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## Minutes of the expert meeting on specific immunotherapy Held in London on 18 January 2010

**Chairpersons:** Irmgard Eichler / Daniel Brasseur

**EMA participants:**

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**Experts:**

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### Introduction

The meeting started with a short introduction of all participants, followed by a presentation by Dr. Vieths (Paul Ehrlich Institute, PEI) explaining that 60 % of allergen products for specific immunotherapy (SIT) marketed in Germany are used under a 'Named-Patient' basis, without a marketing authorisation in the meaning of Directive 2001/83/EC. To avoid a potential serious risk to public health, a change in the German law now requires that "Named-Patient products" for the treatment of the most prevalent allergies must have a marketing authorization (MA) in Germany. All applications for MA have to be submitted by 1 December 2010 to the German authorities.

The European Paediatric Regulation mandates that any MA application for a new medicinal product should include either the results of studies conducted in compliance with an agreed paediatric investigation plan (PIP), or an EMA decision on a waiver or on a deferral. Consequently, for all those products that are subject to the Regulation for Therapy Allergens in Germany, EMA decisions on agreed PIPs must be included in the application for marketing authorization by 1 December 2010.

Considering the large number of expected applications (178 applications for MA announced; concept of "Homologous Groups" may reduce the number of "representative" PIPs to approximately 80) and in order to speed up such a procedure, a draft standard set of measures has been defined which applicants should include in their application for a PIP, a so-called draft standard PIP for allergen products for immunotherapy. To finalise the standard PIP experts were asked to comment on the questions listed below. The morning session focused on paediatric specific issues with regards to allergic rhinitis, rhino-conjunctivitis. Paediatric specific issues with regards to insect venom allergy were discussed in the afternoon.



# 1. Allergic rhinitis, rhino-conjunctivitis

Some experts were asking why the standard PIP only focuses on allergic rhinitis / rhino-conjunctivitis due to pollen and house dust mite and does not cover allergies to cat, dogs and molds. It was clarified that specific immunotherapy for allergy to animals (cat/dog) and molds is less frequent and therefore these were not included in the German regulation.

## 1.1. Study population:

### Q: How to document skin prick test results?

**A:** The documentation of skin prick test results is clearly stated in position papers (wheal  $\geq$  3 mm, positive control positive (wheal  $\geq$  3 mm) and negative control negative (no reaction at all). Skin prick test results are documented in the following way: twenty minutes after the skin tests execution, the wheal contours are outlined using a fine-tip rolling pen, the outline is transferred by means of adhesive cellulose tape to a record sheet. A late cutaneous response should be monitored. Position Paper: Allergen Standardization and Skin Tests. Dreborg S & Frew A. Allergy 1993: 48(suppl 14):49-82).

Skin prick test can only be used to define the sensitisation status, not to define disease severity.

### Q: Should an upper limit of total IgE be included?

- Inclusion criterion: "specific IgE level  $\geq$  0.7 kU/L to allergen in question"; when a child has highly elevated total IgE, specific RAST results are falsely positive for most allergens.

**A:** Specific IgE level is just one of the inclusion criteria, together with a positive skin prick test result and a suggestive clinical history. Specific IgE level should always be seen in conjunction with clinical history which per se must already be conclusive. Total IgE may be measured but should not be an inclusion or exclusion criterion.

### Q: Is there a need to obtain information on the sensitization profile?

**A:** Yes; there was general consensus that determination of the individual sensitization profile at baseline and after therapy with sub-group analyses should be performed for recombinant allergens. Whether this requirement should also apply to allergen extracts was debated. It was discussed that this would strongly support one single company, the only one which offers tools for detection of IgE to individual allergens. No general consensus was reached.

## 1.2. Choice of allergen extract for treatment:

The progress in allergen research achieved by the use of recombinant DNA technology, allowing component-resolved diagnosis and immunotherapy for the most prevalent allergies (i.e. birch pollen, grass pollen and house dust mite) raises the question what is the most appropriate allergen extract to be used for SIT (single allergen extract with most relevant allergen) and whether there is a need for allergen mixtures in the paediatric population and if so what mixtures? To mix all potential allergens?

### Q: Can major/relevant allergens for extracts of one homologous group be listed?

**A:** Yes: Dr. Graham Roberts and Dr. Vieths volunteered to help defining such a list.

### Q: Would it make sense to define a minimum content needed to ensure that the product is effective?

**A:** There was consensus that:

- It is important to know the concentration of the major allergen in a specific allergen extract;

- There's a need for a validated assay (ELISA) to measure the concentration. However, at present, there is no generally agreed and validated method available to quantify the content of major allergens. Every company use their own in-house reference materials, their own measurement systems and their own unique units to express potency. Thus, the results are not comparable. A European wide project (CREATE project) has been completed to introduce major allergen based standardization of allergen extracts. This project failed in establishing validated ELISAs and reference components. A follow-up project (BSP090) is coordinated by the EDQM and focuses on the validation of allergen-specific ELISA assays. An assay for the major allergen of grass pollen (Phl p 5a) and birch pollen (Bet v 1) is expected to be approved by 2012. These should be implemented in the European Pharmacopoeia. Once such officially approved assays are available companies would have to use them to quantify the allergen content. Until such validated assay for major allergen measurement is universally available, the information on companies' internal allergen standardization has to be assessed case by base. As a general requirement, companies have to follow the requirements outlined in the EMEA/CHMP/BWP/304831/2007 Guideline on Allergen Products: Production and Quality Issues.

**Q: Is there evidence that the use of allergen mixtures within one homologous group achieves better/worse outcome and is equally safe than single allergen extracts?**

**A:** No evidence.

**Q: Is there evidence that the use of different homologous groups achieves better/worse outcome and is equally safe than single allergen extracts?**

**A:** No evidence.

**Q: If there is only limited (or no) evidence to answer these questions - is there a need to generate these data in the paediatric population?**

**A:** Yes, there is a need to generate evidence, but first in adults.

**Q: Can allergen extracts of different homologous groups be mixed?**

**A:** There is a potential practical benefit for the patient to be treated with only one course of treatment to treat two allergies. Thus, if efficacy and safety would be shown for an individual product, there is a rationale for using such a product, even in children (faster and easier treatment of two allergies).

Several aspects to consider:

Safety aspect:

- With mixed allergens, potentially higher risk to have an adverse reaction; however that seems to be based more on personal experience than on literature;
- When mixing allergens one doesn't know which one might be causing an adverse reaction.

Efficacy aspect:

- How to ensure minimum content of relevant allergen?
- Dose finding has to be done in adults.
- To achieve successful immunotherapy, a minimum dose of major allergen must be administered. The problem of using different homologous groups is that this means that a large amount of allergen must be given to achieve this minimum dose per each allergen group. Often, this minimal dose is not achieved in which case the result is sub-optimal. Additionally, with each allergen being added there is the additional risk of allergic side effects anecdotally. There is some evidence that

SLIT, with a limited number of mixed allergens (different homologous groups), does not increase the risk of side-effects in children. (Agostinis F et al. *The safety of sublingual immunotherapy with one or multiple pollen allergen in children. Allergy, 2008, 63, 1637-1639*).

- The problems arising from dilution of extracts and degradation of extracts resulting from adding additional extracts to a mixture are confirmed. The published literature of the use of multiallergen extracts in subcutaneous and sublingual immunotherapy indicates that multiallergen extracts are effective when given by injection, but a similar efficacy has not been established for them when administered sublingually. Summary: Multiallergen extract mixes are probably effective for subcutaneous immunotherapy provided attention is paid to the concentration of each allergen in the mix and mixing of protease containing extracts with pollen and dander extracts is avoided. Further studies are needed to determine if multiallergen mixes are effective in sublingual immunotherapy. (Nelson, Harold S. *Specific immunotherapy with allergen mixes: what is the evidence? Current Opinion in Allergy and Clinical Immunology: 2009 – Vol. 9 - Issue 6 - p 549-553*)

General agreement:

- Mixtures of allergens of maximum two different homologous groups (grass and birch group; or grass and weed group) are possible, however, the following pre-requisites are necessary:
  - an efficacy / safety study must be performed in patients suffering from both allergies;
  - efficacy endpoints must be evaluated and presented for each allergen season separately.
  - documenting the exposure to the relevant allergens and defining in the study protocol the minimum pollen count which has to be reached to define the evaluation period for both seasons is mandatory

Representatives from the Paul Ehrlich Institute (PEI) explained the specific situation in Germany. PEI agreed with companies that in case of evaluating mixtures of grass and weed pollen extracts, patients must have documented allergy to both allergens, however, efficacy will only be evaluated for grass pollen, as

- the number of patients allergic to weed pollen is too small in Germany to allow adequately powered clinical studies to evaluate efficacy separately in both seasons
- there is an overlap in the grass pollen season and weed pollen season

As a PIP application for such an extract (mixture grass/weed pollen) has already been submitted, the PDCO must discuss what to request for the paediatric population.

### **1.3. Outcome parameters:**

## **Symptom scores and medication scores for children**

**Q: Are (paediatric specific) symptom and medication scores available?**

**A:** Not at present, no validated symptom score exists.

**Q: Is there a need to generate scores? Is there a preference for specific scores? Can companies be recommended or encouraged to follow one?**

**A:** A standard procedure for assessing symptoms and evaluating the use of rescue medication appears vital in order to draw correct conclusions from a study. Therefore, companies should be asked to validate whatever score they are proposing to use. In addition, it was proposed that the PDCO takes the initiative for obtaining information needed to establish such a balanced and validated scoring

system. Therefore the symptom score which is recommended by the EMEA Guideline on the Clinical Development of Products for Specific Immunotherapy for the treatment of Allergic Diseases (CHMP/EWP/18504/2006) should be always implemented as secondary endpoint. This score was already used in successful paediatric trials and give the opportunity to collect data with one score similar in all studies in addition to the well defined primary endpoint proposed by the applicant.

It is the same score as given below for the definition of a minimum level of symptoms for inclusion.

### **Definition of appropriate minimum level of symptoms for inclusion**

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).

Symptoms for allergic rhino-conjunctivitis to be scored are:

- nasal itching;
- sneezing;
- rhinorrhea,
- nasal obstruction;
- ocular itching/grittiness/redness; and
- ocular tearing.

#### **Q: Taking the above example with a total score of 18 - what could be considered to be a relevant minimum level of symptoms for inclusion?**

**A:** Majority replied: a total score of 10 -12; however one must taken into consideration that scores at time of inclusion determine severity of disease under pharmacotherapy to relieve allergy symptoms; thus a score of > 10 - 12 might be too high.

Finally general consensus: minimum level of symptoms prior to randomization to be defined as at least moderate level in 2 symptom categories.

### **Definition of clinically relevant treatment effect**

#### **Q: What could be considered a clinically relevant treatment effect?**

**A:** Need to ask the patient and see if what they perceive relevant is the same as the effect measured. At present there is no data available. Only with regards to Juniper QoL questionnaires: a 0.5 unit difference reported to be perceived as relevant improvement.

The following aspects were discussed:

- For both treatments (SCIT and SLIT) an efficacy of 20% over placebo e.g. in the symptom/medication score may be regarded as a clinically relevant effect. However, due to the higher risks of SCIT, an efficacy of 20% is unlikely to lead to a positive benefit-risk-ratio.

Recent antihistamines reach an efficacy of approximately 20% over placebo, too. For SLIT, 20% efficacy may lead to a positive benefit-risk-ratio, since the risk of severe adverse events is low and the option for a disease-modifying effect is given. In contrast, for SCIT there is a clear risk to suffer of severe adverse events (up to serious events like anaphylactic shock). Therefore, an efficacy of at least 30% must be given, to compensate for the higher risk.

- To pre-define a responder, whatever score used, would increase the sample size dramatically.

Final consensus:

- Requirement to demonstrate improvement of both symptom and medication score.
- Improvement of one category in two symptoms considered as clinically relevant.

Companies must provide:

- Detailed information on the symptom score and the medication score proposed to use.
- Definition of the primary endpoint(s).
- If a combined symptom-medication score is applied, the method to combine both scores has to be pre-specified and justified.
- Regardless of the choice of the primary efficacy parameter(s), the applicants should provide a definition of a clinically meaningful effect in the primary endpoint(s) and the basis for choosing this value. The validity of the assumptions on the expected treatment effects and variability used for the sample size calculation should be thoroughly considered and be supported by data and/or literature references.

## **Immunologic markers:**

**Q: What immunologic markers are warranted as secondary endpoints?**

**A:**

- Allergen specific IgG and IgG4.
- Regulatory T cells in a subgroup of patients as exploratory endpoint (recommended but not mandatory).

### ***1.4. Statistical analysis:***

**Q: What power to detect effect over placebo: 80 vs. 90% - taking into account that long-term efficacy in adults has to be demonstrated prior to paediatric trials?**

**A:** 80%

### ***1.5. Dose-finding studies in children:***

**Q: Is it acceptable that dose can be extrapolated from adults?**

**A:**

**Majority:** Yes - up to now all products are used in children at the same dose as in adults without safety concerns; the effective major allergens concentration should be the same in adults and children with the rationale that the higher the dose, the more effective the treatment is; children seem to have less adverse effects than adults and, therefore, can tolerate these higher doses relative to their body weight.

### **One expert:**

- No, taking into account that SLIT dosing is less effective in paediatric population in some studies.
- No, if considering that the adequate dosing regimen is particularly unknown in very young children and the age limit with 5-6 years is arbitrary and that it would make sense to even start earlier.
- No, if considering the effect of preventive immunotherapy – for which at present no idea what kind of dose, how long, which regimen would be the best.

Final consensus:

First to obtain data from dose-finding studies in adults; then to evaluate and to decide in children on a case by case basis.

### **Q: Does this apply for both SCIT and for SLIT or only for SCIT?**

**A:** To both

### ***1.6. (Long-term) efficacy / safety extrapolation from adults:***

At present evidence is still lacking to allow a final conclusion whether or not long-term efficacy in children might be extrapolated from adult data. Some data, demonstrating long-term clinical effects and the potential for preventing development of asthma in children with allergic rhinoconjunctivitis up to 7 years after a 3-year course of specific immunotherapy (SIT) with standardized allergen extracts support the proposal for extrapolation (Jacobsen L et al. Allergy 2007).

Divergent positions argue that at present the exact mechanism of how the immune-modulating effect of SIT is achieved is unknown; therefore extrapolation does not seem appropriate.

### **Q: Can long-term efficacy be extrapolated provided that long-term efficacy has been shown in adults, and that short-term studies in children have shown comparable efficacy as in adults?**

**A:** The following questions were raised:

- What level of evidence is needed to state long-term efficacy in children?
- Is it sufficient, if long-term efficacy in children is shown for some products to extrapolate these results to other products including the same allergen?
- If for some products long-term efficacy was shown in children, is there a need for further products for the same indication?
- Are placebo-controlled long-term studies in children necessary for each product if the same allergens are included or is it sufficient to have one or two products with proven efficacy for the treatment of children? Further products may be given a waiver and be excluded from the indication for long-term efficacy in children, except in case that superiority will be shown over an already approved product.

The following aspects were discussed:

- There is no evidence, that long-term efficacy can be extrapolated; otherwise there is even no evidence, that the mechanism of action is different between adults and children. There are some studies (unfortunately open - but controlled - studies) which gave evidence for disease modifying effect of SIT in general in children.

- The effect of treatment might be different in paediatric population compared to adult population; Because of the plastic nature of the paediatric immune system, the long-term benefit in children might be expected to be even better than in adults.
- Thus a disease modifying effect of immunotherapy in children as well as the long-term efficacy cannot be extrapolated from adults.
- Without long-term reduction in disease severity and disease modifying capability, immunotherapy may not be cost-effective and consequently not be a real alternative to pharmacological treatment. Children are the ideal population in which to start prevention.
- Prescribing physicians prefer to use products with proven long-term efficacy.
- 3 years placebo-controlled studies will be very challenging, particularly for SCIT (will they be accepted by ethics committee? Feasibility to recruit enough patients?).
- According to the data provided by the PEI, approx. 80 PIP applications (by a total of 8-9 different companies) are expected. As it is unfeasible to perform 80 placebo-controlled, long-term efficacy and safety studies in children, companies will have to decide on which allergen extract to focus to perform the required placebo-controlled, long-term efficacy and safety studies.

Final conclusion:

At present evidence is lacking whether or not long-term efficacy can be extrapolated. Until such evidence is available, long-term studies have to be performed in the paediatric population. This requirement might be revised with evolution of knowledge and an increased availability of data.

**Q: Should paediatric trials be deferred until long-term efficacy has been established in adults - or could it be considered unethical to prevent paediatric population to be investigated once short-time treatment is demonstrated in adults?**

**A:** There is a need to treat children as soon as possible with a disease modifying treatment to prevent the so called "allergic march". As a disease modifying effect is assumed for specific immunotherapy and has been demonstrated in several cases, it could be considered unethical to not perform clinical trials in the paediatric population once short-time efficacy is demonstrated in adults.

Final consensus:

Paediatric trials should be initiated as soon as

- a tolerated dose range;
- a dose-response relationship for clinical efficacy;
- short-term efficacy; and
- safety data demonstrating no increased risk of anaphylactic reactions from adult trials (possibly including adolescents) are available.

**Q: What minimum treatment duration and minimum post treatment follow-up period to request? (Seasonal / perennial rhinitis).**

**A:** General consensus:

- It is standard to maintain immunotherapy for at least 3 years.
- At least 2 years if not 3 years minimum treatment-free follow up period.

### **1.7. Age groups:**

In studies with different age groups including adolescents, it is recommended that parents should rate for all age groups to achieve consistency.

#### **Q: from your experience is this realistic for adolescent patients?**

**A:** The relevant answer comes from the adolescents, rather than the parents. It must be ensured that the symptoms are always rated in the same way throughout the study either by the parent or the patient depending on the age groups. Since different scoring may bias the results, adolescents should either be included in adult studies where it is assumed that adolescents will rate themselves; in case adolescents are included in a paediatric study and adolescents rate themselves, a sub-group analysis has to be performed.

### **1.8. Waiver for clinical studies:**

#### **Q: In children below 5 years acceptable? Does this apply for both SCIT and for SLIT?**

**A:** Yes, for both

### **1.9. Animal studies:**

#### **Q: Is there a need for further (juvenile) animal toxicity studies in addition to pre-clinical program for adults?**

**A:** No

## 2. INSECT VENOM ALLERGY

For insect venom allergy it is considered unethical to place allergic subjects at high risks by providing placebo in the control group. Therefore non-inferiority active controlled trials are requested.

### **Q: What comparator to use?**

**A:** Another product with proven efficacy in paediatric studies.

Immunological parameters in insect venom therapy are not recognized as an accepted proof of efficacy of an insect venom preparation. Efficacy in adult studies is shown using insect sting challenge.

### **Q: What endpoint to evaluate efficacy in paediatric trials?**

**A:** At present the only method able to evaluate the efficacy is sting challenge both in adults and children. Sting challenge is suitable also for children. With regard to controlled sting versus field sting challenge: It might be unethical not to do sting challenge in the lab (under controlled conditions and appropriate medical care) and risk the kid to be stung in the fields with no medical care available. In addition, performing a controlled sting challenge offers the additional benefit of educating caregivers/parents what to do in case of adverse effects.

### **Q: How can assay sensitivity be ascertained?**

**A:** Maybe in future by using recombinant insect venom allergenic molecules (Ves v1, Ves v5,) in order to exclude the carbohydrate groups potentially responsible for clinically irrelevant cross-reactivities.

### **Q: What constitutes an appropriate non-inferiority margin?**

**A:** A properly non-inferiority margin should ensure that the test drug has a clinically relevant effect. Thus, the choice of the non-inferiority margin depends on the treatment effect of the comparator. For vespid venom allergy approximately 5% chance for therapeutic failure after a VIT (licensed preparation) is well documented; for honey bee venom allergy the expected failure rate at treatment with a licensed product is about 15%. Beatrice Bilo, chair of EAACI insect venom hypersensitivity interest group, suggested that a 10% of failure rate for vespid and a 25% for honeybee venoms (using the standard maintenance dose of 100 mcg) could be acceptable. However, there was no general consensus which failure rate could be considered acceptable for a clinical trial.

PDCO to decide case by case

### **Q: What should be the minimum study duration requested for - ultra-rush / - rush / - slow regimens?**

**A:** Three years in all cases. Ultra-rush and rush have their clinical importance in cases of danger of re-sting in near future as the patient can be protected after a few days of rush therapy, but to obtain maintenance of the protection at least 3 years treatment are needed.

However, after 6 months of a well tolerated (no systemic allergic symptoms without antihistamine prophylaxis) standard maintenance dose (100 mcg) normally a sting challenge will be tolerated. Therefore, in controlled double-blind studies a well tolerated standard maintenance dose (100 mcg) must be administered for at least 6 months before the sting challenge and the primary efficacy analysis will be performed. Open-label treatment must be continued until results of the primary efficacy analysis are available. Provided the product is found to be non-inferior to the comparator, treatment must be continued for a total of three years; thereafter patients must be followed for additional (2) - 3 treatment-free years to evaluate long-term efficacy.

**Q: Minimum requirement for duration of follow-up period?**

**A:** At least three years.

**Q: To generally request serum tryptase investigation as marker for latent mastocytosis as inclusion criterion?**

**A:** Clinically, latent mastocytosis should be looked for in patients with venom immunotherapy. Serum tryptase is a simple marker of a patient who has the potential to have a severe anaphylactic reaction and which could influence the duration of treatment (potentially life-long). Although mastocytosis/elevated serum tryptase does not seem to be a risk factor of insect venom allergy in children (albeit only few data on this topic), it should be documented as part of the pre-treatment evaluation and presented in the results, maybe with subgroup-analysis.

**Q: Any additional comments / issues considered necessary to discuss?**

**A:**

- Inclusion criteria for VIT are different between children and adults: children included only with a higher severity grade of sting reaction.
- Some risk factors for more severe side effects of VIT not present in children (cardiovascular co-morbidity).
- Children more often suffer from bee venom allergy (which is the less tolerable and less effective venom, at least in the standard dose of 100 µg venom). Therefore results of studies in adults may be not comparable to those with children.

## Conclusion

As a consequence of the discussion with the experts the draft standard PIP for allergen extracts for specific immunotherapy was revised and adopted by the PDCO. It is published on the EMA webpage:

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/11/WC500015814.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500015814.pdf)