route of application appropriate clinical studies have to be performed. To compare the efficacy of different routes of application a double-blind, double-dummy design, also involving a placebo group is required.

4.3 Efficacy in children

Since specific immunotherapy has an indication for treatment of children, products for specific immunotherapy should be tested for efficacy and safety in children. In general, all European regulations regarding this specific vulnerable population (e. g. ICH Topic E11, European Paediatric Board, etc.) have to be followed. Studies of specific immunotherapy in paediatric patients involve additional problems, e.g. recording symptoms and use of rescue medication, safety and acceptance, especially in very young children. Therefore, the efficacy of products for specific immunotherapy has to be evaluated in special trials in children and not in combined trials in children and adults. Adolescents and adults can be investigated as a combined population.

In general, the recommendations reported above remain valid for studies in children. In young children, who are not able to score for themselves, parents should assist the children in scoring their symptoms and use of medication. If Quality of Life Questionnaires should be used as secondary endpoints it should be considered that special Quality of Life Questionnaires are available for children suffering from allergic rhino-conjunctivitis [8] or asthma [9].

4.4 Safety

In general the existing guidelines on safety have to be followed. All adverse events should be documented and rated in regard to treatment relation. Untoward events specifically related to treatment must be described in detail. Expected allergic side effects should be distinguished into local and systemic effects and reported separately. The severity grading of systemic effects of the European Academy of Allergy and Clinical Immunology (EAACI) may be used. Other safety parameters which should be addressed are vital signs, routine laboratory haematology, biochemical tests and urinalysis.

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