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Clinical Study Report
A multicentre, multinational randomised placebo-controlled double-blind pivotal clinical trial for evaluation of safety and efficacy of specific immunotherapy with a cocktail of recombinant major allergens of Timothy Grass Pollen (Phleum pratense) adsorbed onto aluminium-hydroxide in patients with IgE-mediated allergic rhinoconjunctivitis with/without controlled asthma (AMETHYST)

Name of test drug/investigational product:	Cocktail of recombinant major allergens of Phleum pratense or placebo
Indication studied:	IgE-mediated allergic diseases including symptoms of allergic rhinoconjunctivitis with or without controlled asthma triggered by grass pollen allergens.
Name and address of the sponsor:	ALLERGOPHARMA GMBH & CO. KG. Hermann-Körner-Straße 52, 21465 Reinbek, Germany
Protocol identification (code or number):	AL0704rP
Development phase of study:	III
Study initiation date (First patient entered):	29-Feb-2008
Date of early study termination	NA
Study completion date (Last patient completed):	End of double-blind phase: 31-Aug-2011 End of bridging phase and study: 29-Mar-2012
Name and affiliation of principal or coordinating investigator(s) or sponsor's responsible medical officer (SRMO):	[redacted]
Sponsor's contact person:	See accompanying letter from the regulatory approval application.
Statement of Good Clinical Practice (GCP) compliance:	This study was performed in accordance with the Good Clinical Practice regulations as set forth in the ICH Consolidated Guideline E6 (CPMP/ICH/135/95).
Responsible person for archiving of essential documents:	[redacted] Allergopharma GmbH & Co. KG
Date of the report:	Final 1.0 20-Mar-2013

2 Synopsis

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Title of study:
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Investigators:
32 recruiting investigators in Germany, 3 in Italy and 18 in Poland. A complete list of investigators including the country coordinating investigators can be found in ~~Appendix 16.1.4.~~

Study site(s): 53 active sites; 32 in Germany, 3 in Italy and 18 in Poland

Publication (reference): None

Study period (years): Date of first patient enrolment: 29-Feb-2008 Date of last patient completed: - Double-blind phase: 31-Aug-2011 - Bridging phase: 29-Mar-2012	**Phase of development:** III

Objectives:
The objectives of this clinical trial were:

- to prove the hypothesis that efficacy of a specific immunotherapy (SIT) with a recombinant major allergen preparation of grass pollen is statistically and clinically superior to placebo in a representative number of grass pollen allergic patients suffering from allergic rhinoconjunctivitis with or without controlled asthma.
- to evaluate the safety of the preparation of the recombinant major allergens of Timothy Grass Pollen (rPhleum) for perennial treatment.
- to assess immunologic parameters during the course of the study in order to obtain evidence of the immunologic effects of the recombinant major allergen of grass pollen.

Methodology:
This pivotal phase III study had a multicentre, randomised, placebo-controlled, double-blind study design with three parallel groups (placebo and two active dose groups). The placebo group was split into two groups to allow blinding of the two treatment arms which used two different up-titration schemes and maintenance dosage.

Within the sites the patients were assigned to the treatment groups according to a balanced randomisation, i.e. that within the sites the number of enrolled patients in each of the three treatment groups was approximately equal.

The study was planned to include a baseline grass pollen season followed by a double-blind treatment phase for 2 years perennially. Originally the baseline period was planned to start in 2008 but due to insufficient recruitment the baseline period was restarted in 2009. The double-blind phase with treatment of study medication or placebo started in Nov-2009 and ended in Aug-2011. Prior to the start of the pollen season in 2010

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a blinded safety analysis, was performed, that compared patients enrolled in either the lower maintenance dose group (up to [redacted] - group A and respective placebo-group) or higher maintenance dose group (up to [redacted] - group B and respective placebo-group). Two grass pollen seasons (2010 and 2011) were covered during the double-blind phase. Analysis of the primary endpoint was performed as soon as the data of all patients who finished the last visit and assessments were available for analysis. Treatments were continued unchanged until the time of unblinding. This bridging phase started in Sept-2011 and ended in Mar-2012. The study ended after analysis of the double blind phase and the bridging phase. The entire study is reported in this CSR

Number of patients (planned and analysed):

Planned: Approximately 750 patients to be screened and 342 patients to be randomised into the study to provide 228 actively treated patients (114 patients for rPhleum maintenance dose [redacted] (Active - [redacted] group), 114 patients for rPhleum maintenance dose [redacted] (Active - [redacted] group)) and 114 patients for placebo treatment.

Analysed: In total 1338 patients were screened in order to randomise 256 patients into the study; 170 patients to the two active treatments groups (84 patients Active - [redacted], 86 patients Active - [redacted]) and 86 patients to placebo treatment. All of those 256 patients were evaluated in the Safety Set. A total of 241 patients (165 active (Active - [redacted]: 81; Active - [redacted]: 84) and 76 placebo) were evaluated in the efficacy analyses of the Full Analysis Set.

Diagnosis and main criteria for inclusion:

Diagnosis:

IgE-mediated allergic disease manifested as symptoms of allergic rhinoconjunctivitis with or without controlled asthma, triggered by grass pollen allergens.

Inclusion criteria:

- A signed informed consent before initiation of any study related procedures
- Male and female outpatients
- Age 18-60 years
- IgE-mediated, moderate to severe seasonal allergic rhinitis with or without controlled bronchial asthma (peak expiratory flow (PEF) and/or forced expiratory volume in one second (FEV_1) at least 80% predicted normal) attributable to grass pollen
- Major allergy symptoms during grass pollen season
- Symptoms of allergic rhinoconjunctivitis against grass pollen allergens requiring medication during the last grass pollen season
- Proven clinical relevance of grass pollen allergy by positive conjunctival provocation test (CPT) result using natural grass pollen cocktail
- Positive skin prick test reaction to natural grass pollen allergens demonstrated by grass pollen allergen weal diameter ≥ 5mm (to be demonstrated in a valid skin prick test: Negative NaCl control weal < 3 mm, positive Histamine (0.1%) control weal ≥ 3 mm)
- Positive enzyme-linked allergosorbent test (EAST) to grass pollen ≥ 1.5 kU/L determined in a central laboratory
- For female patients: effective contraception and negative pregnancy test result.

At the beginning of the treatment phase:

- Patients must have demonstrated moderate to severe symptoms of allergic grass pollen disease during the baseline season in 2009.

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Test product, dose and mode of administration, batch number:
Cocktail of recombinant major allergens of Phleum pratense in sterile suspension for subcutaneous injection in the upper arm in the following strengths: Strength 1 ([redacted]), Strength 2 ([redacted]), Strength 3 ([redacted]), Strength 4 ([redacted]).

Duration of double-blind phase: 2 years

Reference therapy or comparator, dose and mode of administration, batch number:
Placebo in sterile suspension containing histaminedihydrochloride in two different strengths for subcutaneous injection in the upper arm.

Criteria for evaluation:

Efficacy:

Primary Endpoint:

- The change of the area under the curve (AUC) of the Rhinoconjunctivitis Symptom and Medication Score (RC-SMS) from the baseline season (2009) to the season after 2 years of double-blind treatment (2011).

Secondary Efficacy Endpoints:

- Changes of rhinoconjunctivitis specific Quality of Life at peak pollen season
- Changes in specific conjunctival reactivity to grass pollen allergens
- Changes of RC-SMS after the first treatment year
- AUC of Rhinoconjunctivitis Symptom Score by year
- AUC of Rhinoconjunctivitis Medication Score by year
- AUC of SMS by year
- AUC of Symptom Score by year
- AUC of Medication Score by year
- Changes of overall symptom medication score of rhinoconjunctivitis and asthma (SMS)
- Response (Improvement of AUC of RC-SMS of at least 40% after 2 years of treatment)
- Immunologic changes in specific IgE, IgG_1, IgG_4

Safety:

- All adverse events
- Serious adverse events
- Systemic reactions
- Local reactions
- Adverse events with at least possible relationship to the study medication
- The analysis of all treatment emergent adverse events by intensity (mild, moderate and severe)
- All adverse events with at least possible relationship to study medication during the up-titration phase and during the maintenance phase, respectively, displayed by MedDRA primary SOC and preferred term
- All adverse events with at least possible relationship to study medication displayed additionally according to TRYBA classification, SOC and preferred term
- Clinical laboratory values (clinical chemistry, haematology, urinalysis) and vital signs

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Statistical methods:

The analysis of the primary efficacy variable was performed by applying an analysis of covariance (ANCOVA) model with treatment and combination of sites as fixed effects and the baseline value of the RC-SMS as a covariate. Three hypotheses were to be tested: A global hypothesis regarding the equality of all treatment groups and hypotheses regarding the equality of each active treatment group and the placebo group. In the first step, the global hypothesis was tested with an analysis of covariance with the factors treatment and site and the baseline value of the RC-SMS as a covariate at the level α=0.05. If this hypothesis could not be rejected, the procedure stopped and the hypothesis of no treatment effect could not be rejected. If the treatment effect was found to be significant, the two hypotheses of no difference between each active treatment group and placebo were tested at level α in the ANCOVA model. Due to the hierarchical test procedure no further α-spending was required. All further statistical considerations had exploratory character, only. Exploratory tests were carried out concerning exploratory issues of the primary endpoint, secondary endpoints or exploratory endpoints/objectives, e.g. in the context of homogeneity testing.

DEMOGRAPHY OF STUDY POPULATION

A total of 256 patients were eligible for randomisation in the study. 170 patients were randomised to active treatment and 86 patients were randomised to placebo treatment. Among the 170 patients randomised to active treatment, 84 patients were randomised to [redacted] active treatment (Active - [redacted] group) and 86 patients to the [redacted] active treatment group (Active - [redacted] group). All of the 256 randomised patients were treated and therefore included in the Safety Set for safety evaluation.

A total of 241 patients, 81 patients in the Active - [redacted] group, 84 patients in the Active - [redacted] group and 76 patients in the placebo group who had received at least one dose of study medication and had sufficient information available for any efficacy assessment were eligible for the efficacy evaluation in the full analysis set (FAS). 180 patients were eligible for the Per-Protocol Set (PPS); this included 57 patients (67.9%) in the Active - [redacted] group, 63 patients (73.3%) in the Active - [redacted] group and 60 patients (69.8%) in the placebo group.

Median age at baseline in the Safety Set was 28.5 years in the Active - [redacted] group, 29.5 years in the Active - [redacted] group and 29.0 years in the placebo group. In the Safety Set the percentage of males (66.7% Active - [redacted], 60.5% Active - [redacted]) was higher in both active treatment groups but this difference was not seen in the placebo group (males 47.7% vs. females 52.3%). Bronchial asthma was documented in 27.9% of the actively treated patients (25. 9% Active-[redacted], 29.8% Active-[redacted]) and 26.3% of the placebo patients. Smoking characteristics, history of allergic symptoms, and lung function tests were similar between the two active treatment groups and the placebo treatment group both in the Safety Set and in the FAS.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

For the Active - [redacted] group, the mean of the AUC of RC-SMS decreased from 553.9 at baseline to 422.8 after two years of active treatment which was a mean change of -134.9. For the Active - [redacted] group, the mean AUC of RC-SMS decreased from 558.7 at baseline to 394.4 after two years of active treatment which was a mean change of -165.2. For the placebo group, the mean of the AUC of RC-SMS was 580.1 at baseline and decreased to 440.1 after two years of placebo treatment which was a mean change of -136.0.

The global statistical null-hypothesis of no difference between the mean changes of the AUC of RC-SMS between treatment groups (Active - [redacted] = Active - [redacted] = Placebo) was tested in a confirmatory sense. The difference in the changes of the AUC of RC-SMS between the treatment groups were not statistically significant (p=0.4153) at a significance level of α=0.05. Therefore, superiority of active treatment over placebo after two year of SIT could not be demonstrated.

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When the data were reanalysed without site 39, the results from the ANCOVA model showed greater differences in mean changes of the AUC of RC-SMS for the Active - [redacted] group compared to placebo (p=0.0202) as well as a borderline difference for the Active - [redacted] group (p=0.0738).

Results from the total AUC of the SMS, the AUC of the symptom score and the RC-symptom score as well as the AUC of the medication score and the RC-medication score were similar to those observed for the AUC of RC-SMS.

Changes in specific conjunctival provocation test results (threshold concentration) between baseline and the assessment after two treatment years were evaluated. For patients in both active treatment groups, the changes from the threshold concentration at baseline to end of treatment in the second treatment year showed a statistically significantly greater positive shift to a higher concentration or a negative response indicating a higher tolerance of allergen concentration after active treatment (Active - [redacted] vs. Placebo p=0.050, Active - [redacted] vs. Placebo p=0.019). In the Active - [redacted] group 53.7% of the patients improved and in the Active - [redacted] group 58.6% improved as compared to the placebo group where 37.7% improved.

For the Active - [redacted] group, there was a mean improvement of -0.36 in the RQLQ score after two years of active treatment. For the Active - [redacted] group, there was a greater mean improvement of -0.73 in the RQLQ score. For the placebo group, there was a mean improvement of -0.22 in the RQLQ score. The difference in improvement in RQLQ scores between the Active - [redacted] group and placebo group was statistically significant (p=0.0234).

The median changes of the allergen specific IgG_4 and IgG_1 levels from baseline to last visit were greater in both active treatment groups than for the placebo group which confirmed the immune stimulating effect of the active treatment.

SAFETY RESULTS:

The evaluation of safety included the results of safety evaluation during the double-blind phase (DBP) of the study as well as the safety results from the bridging phase (time after DBP (Visit III/15) until the study end).

During the DBP of the study, 84 patients in the Active - [redacted] treatment group, 86 patients in the Active - [redacted] treatment group and 86 patients in the placebo group have received at least one dose of study medication and were eligible for the Safety Set. The median duration where injections of study medication were administered was 569.5 days in the Active - [redacted] treatment group, 568.0 days in the Active - [redacted] treatment group and 568.0 days in the placebo group. The median duration where injections of study medication were given after the maintenance dose was reached was 472.0 days in the Active - [redacted] treatment group, 468.5 days in the Active - [redacted] treatment group and 482.5 days in the placebo group.

During the bridging phase, the treatment allocation continued to remain blinded. The median duration where injections of study medication were given during the entire study including the bridging phase was 740.0 days in the in the Active - [redacted] group, 745.5 days for the Active - [redacted] group and 711.0 days for the placebo treatment group.

In the first year of treatment, the median total amount of injected study medication was [redacted] (range: [redacted] - [redacted]) for the Active - [redacted] group and [redacted] (range: [redacted] - [redacted]) for the Active - [redacted] group. The median total amount of injected study medication in the second year of treatment was [redacted] (range: [redacted] - [redacted]) for the Active - [redacted] group and [redacted] (range: [redacted] - [redacted] for the Active - 120 µg group. The median total amount of injected study medication during bridging phase was [redacted] (range: [redacted] - [redacted]) for the Active - [redacted] group and [redacted] (range: [redacted] - [redacted]) for the Active - [redacted] group.

Overall, more patients in both active treatment groups compared to the placebo group reported at least one adverse event (AE) during the DBP of the study: 69 patients (82.1%) in the Active - [redacted] group, 72 patients

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(83.7%) in the Active - [redacted] group and 57 patients (66.3%) in the placebo treatment group experienced at least one adverse event with onset on or after first administration of study medication. Patients in the active treatment groups reported more frequently (59.5% of Active - [redacted] group and 61.6% of Active - [redacted] group) than placebo patients (23.3%) at least one AE related to the SOC 'General disorders and administration site conditions'. This difference was primarily due to the preferred terms 'injection site swelling', 'injection site pruritus', 'injection site pain', and 'injection site erythema'. Patients with at least one AE frequently reported AEs belonging to the SOC 'Infections and infestations' but these occurred with similar frequency in the active groups (50.0% of Active - [redacted] group and 51.2% of Active - [redacted] group) and the placebo group (51.2%). 'Nasopharyngitis' was the most frequently reported preferred term in all groups. Patients in the active treatment groups reported more frequently than placebo patients at least one AE related to the SOC 'Respiratory, thoracic and mediastinal disorders' (29.8% of Active - [redacted] group, 20.9% of Active - [redacted] group vs. 14.0% placebo).

A total of 18 patients had at least one **serious adverse event** with onset on or after first administration of study medication during the DBP of the study. The number of patients with at least one serious adverse event (SAE) was similar across the treatment groups during the DBP of the study. Six patients (7.1%) in the Active - [redacted] group, 5 patients (5.8%) in the Active - [redacted] group and 7 patients (8.1%) in the placebo treatment group experienced at least one SAE during the DBP of the study. Three patients in the active treatment groups (one in the Active - [redacted] group and two in the Active - [redacted] group) and one placebo patient reported an anaphylactic reaction after erroneous administration.

More patients in the active treatment groups than in the placebo group reported at least one **AE that was at least possibly related** to study medication: Fifty-seven patients (67.9%) in the Active - [redacted] group, 57 patients (66.3%) in the Active - [redacted] group and 28 patients (32.6%) in the placebo treatment group.

Patients in the active treatment groups reported more frequently (58.3% of Active - [redacted] group and 59.3% of Active - [redacted] group) than placebo patients (23.3%) at least one AE with at least possible relationship to study medication under the SOC 'General disorders and administration site conditions'. This difference was primarily due to the preferred terms 'injection site swelling' (45.2% of Active - [redacted] group, 48.8% of Active - [redacted] group vs. 14.0% placebo), 'injection site pruritus' (32.1% of Active - [redacted] group, 37.2% of Active - [redacted] group vs. 5.8% placebo), 'injection site pain' (20.2% of Active - [redacted] group, 17.4% of Active - [redacted] group vs. 9.3% placebo), and 'injection site erythema' (10.7% of Active - [redacted] group, 12.8% of Active - [redacted] group vs. 3.5% placebo). Patients in the active treatment groups reported more frequently than placebo patients at least one AE related to the SOC 'Skin and subcutaneous tissue disorders' (15.5% of Active - [redacted] group, 22.1% of Active - [redacted] group vs. 5.8% placebo) with 'urticaria' being the most frequent preferred term. Patients in the active treatment groups reported more frequently than placebo patients at least one AE related to the SOC 'Respiratory, thoracic and mediastinal disorders' (20.2% of Active - [redacted] group, 14.0% of Active - [redacted] group vs. 7.0% placebo).

Most patients had clinical chemistry, haematology, urinalysis, and vital sign values within the normal range both at Visit I/1 and at end of the double-blind phase as well as end of the entire study.

Results from the safety evaluation during the entire study including the bridging phase were similar to the results observed during the double-blind phase.

CONCLUSION:

With respect to the primary endpoint change in AUC of the RC-SMS, no statistically significant superiority of either of the treatment groups was shown compared to placebo in this double-blind study. Results from the Rhinoconjunctivitis Quality of Life Questionnaire and the conjunctival provocation test showed dose-dependent effects with a statistically significant and clinical relevant improvement for the highest maintenance dose (Active - [redacted] group) compared to placebo. Regarding immunological parameters (grass pollen specific IgG_1 and

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IgG_4), both dose active groups revealed a statistically significant increase for IgG_1 and IgG_4 compared to placebo and a statistically significant decrease for specific IgE, which confirmed the immune stimulating effect of the active treatment. The safety profile of both active dose groups is in line with reported adverse reactions of specific subcutaneous immunotherapies (local reactions and reactions apart from the injection site). No specific or new adverse events beyond those known for specific subcutaneous immunotherapy were detected. There were no noteworthy differences between the treatment groups in clinical chemistry, haematology, and urinalysis. There were no clinically relevant changes from baseline to last assessment in systolic and diastolic blood pressure or heart and respiratory rates.

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