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

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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 products (i.e. products based on active substances of e.g. allergen extracts, recombinant allergens, purified native allergens, modified allergens etc.) being developed for specific immunotherapy of allergic diseases (e.g. the long-term treatment and management of allergic conditions like rhino-conjunctivitis and allergic reactions to insect venoms).

1. INTRODUCTION

The worldwide increase in atopic diseases such as allergic rhinitis/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, insect venoms, and food.

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

Specific immunotherapy is an established treatment of allergic diseases caused by inhalational allergens and insect venoms with a disease modifying effect [1, 2, 3, 5]. 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.

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. For example, specific immunotherapy is accompanied by an increase in allergen specific “blocking” IgG (e.g. IgG4 and IgA) antibodies, a constant or decreased allergen specific 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 of successful specific immunotherapy. However, up to now the mechanism is not fully understood and at present none of the mentioned changes of the immune response has been shown to be predictive for the clinical outcome. Nevertheless clinical studies to correlate immunological changes to clinical outcome are recommended.

Up to now there is a wide variety of study designs in terms of e. g. dosages, 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 product (e.g. extracts, purified allergens, modified allergens, adsorbed allergens) or the route of administration (e.g. subcutaneous, sublingual).

This guideline does not cover atopic eczema/dermatitis or asthma without allergen established as cause.

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/EWP/1776/99 Points to Consider on Missing Data

CPMP/2330/99 Points to Consider on Application with 1.) Meta-analyses and 2.) One Pivotal study

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/ICH/2711/99, ICH Topic E11 Step 4 Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population.

CPMP/ICH/363/96, ICH Topic E9 Step 4 Note for Guidance on Statistical Principles for Clinical Trials.

CPMP/ICH/364/96, ICH Topic E10 Step 4 Note for Guidance on Choice of Control Group for Clinical Trials

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

CPMP/BWP/304831/07 Guideline on Allergen Products: Production and Quality Issues - Draft

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

CPMP/ICH/5721/03, ICH Topic Q5E Step 5 Note for Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

CPMP/ICH/377/95, ICH Topic E2A Step 4 Clinical safety data management: Definitions and Standards for Expedited

CPMP/ICH/137/95, ICH Topic E3 Step 5 Structure and Content of Clinical Study Reports

CPMP/ICH/378/95, ICH Topic E4 Step 5 Dose response Information to Support Drug Registration

CPMP/ICH/135/95, ICH Topic E6 (R1) Step 5 Guideline for Good Clinical Practice

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 IgE-mediated diseases such as allergic rhinitis/rhino-conjunctivitis or allergic asthma should cover at least 2 consecutive years for seasonal and 1 year for perennial allergy, and diagnosis should follow current international guidelines [6, 7].

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 [8].

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 it is difficult to include only mono-sensitised patients in specific immunotherapy studies. However, preferably patients with sensitisations to a limited number of allergen sources should be included. Overall, it is necessary that the causal role of the allergen is documented and that appropriate testing excludes the relevance of other allergens to which the patient is sensitised. These should be documented by skin testing and IgE determinations (validated quantitative system for detecting allergen-specific IgE) to the relevant allergen to be studied with specific immunotherapy and to other allergens that may bias the study outcome. This is important for seasonal allergic rhinitis/rhinoconjunctivitis, triggered by pollen or moulds, as well as perennial allergic rhinitis/rhinoconjunctivitis, 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. 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 sensitisations to perennial allergens if relevant in the collection data period. Trials with perennial allergens should not include patients with clinically relevant other perennial allergies. For patients with clinically relevant seasonal allergies the control periods for collection of efficacy data of perennial allergens 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 and a sufficient period of persistent symptoms before enrolment. It is recommended to investigate the level of symptoms during a baseline period rather than by retrospective scoring of symptoms. Patients who have received specific immunotherapy for the tested allergen or a cross-reacting allergen in the previous 5 years or are receiving immunotherapy for any allergen are not eligible for study enrolment.

Patients in clinical trials of insect venom immunotherapy should be screened for mastocytosis. Due to a higher risk of anaphylactic reactions to insect venom immunotherapy and insect stings a diagnosis of mastocytosis should be considered for selection and assessment of efficacy and safety.

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

4.2 Therapeutic agents other than allergens

4.2.1 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).

4.2.2 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. If in asthmatic patients controller medication is necessary it has to be handled as rescue medication. 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.

4.3 Strategy and designs of clinical trials

4.3.1 Early studies

Classical phase I studies in healthy individuals are not appropriate for allergen products, 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. However, in order to test for irritancy healthy subjects may be investigated. The investigational products should be tested at different doses to provide preliminary data on safety and tolerability with regard to the maximum tolerated dose and a suitable dose escalation scheme. Depending on the nature of the product dose escalation may be necessary or not to reach the maintenance dose. This has to be shown in suitable trials.

4.3.2 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, nasal or bronchial provocation or allergen exposure in allergen challenge 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.

4.3.3 Pharmacokinetic / Pharmacodynamic studies

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

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

4.3.4 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 symptom 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. An 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.

In studies for specific immunotherapy only patients should be enrolled who experience an appropriate minimum level of symptoms prior to randomisation during their relevant period of complaints. Retrospective scoring of symptoms might be used for this issue but suffers from memory bias and therefore should not be used further in the comparisons or analyses. Another approach is a prospective baseline period which has the advantage of a controlled collection of symptoms with knowledge of the allergen exposure and therefore is recommended whenever possible. However, the unpredictability and variability of allergen exposure especially to pollen allergens may limit the value of information obtained from both approaches. Titrated provocation tests may be useful for selecting subjects with a desired minimum level of symptoms.

In case of seasonal allergies it is mandatory to document the exposure to the relevant allergens and to define in the study protocol the minimum pollen count which has to be reached to define the evaluation period as well as the baseline period.

For trials in the perennial indication it is important to minimize variations in the levels of indoor allergens. Thus, if sanitation measures are planned they should be finished before the start of a clinical trial and measurement of baseline symptoms should be performed after sanitation. No further sanitation measures should be performed during the trial. In addition, it is recommended to document the exposure level for the individual patient especially for the evaluation periods to evaluate the variation of indoor allergens.

- 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 rhinitis/rhinoconjunctivitis 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. Moreover, long-term studies can be planned to serve in addition for documenting effects on prevention

of asthma and spread of the sensitisation spectrum. 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 the 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 increase 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.

- 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/rhinoconjunctivitis :

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/rhinoconjunctivitis with or without allergic asthma. Such symptom scores should be collected on a daily basis during the pre-defined assessment period. Up to now, no validated symptom score exists, but the measurement of symptoms on a 4-point rating scale with the following definition is generally accepted:

- 0 = absent symptoms (*no sign/symptom evident*);
- 1 = mild symptoms (*sign/symptom clearly present, but minimal awareness; easily tolerated*)
- 2 = moderate symptoms (*definite awareness of sign/symptom that is bothersome but tolerable*);
- 3 = severe symptoms (*sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping*).

Favourably scored symptoms for allergic rhinoconjunctivitis are: nasal itching, sneezing, rhinorrhea, 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, as well as the magnitude and duration of effect 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.

Provocation tests (skin, eye, nose, bronchi, allergen challenge chamber) and objective measurements such as paraclinical parameters (e.g. changes in allergen-specific IgE and IgG levels, Cytokines, other inflammatory markers) can give additional information but are no surrogate markers and cannot replace the measurement of clinical symptoms. In case of provocation tests objective measurements (e.g. rhinomanometry) should be preferred. 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.

In long-term studies information on prevention of asthma as well as on the occurrence of new sensitizations e.g. by skin prick test may be collected.

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 [8].

- 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.

4.3.5 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) [9]. 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, it is recommended to request scientific advice by competent authorities on a case by case basis for such clinical studies.

4.3.6 Purified allergens (native/recombinant/synthetic peptides)

Purified allergens mean all pure allergens, regardless if purified from native extracts, or produced by recombinant DNA technology. In addition, chemically synthesised peptides derived from allergen sequences are considered as purified allergen components. 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% specific IgE-binding prevalence) or minor (<50% specific IgE-binding 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, even if not all included allergens may be relevant for her/his individual allergy. By using purified allergens the spectrum of allergens is reduced, but in contrast to extracts from natural allergen sources the allergens can be chosen according to their importance and included in a dose that is adequate to achieve the desired clinical improvement 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).

4.3.7 Cross-reacting allergens

The concept of cross-reacting allergens ("allergen families" or "homologous groups") as defined in the draft of the "Guideline on Allergen Products: Production and Quality Issues (CPMP/BWP/304831/07)" can 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 applicability of the concept of "homologous groups" to purified allergens (native/recombinant/synthetic peptides) has to be justified on a case by case basis.

4.3.8 Non-cross-reacting allergens

If combinations of different non-cross reactive allergen sources (mixtures of allergen extracts) or allergens (e.g. purified allergens (natural, synthetic, derived from rDNA technology)) are used, the applicant is advised to request scientific advice.

4.3.9 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.

4.3.10 Different routes of administration

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

It is not possible to transfer study results between different routes of administration. For each route of administration appropriate clinical studies have to be performed. To compare the efficacy of different routes of administration a double blinded, double dummy design is required and involving a placebo group is normally needed.

4.4 Efficacy in paediatric populations

Since specific immunotherapy has an indication for treatment of the paediatric population, products for specific immunotherapy should be tested for efficacy and safety in paediatric populations. 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 patients. Therefore, the efficacy of products for specific immunotherapy has to be evaluated in special trials in the paediatric population and not in combined trials with paediatric population and adults. Adolescents and adults can be investigated as a combined population.

In general, the recommendations reported above remain valid for studies in paediatric populations. In young patients, who are not able to score for themselves, parents should assist their 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 validated Quality of Life Questionnaires are available for paediatric patients suffering from allergic rhino-conjunctivitis [10] or asthma [11].

4.5 Safety

In general the existing guidelines on safety have to be followed. All adverse events should be documented, classified as mild, moderate or severe and assessed for relationship to study medication. The adverse events should be coded using MedDRA terminology. Serious adverse events (especially those related to treatment) must be described in detail. Expected allergic side effects should be distinguished into immediate or delayed effects according to the time of appearance (immediate when the onset of the reaction is during the first 30 minutes after the administration and delayed when the onset is after the first 30 minutes of the administration) and into local and systemic effects according to the site of the appearance of the reaction (local when the reaction takes place in the administration site and systemic when the reaction takes place far from the administration site) and reported separately. For systemic allergic reactions 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.

DEFINITIONS and ABBREVIATIONS

- An **allergen** is a molecule capable of inducing an IgE response and/or a Type I allergic reaction.
- **Allergen extracts** are extracts from **natural** biological source materials containing a mixture of allergenic and non-allergenic molecules.
- **Purified** allergens mean all pure allergens, regardless if purified from native extracts or produced by recombinant DNA technology.
- **Modified allergens** are allergens which are chemically modified to reduce IgE reactivity (allergoids)
- **Adsorbed allergens** are allergens or allergen extracts, which are adsorbed to a solid phase (e.g. aluminium hydroxide, tyrosine) to achieve a depot formulation.
- **Allergen products** are medicinal products containing allergens or derivates of allergens for the purpose of treatment of allergic diseases.
- **Major/minor allergens** are allergens, against which at least 50% (major allergens) or less than 50% (minor allergens) of the patients tested have allergen-specific immunoglobulin E (IgE) antibodies.
- **Dose escalation scheme** means a series of administrations of the allergen product with increasing concentrations to reach safely the maintenance dose
- **Homologous groups:** Allergen extracts prepared from different species different genera or different families and finished products derived from these allergen extracts may be grouped in homologous groups based on the composition and the physiochemical biochemical properties of the source material, the cross-reactivity/structural homology of allergens, the formulation of the finished product and the production process of the allergen extract and of the finished product.
- **Ig**: Immunoglobulin
- **Th**: T-helper-lymphocytes
- **IL**: Interleukin
- **TGF β**: Transforming growth factor
- **HRQoL**: Health related quality of life
- **VAS**: Visual analogue scale
- **DBPCFC**: double-blind, placebo-controlled food challenge

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