2 SYNOPSIS

NAME OF COMPANY: Allergopharma GmbH & Co. KG	NDIVIDUAL STUDY TABLE REFERRING TO PART ……OF THE DOSSIER Volume: not applicable Page: not applicab	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: Allergopharm® Skin Prick Test Solution		
NAME OF ACTIVE INGREDIENT: Allergen-Test Solutions: 6-grass pollen mixture, house dust mite (Dermatophagoides pteronyssinus), birch pollen, mugwort pollen		

Title of study:

Design of optimally-diagnostic skin test solutions for diagnosis of sensitisation to a 6-grass pollen mixture, house dust mite (Dermatophagoides pteronyssinus), birch pollen and mugwort pollen

Principal Investigator (according to AMG):

[redacted]

Study centres:

The study was conducted in six study centres in Germany.

[redacted]

Publication (reference):

None

Study period:	**Phase of development:**
01/2008 - 07/2008	III/IV

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Objectives:

The objective of this study was to identify the most appropriate concentration range of allergen extracts to diagnose a sensitisation for each investigational allergen by Skin Prick Testing.

Methodology:

This clinical trial was performed as a multicentre phase III/IV study to generate the ROC curves to assess diagnostic sensitivity and specificity and analyse the safety for the investigational Skin Prick Test solutions.

Number of patients (planned and analysed):

Planned:

It was planned to screen 500 patients.

Analysed:

Altogether 435 patients were screened and 431 patients were analysed in the Safety Set and 387 patients were analysed in the Full Analysis Set (FAS)

A Per-Protocol (PP) analysis was not done as the PP patient group was not more than 10% smaller than the FAS patient group.

Diagnosis and main criteria for inclusion:

- Patients with an anamnesis referring to suspicion of an IgE-mediated allergy (type I acc. to COOMBS and GELL) against at least one of the investigational allergens;
- Sensitisation to at least one of the investigational allergens evaluated by a Skin Prick Test not older than 12 months in the medical history;
- Male and female outpatients, 18-60 years;
- For female patients: effective contraception and negative pregnancy test result.

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Test product, dose and mode of administration, batch no.:

Test product for detection of sensitisation:

Skin Prick Test solutions for the allergens 6-grass pollen mixture (Holcus lanatus, Dactylis glomerata, Lolium perenne, Phleum pratense, Poa pratensis, Festuca elatior), house dust mite (Dermatophagoides pteronyssinus), birch pollen and mugwort pollen.

The test product was provided in vials containing five different concentrations for each allergen increasing in threefold steps of [redacted], [redacted], [redacted], [redacted] and [redacted].

Skin Prick Test solutions were applied in a blinded way according to allergen, the tested different concentrations, and negative and positive control. Neither the patient nor the investigator knew, which solution was tested at which area on the volar sides of the forearms.

Batch numbers:

Allergen	**Concentration of Skin Prick Test solution** [redacted]
6-grass pollen Mite (D. pteron.) Birch pollen Mugwort pollen	[redacted]

Positive controls	histamine dihydrochloride, [redacted] histamine dihydrochloride, histamine dihydrochloride,	[redacted]
Negative control	saline solution	[redacted]

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Duration of treatment:

The four investigational Skin Prick Test solutions were applicated once at visit 2.

Reference therapy, dose and mode of administration, batch no.:

not applicable

Criteria of evaluation:

Efficacy:

Optimal diagnostic concentrations of the investigational Skin Prick Test solutions defined as optimal trade-off between sensitivity and specificity done by the method of the Receiver Operating Characteristic (ROC) analysis. The ImmunoCAP™ fluoro enzyme immuno essay, the anamnesis and a Skin Prick Test in the medical history were used as “absolute standard” according “Points to Consider on the Evaluation of Diagnostic Agents (CPMP/EWP/1119/98).

Safety:

Adverse Events
A global assessment of tolerability was to be carried out by the investigator.

Statistical methods:

Receiver Operating Characteristic (ROC) analysis was carried out to detect the Optimal Diagnostic Concentration (ODC) for each allergen and each defined absolute standard. The null hypothesis that the estimated area under the ROC equals 0.5 was tested confirmatively ($\alpha = 0.05/12$ under consideration of the multiplicity problem resulting from usage of the data from the same patients for the determination of the ROC for four allergens and three different “absolute standards”).

Determination of sensitivity and specificity for each concentration of each allergen and each defined absolute standards.

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Summary and conclusions:

Efficacy results:

The ROC curve showed that all three “absolute standards” could be used as “absolute standards” for Skin Prick Test solutions to achieve the primary objective of finding an appropriate concentration. This analysis was based on testing the area under the ROC curve, using the null hypothesis that this area is equal to 0.5. All 12 hypotheses where highly significant, in spite of the Bonferroni correction used to correct for multiple testing.

The ImmunoCAP™ as absolute standard gives the largest AUC for all allergens tested followed by the historical Skin Prick Test and the anamnesis. In the case of ImmunoCAP™ the AUC of birch pollen was as high as 0.9. It may thus be considered the absolute standard of choice for the study allergens.

Secondary objective of the study was the evaluation of an optimal trade-off between sensitivity and specificity for the presence of specific IgE by the method of the ROC analysis. Specificity as well as sensitivity of at least 80% was the desired objective of this study. Comparing ImmunoCAP™ being the test with the highest accuracy based on the AUC of the ROC curve the following extracts and concentrations fulfilled this optimal criterion of sensitivity as well as specificity of over 80%: 6-grass mixture and birch pollen [redacted], [redacted] and [redacted] and dust mite (D. pteron.) [redacted] and [redacted]. This optimal criterion with sensitivity as well as specificity of at least 80% was not fulfilled for any concentration for the allergen mugwort pollen. The highest sensitivity of 60.3% was achieved with a specificity of at least 80% at a concentration of [redacted].

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Summary and conclusions (continued):

Safety results:

The Skin Prick Test for all allergens was very well tolerated. There was no serious adverse event reported. Only one systemic event (dizziness for one minute) occurred. This event was assessed as non-serious. The local adverse events were all expected.

2 SYNOPSIS (continued)

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Summary and conclusions (continued):

Conclusion:

Based on the results of this clinical trial the absolute standard of choice is the ImmunoCAP™ followed by the historical Skin Prick Test. The anamnesis as "absolute standard" did not give satisfactory values for sensitivity and specificity. For all four allergens and the absolute standard ImmunoCAP™ the highest sensitivity based on a specificity of at least 80% was observed for the skin prick solution of [redacted]. The sensitivity for 6-grass pollen, birch pollen, house dust mite and mugwort was 93.5%, 94.8%, 85.0% and 60.3%.

These tests can only confirm clinical symptoms and identify responsible allergens. For this reason it is always important to interpret diagnostic test results in the context of the medical history and relevant allergen exposure as well as the performance characteristics of the diagnostic test (e.g. sensitivity and specificity) for the chosen allergy test system. Any therapeutic decision can not be executed on the base of skin prick results alone.

For mugwort a sensitivity of 60.3% was reached with the concentration of [redacted]. Because a specificity of less than 80% seems not to be acceptable a dose of [redacted] with a sensitivity of 60.3% seems to be the best diagnostic concentration.

Further the study confirmed the appropriateness of the saline solution used as negative control for Skin Prick Testing in this clinical trial. For 97.4% of the Safety Set (420 of 431) the reaction with the saline solution was < 3mm as required for a valid Skin Prick Test.

Commercial Allergopharma Skin Prick Test solutions have been used for years routinely in the diagnosis of IgE-mediated type I allergies. The safety of these products is excellent. The intended dosage is appropriate and generally recognised. The benefit-risk assessment is a favourable one, as is the product's safety and tolerability profile.

Date of revised final report:
17/02/2015