2 SYNOPSIS

NAME OF COMPANY: **Allergopharma Joachim Ganzer KG, Reinbek** **NAME OF FINISHED PRODUCT:** Phleum Cocktail **NAME OF ACTIVE INGREDIENT(S):** Cocktail of recombinant major allergens of Phleum	**INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF DOSSIER** **Volume:** **Page:**	**(FOR NATIONAL AUTHORITY USE ONLY)**
Title: A double-blind placebo-controlled dose-response study for evaluation of safety and efficacy of immunotherapy with a cocktail of recombinant major allergens of Timothy Grass Pollen (Phleum pratense) adsorbed to aluminium hydroxide in patients with IgE-mediated allergic rhinitis/rhinoconjunctivitis with or without bronchial asthma **Trial No.** Al0701rP**;** Trial Protocol Amendment 3 of January 22, 2008;		
Investigator: [redacted]		
Study centre: [redacted]		
Publications: The publications are given in Appendix 0.		
Study period: November 2007- May 2008 Patients were offered three years of therapy after study end.		**Clinical phase:** II
Objectives: The aim of this study is to measure the tolerance and efficacy of 4 concentrations of a cocktail of recombinant major allergens of timothy grass (Phleum pratense) for specific immunotherapy (SIT) in grass pollen allergic patients suffering from allergic rhinitis / rhinoconjunctivitis with or without asthma (GINA I and II).		

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Methodology:

This study is a randomised, double-blind, placebo controlled, dose-response study with five arms including placebo. The study treatment will be carried out up to five month prior to the grass pollen.

Number of subjects:

After screening 73 patients, 50 patients were enrolled to the five treatment arms, 10 per arm. All patients enrolled were evaluated in the ITT set.

All 73 patients screened were of Caucasian ethnic affiliation, with mean age 32 years and a proportion of 49% male (n = 36) and 51% female (n = 37) In the ITT Set there were 27 (54%) males and 23 (46%) females. The mean age of the ITT set was 32 years as in the All Patient set. In the ITT set 74% of the patients were between 18 and 39 years of age, with 26% between 40 and 64 years of age.

There were 2 study dropouts (excluded from the PP set), patient 25 in the placebo arm after 3 injections and patient 34 in arm 3 after 8 injections.

Diagnosis and criteria for inclusion:

Patients age 18-50 yrs, diagnosed with IgE-mediated allergic diseases including:

Patients with IgE-mediated, moderate to severe seasonal allergic rhinitis with controlled asthma (FEV1 at least 80% predicted normal according to ECCS (GINA 2006)), attributable to grass pollen allergens

Main symptoms of allergic rhinitis/rhinoconjunctivitis against grass pollen allergens ***and***

Proven clinical relevance of grass pollen allergy by positive conjunctival provocation test result using natural grass pollen extract ***and***

Positive prick test reaction to natural grass pollen allergen demonstrated by allergen weal at least as large as histamine control reaction (histamine-dihydrochloride 1,7mg/mL = 1 mg/mL Histamine, 0.1%) and $\geq$ 5mm diameter and a negative control test (saline solution). A positive

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histamine control reaction is demonstrated by weal diameter ≥ 3mm, a negative control test is demonstrated by weal diameter <3mm) ***and***

Positive EAST (Allergopharma Joachim Ganzer KG) to grass pollen ≥ 2 measured by Central Lab

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

Cocktail of recombinant major allergens of Phleum pratense (timothy grass) with 4 strengths

Injections were to be given subcutaneously at weekly intervals provided that the previous dose was well tolerated; otherwise dose modifications were recommended.

Dosage guideline:

Strength 1 ([redacted]),
Strength 2 ([redacted]),
Strength 3 ([redacted]),
Strength 4 ([redacted])

Batch No. PK

[redacted]

Duration of treatment:

The treatment period was from November 2007 through April 2008. Data from a follow-up phase will be summarised in a separate document attached to this clinical study report. All patients are being offered an active treatment of 3 years (acc. to WHO-recommendation)

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

Placebo: **$Al(OH)_3$-Placebos with histamine-dihydrochloride** analogue Allergen-Adsorbate rPhleum strengthes 1 to 4.

Batch No. PK

[redacted]

Dosage guideline according to active treatment: strength, treatment was to be stopped with the start of the pollen season. Recommendations for supervision of the patient and for dosage modification were the same as for the active trial preparations.

Criteria for evaluation:

Distribution of the patients to one of the five groups was performed randomly according to the double-blind design.

Safety:

Primary endpoint:
The primary endpoint of this study is the number of patients with at least one systemic reaction (according to Tryba Grade 1-4) with possible, probable or definite relationship to the study medication determined at the end of the uptitration phase.

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Efficacy:

Secondary endpoints:

- Changes of the Late Phase Reactions in specific intracutaneous test with natural allergen before and at the end of the double-blind placebo controlled phase before grass pollen season
- Changes in specific conjunctival reactivity with natural allergen before and at the end of the double-blind placebo controlled phase before grass pollen season
- Immunologic changes of allergen specific IgE, IgG_1 and IgG_4.

Statistical methods: The study data were evaluated by means of non-parametric methods. The homogeneity between the five treatment groups was tested using Fisher's Exact Test

The level of significance determined for the primary endpoint was $\alpha = 0.05$. Tests for all other parameters were also considered as being significant at the 5% level.

The Statistics Department of Allergopharma Joachim Ganzer KG, Reinbek, performed the biometric evaluation.

Summary and Conclusions:

Efficacy: The main objective of this study was safety considerations. None the less three different efficacy parameters were included for evaluation. These were the IC-Test, the CPT, and the immunological parameters IgE, IgG_1 and IgG_4.

Changes from baseline in the IC-Test can not be evaluated at present because it was stopped for all patients during the final visit for the reasons given in 11.4.1.2.1. An amendment to this study stipulated that the IC-Test be done in a follow-up on those patients who had not been in the placebo treatment group. The result of this follow-up will be documented in a separate document attached as it is not part of this study.

From the data available at screening it can clearly be seen that both the weal and erythema increase with increasing concentrations of allergens.

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This holds for the early and late phase reactions. The few observations available at the final visit show the same pattern of increase in reactions with increasing concentrations of allergens. Further, from the very few observations available after therapy it can tentatively be observed that the reactions of the placebo patients seem to be greater than those of the patients treated with verum.

The results of the conjunctive provocation test showed no significant difference in the improvement between treatment groups. This was hardly to be expected amongst five treatment groups each including 10 or fewer patients. Considering all patients in a verum treatment arms (arm 1 to arm 4), 29 or 74.4% improved and 10 or 25.6% remained the same. By comparison in the placebo treatment group 4 or 50% improved and 4 or 50% remained the same. This result is however also not statistically significant.

In the placebo treatment group, the mean IgE levels remain nearly constant over the five blood samples. In the verum groups the mean IgE values decrease between screening and the final visit after therapy.

For the IgG_1 and IgG_4 parameters there is again no change in the mean values for the placebo treatment group. In the verum groups the means tend to increase, however the data is highly variable with many outliers.

Descriptive and graphical interpretation of the efficacy parameters indicates that the patients receiving verum tended to have a better improvement in their condition in comparison to the placebo treatment group. This is especially true of the CPT. Considering however the small sample size of each of the five treatment groups, these results remain without statistical significance.

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Safety: There was no significant group difference in the number of systemic reactions as defined for the primary safety parameter. The number of systemic reactions in each treatment group was equal to or less than that which was assumed for the power calculation of the study. Thus in particular for the higher doses the injections were well tolerable.		
Conclusions: Treatment with even very high doses of a cocktail of recombinant major allergens of timothy grass has been shown to be safe. The intracutaneous test suggests that skin reactivity decreases with rising doses. Moreover, the immunogenic activity of the active trial medication could be demonstrated by the induction or increase of allergen specific IgG_1 and IgG_4.		