



European Medicines Agency

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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**CONCEPT PAPER ON THE PREPARATION OF A GUIDELINE ON THE CLINICAL
DEVELOPMENT OF PRODUCTS FOR SPECIFIC IMMUNOTHERAPY FOR THE
TREATMENT OF ALLERGIC DISEASES**

AGREED BY EFFICACY WORKING PARTY	11 January 2006
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END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 April 2006

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1. INTRODUCTION

Clinical issues in allergic disease are partially addressed by the ‘Guideline on the Clinical Development of Medicinal Products for the Treatment of Allergic Rhino-Conjunctivitis (CPMP/EWP/2455/02)¹’ and the ‘Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Asthma (CPMP/EWP/2922/01)²’. However, both documents focus exclusively on the development of medicinal products to treat allergic symptoms. They do not include specific immunotherapy (SIT); a treatment which alters the course of allergic diseases. Moreover, there are additional indications where SIT is used as first line treatment to prevent anaphylactic reactions (e.g. insect venom allergy) or is currently under investigation e.g. for atopic dermatitis or food allergies; these allergic conditions are not considered in the existing guidelines. Taken together, there is a need to draft a new guideline rather than revising the existing ones.

As no common agreement exists on clinical trials with SIT, guidance is required to harmonise the requirements for such clinical trials within the European Union. This is particularly important in light of the fact that several Phase II and III clinical trials are ongoing with both natural and recombinant allergen products.

2. PROBLEM STATEMENT AND DISCUSSION

Up to now, no common agreement exists on the performance of clinical trials in SIT. The application of existing guidelines is not sufficient to solve specific problems in the design of such studies and to facilitate a robust design of clinical trials which are accepted by all member states of the European Union. In addition, no consensus view exists on the evaluation and interpretation of results of SIT studies.

Although the term “Allergy Vaccination” is frequently used for SIT, it is an immunomodulatory treatment for diseased individuals. The therapy is performed by administering the allergen to which the patient is sensitised and which elicits allergic symptoms. These allergens are mostly naturally occurring (glyco)-proteins which are not harmful to healthy individuals. They originate e.g. from seasonal allergen sources (e.g. tree, grass or weed pollen), perennial allergen sources (e.g. animal epithelia, moulds, mites) and venoms (e.g. bee and wasp venom). Although used for several decades, the complex immunological mechanisms of SIT are not completely understood. Moreover, the amount of allergen administered is relatively low (in the range of 5-20 µg of major allergen per single administration for subcutaneous immunotherapy (WHO Position paper³)) making its detection in organs and body fluids rather difficult. In addition, the use of the principle of “allergen families” (i.e. a representative allergen for a group of allergens) in the clinical evaluation has not been defined. Thus, guidance is required in relation to whether and to what extent pharmacokinetic and pharmacodynamic data are needed, the relevance of structurally related (cross-reacting) allergens for performing SIT and specific issues concerning seasonal and perennial allergens.

Most adverse events related to SIT are allergic reactions. Thus, adverse events, in addition to clinical efficacy have to be assessed in allergic subjects. Moreover, clinical efficacy cannot be determined in poly-sensitised subjects allergic to different allergens with overlapping seasons. Taken together, these factors limit the number of study subjects available for clinical trials. Guidance is needed on general requirements for the development and performance of clinical studies and criteria for patient inclusion.

Moreover, there is limited consensus on multiple issues such as primary and secondary endpoints, minimum required clinical efficacy, duration of studies, measurement of long-term efficacy, and calculation of the minimum number of study subjects required to adequately determine safety and efficacy.

SIT can be administered by different routes which may have different paths and mechanisms of modulating the immune system. While experience (including long term) exists for the subcutaneous route of allergen administration, the sublingual route is currently under extensive investigation in

clinical trials. Only few data on its mechanism of action are available to date. The transferability of data between both application routes is the subject of ongoing debate.

In summary, detailed guidance on the planning and design of clinical trials in SIT is necessary to harmonise the marketing authorisation process for medicinal products for SIT within the European Union.

3. RECOMMENDATION

It is proposed that a CHMP guidance document on the clinical development of medicinal products for specific immunotherapy with protein allergens be prepared. This document should address the appropriate and correct planning of clinical trials in SIT.

The following topics were regarded as particularly important:

- Requirements regarding pharmacokinetic and pharmacodynamic studies (generally and with regard to different SIT application routes)
- Role, relevance and timing of provocation tests and laboratory parameters as efficacy markers
- Study design aspects:
 - inclusion / exclusion criteria,
 - choice of endpoints,
 - study duration,
 - dose regimen and dose-response studies,
 - comparator,
 - measurement of long-term efficacy (preventive effects),
 - safety data
- Specific aspects of seasonal versus perennial allergens
- Define qualitatively and quantitatively beneficial effects in patients which are considered clinically relevant
- Relevance of cross-reacting allergens and of the principle of “allergen families” in clinical trials
- Specific aspects regarding natural allergen extracts versus recombinant allergens or allergen peptides
- Extrapolation of study results between different routes of application
- Special issues regarding SIT trials in children

4. PROPOSED TIMETABLE

It is anticipated that draft CHMP guidance documents be available 12 months after adoption of the Concept Paper.

5. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this Guideline will involve the EWP only.

6. IMPACT ASSESSMENT (ANTICIPATED)

The guidance document will provide guidance to both Industry and Regulatory Authorities regarding the clinical development and assessment of allergen products for specific immunotherapy. This should result in a more consistent approach and contribute to improved harmonisation and consequently

increased availability of allergen products with enhanced clinical efficacy and safety, thereby providing public health benefits.

7. INTERESTED PARTIES

European Academy for Allergy and Clinical Immunology (EAACI)

European Federation of Allergy and Airways Diseases Patients Associations (EFA)

8. REFERENCES TO LITERATURE, GUIDELINES ETC

- 1 Guideline on the Clinical Development of Medicinal Products for the Treatment of Allergic Rhino-Conjunctivitis (CPMP/EWP/2455/02)
- 2 Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Asthma (CPMP/EWP/2922/01)
- 3 WHO Position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. Geneva: January 27-29 1997. Allergy 1998;53(44 Suppl):1-42