2 Synopsis

Name of sponsor/company: Allergopharma GmbH & Co. KG	**Individual trial table referring to part V of this dossier** **Volume:** **Page:**	**(For national authority use only)**
Name of finished product: Allergovit® *Phleum pratense*		
Name of active ingredient: Aluminium hydroxide adsorbated allergoid of Timothy grass (*Phleum pratense*)		

Title of trial:

Double-blind, placebo-controlled study to investigate the dose response of an allergoid preparation of *Phleum pratense* in adult patients with IgE mediated allergic Rhinitis / Rhinoconjunctivitis with or without controlled bronchial Asthma

Coordinating investigator (according to AMG):

[redacted]

Trial centre(s):

The trial was conducted in 10 centres in Germany.

Publication (reference):

Not applicable (n.a.)

Trial period (years):	**Development phase:**
Date of first enrolment: 12-Mar-2012 Date of last patient completed: 26-Mar-2013	II

Objectives:

Primary objective

- To investigate the dose response relationship regarding efficacy and safety of an allergoid preparation of *Phleum pratense* in adult patients with IgE mediated allergic rhinitis / rhinoconjunctivitis with or without bronchial asthma.

Secondary objectives

- To investigate the efficacy and safety of a 6-grasses pollen allergen mixture in adult patients with IgE mediated allergic rhinitis / rhinoconjunctivitis with or without bronchial asthma.
- To compare the efficacy and safety of the regular up-dosing regimen of the allergoid preparation of *Phleum pratense* and the 6-grasses mixture.

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Methodology:

This trial was performed as a double-blind, placebo-controlled, randomised multicentre clinical trial investigating 3 groups receiving different doses of the investigational medicinal product (IMP), 1 active reference group, and 1 placebo group.

The trial had an adaptive trial design with one interim analysis.

At screening visit 1 (S1), patients willing to participate in the trial signed an informed consent form and eligibility for trial participation was analysed. At visit S2 a pre-treatment Intracutaneous Test (ICT) was performed with 2 concentrations.

All patients who were eligible for the trial continuation after S1 and S2 could visit an environmental challenge chamber (ECC) on visit S3 before the start of the treatment phase. Eligible patients were randomised on treatment visit 1 (T1) and subcutaneous injection of study medication was performed on the visits T1 - T9.

After the end of treatment all patients who visited the ECC on visit S3 were asked to visit the ECC again (follow-up visit 1 [FU1]) for the post-treatment investigation of their nasal allergic symptoms. At visit FU2 patients were given a post-treatment ICT with only 1 active concentration. The dose used for post-treatment ICT was determined by the late phase reaction (LPR) in the pre-treatment ICT and was defined as a LPR closer to 100mm (mean diameter). This visit was the final visit for safety reasons as well.

Number of patients (planned and analysed):

Approximately 200 patients were to be screened in order to identify 100 patients eligible for randomisation in order to provide 80 patients in the 4 active groups and 20 patients in the placebo group.

Actually, 190 patients were screened of whom 88 were not eligible to be included into the treatment phase of the trial. Thus, 102 patients were randomised with one patient being dropped out of the trial without any treatment.

Of 101 patients who were treated with study medication (Safety Set [SAF]), 98 patients provided post-baseline efficacy data and could be included in the Full Analysis Set (FAS). 93 patients had pre- and post-baseline assessments in the ICT and were available for primary efficacy analysis. 7 patients with major protocol violations were excluded from the Per Protocol Set (PPS) which consists of 91 patients. Dropouts were not replaced.

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Diagnosis and main criteria for inclusion:

At screening:

For inclusion in the trial patients had to fulfil the following criteria:

1. Provision of informed consent before initiation of any trial related procedure. (A trial-related activity was any procedure that would not have been performed during the routine management of the patient.)
2. Male and female outpatients who were legally competent, aged 18 - 65 years, inclusive
3. IgE-mediated seasonal allergic rhinoconjunctivitis with or without controlled asthma caused by grass pollen documented by
   - Skin Prick Test (SPT) wheal for Timothy grass pollen allergens and 6-grasses pollen allergen mixture ≥ 3mm in diameter and
   - histamine (0.1% histamine) wheal ≥ 3mm in diameter and
   - a negative sodium chloride (NaCl) control reaction < 2mm in diameter and
   - immunoglobulin E (IgE) result (Radio Allergo Sorbent Test [RAST]) ≥ 0.70kU/L to Timothy grass pollen and
   - main discomfort in the months: May, June and July.
4. For patients with bronchial asthma at entry: Confirmed diagnosis and asthma classification as "controlled" according to Global Initiative for Asthma (GINA) guidelines (version 2006).
5. Treated with anti-allergic medications for at least 2 years prior to enrolment. (Patients with perennial and continuously treated asthma were excluded).
6. For female patients: Use of effective contraception and negative pregnancy test result.
7. A positive response to at least 1 out of 2 tested ICT concentrations at visit S2. The result of the LPR had to be ≥ 20mm in mean diameter to at least 1 out of the 2 tested concentrations and the swelling area of the lower dose of the test solution was ≤ than the swelling area of the higher dose.

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Test product(s), dose and mode of administration, batch number(s):

The 100% aluminium hydroxide adsorbed allergoid of Timothy grass (*Phleum pratense*) preparation for subcutaneous application was specified in protein nitrogen units per mL (PNU/mL). For the 3 treatment groups 5 concentrations (A1, A2, A3 = B1, B2 and B3) of the preparation were provided:

[redacted] **group:** A1 ([redacted]) and B1 ([redacted]), maintenance dose (MTD): [redacted]. In this clinical trial report this group will be referred to as [redacted] group.

[redacted] **group:** A2 ([redacted]) and B2 ([redacted]), MTD: [redacted]. In this clinical trial report this group will be referred to as [redacted] group.

[redacted] **group:** A3 (=B1) ([redacted]) and B3 ([redacted]), MTD: [redacted]. In this clinical trial report this group will be referred to as [redacted] group.

The batch numbers of the active treatment were as follows: [redacted]

Duration of treatment: 13 weeks

Reference therap(ies) or comparator, dose and mode of administration, batch number(s):

Placebo:

Physiological saline, phenol and aluminium hydroxide corresponding to the active treatment preparations.

Placebo group: Placebo was administered in the same way as the IMPs. In this clinical trial report this group will be referred to as placebo group.

The batch numbers of the placebo treatment were as follows: [redacted] and [redacted].

Active comparator:

The 100% aluminium hydroxide adsorbed allergoid of 6-grasses pollen mixture preparation (Allergovit®) was specified in [redacted]. 2 concentrations of this preparation were provided, equivalent to IMP of the [redacted] group:

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Reference therap(ies) or comparator, dose and mode of administration, batch number(s) - (continued):

6-grasses group: Strength: A ([redacted]) and B ([redacted], MTD: [redacted]. In this clinical trial report this group will be referred to as 6-grasses group.

The batch numbers of the active treatment were as follows: [redacted].

Duration of treatment: 13 weeks

Criteria of evaluation:

Efficacy:

Primary endpoint

The change of the size of the swelling (area in mm²) 6h after intracutaneous testing (LPR) between baseline (visit S2) and after treatment (visit FU2). Therefore, the size of the swelling area measured after application of the individual optimal concentration (determined during visit S2) was subtracted.

Secondary endpoints*:*

- Change of the Total Nasal Symptom Score (TNSS) as measured in the ECC between baseline and after end of treatment.
- Change from baseline in specific total immunoglobulin G (IgG) and IgG_4 and at the end of treatment.
- Change of the amount of nasal secretion in the ECC between baseline and after end of treatment.

Safety:

Safety of treatment during the entire trial period was assessed by

- Adverse events (AE) overall and systemic AEs.
- Size of local reactions (diameter in mm) at the injection site 30 minutes (min) after drug administration.
- Clinical laboratory tests (haematology, clinical chemistry and urinalysis).
- Vital signs (resting blood pressure, pulse rate and respiratory rate).

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Statistical methods:

Primary endpoint evaluation:

For the evaluation of efficacy and for the investigation of the dose-response relationship of *Phleum pratense*, the following statistical evaluations were conducted.

A closed testing system was applied to control the one-sided experiment wise type I error rate of α=0.025. In the first step, it was investigated whether there was any difference between placebo and the 3 active dose levels. If the corresponding null hypothesis could be rejected, the null-hypotheses stating no difference between placebo and 2 active dose levels were tested for all subsets of 2 active dose levels. For those active dose levels for which all related null hypotheses could be rejected, the null-hypothesis of no difference between the active dose level and placebo was tested. According to the closed testing principle this multiple test procedure controls an experiment wise error rate of α, if all tests were performed at the local level α.

Treatment comparisons concerning the active comparator (6-grasses mixture) were to be performed in an exploratory sense. Therefore, the comparator was not included in the closed testing system.

Within the interim analysis, each hypothesis could be rejected, if the p-value of the respective test was at most α_1=0.0102.

The global hypotheses were tested by the Bartholomew Test for unknown but common variances. The null hypotheses of the single doses of *Phleum pratense* versus (vs.) placebo were tested by an analysis of covariance (ANCOVA) with change of the size of the LPR as the dependent variable, treatment group and centre as fixed effects, and the size of the LPR at baseline as a covariate.

Demography of trial population and baseline characteristics:

A total of 102 patients were evaluated for the analyses; 82 patients were randomised to active treatment and 20 patients were randomised to placebo treatment. Among the patients randomised to active treatment, 22 patients were randomised to allergoid *Phleum pratense* [redacted] active treatment ([redacted] group), 19 patients were randomised to allergoid *Phleum pratense* [redacted] active treatment ([redacted] group), and 19 patients were randomised to allergoid *Phleum pratense* 9000PNU active treatment ([redacted] group).

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Demography of trial population and baseline characteristics (continued):

In addition, 22 patients were randomised to the active comparator Allergovit® 6-grasses mixture (6-grasses group). Patient 04-038 randomised to the [redacted] group did not receive any study treatment. All other 101 randomised patients were treated and therefore included in the SAF for safety evaluation. 3 SAF patients (2 patients of the [redacted] group and 1 patient of the [redacted] group) were not evaluated for efficacy due to missing post-baseline efficacy assessments.

Summary and conclusions:

Efficacy results:

Primary endpoint - *Absolute change in Intracutaneous Test (ICT) late phase reaction (LPR)*

For the patients receiving placebo treatment, the mean LPR was 3375.6 ± 1704.1 (mean ± standard deviation [SD]) before treatment and decreased to 2380.5 ± 1642.2 after treatment which resulted in an absolute change of -933.9 ± 1309.4.

In contrast, for the patients randomised to the [redacted] group the mean LPR was 3729.6 ± 1395.2 before treatment and decreased to 1405.4 ± 1340.1 after treatment which resulted in an absolute change of -2324.2 ± 1018.5. A slight further increase of the treatment effect could be seen for patients randomised to the [redacted] group where the mean LPR was 4103.8 ± 1847.0 before treatment and decreased to 1340.4 ± 1392.5 after treatment which resulted in an absolute change of -2763.4 ± 1601.3. No additional treatment effect could be observed for patients randomised to the [redacted] group where the mean LPR was 2976.5 ± 1555.5 before treatment and decreased to 902.3 ± 831.5 after treatment which resulted in an absolute change of -2038.6 ± 1490.4.

For patients randomised to the active comparator Allergovit® 6-grasses mixture (6-grasses group) the mean LPR was 3839.5 ± 1806.7 before treatment and decreased to 1055.1 ± 1247.7 after treatment which resulted in an absolute change of -2593.4 ± 1632.1 which was comparable to the [redacted] group.

According to the closed testing system it was investigated in the first step whether there was any difference between placebo and the 3 active dose levels. The Bartholomew Test of homogeneity for ordered alternatives revealed a p-value of 0.0004 which is far below the boundary for early rejection of a hypothesis within the interim analysis.

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Summary and conclusions (continued):

This result allowed going further in the closed testing system and to test the hypotheses of homogeneity of placebo and 2 active treatment groups. As these hypotheses could also be rejected ($p < 0.01$), the null-hypothesis of no difference between each active dose level and placebo could be tested in a confirmatory sense. All 3 hypotheses comparing the active treatment groups with the placebo group could be rejected within the interim analysis ($p < 0.001$, one-sided ANCOVA p-value) confirming the efficacy of all dose groups.

Although not included in the confirmatory testing strategy, the investigation of the 6-grasses group revealed exploratory evidence for the treatment being statistically significant superior to placebo ($p < 0.0001$, one-sided ANCOVA p-value). The results in this treatment group are comparable with the results of the *Phleum pratense* treatment groups, especially of the [redacted] group.

Environmental Challenge Chamber (ECC)

For the patients receiving placebo treatment, the median area under the curve (AUC) of the TNSS was 28.0 at pre-treatment (visit S3) and decreased to 23.0 at post-treatment (visit FU1) which resulted in a median absolute change of -1.0. For the patients randomised to the [redacted] group, a greater decrease of the TNSS between pre- and post-treatment was observed. The median AUC of the TNSS was 23.0 at pre-treatment and decreased to 19.0 at post-treatment which resulted in a median absolute change of -3.0. A further increase of the treatment effects could be observed for patients in the [redacted] group, where the median AUC of the TNSS was 23.0 before treatment and decreased to 12.0 after treatment which resulted in a median absolute change of -6.0. For patients randomised to the [redacted] group, the median AUC of the TNSS was 23.0 before treatment and decreased to 16.5 after treatment which resulted in a median absolute change of -5.5. Thus, a dose of [redacted] was not more effective than a dose of [redacted] in reducing the TNSS in an ECC. For patients randomised to the 6-grasses mixture group the median AUC of the TNSS was 23.0 before treatment and decreased to 12.5 after treatment which resulted in a median absolute change of -3.0. Overall, all active treatment groups showed greater improvement in the TNSS after treatment than observed under placebo and the greatest improvement was observed for patient in the [redacted] group. The analysis of the amount of nasal secretion during allergen exposure did not reveal any notable results.

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Summary and conclusions (continued):

Immunology - Total IgG, IgG_4 and IgG_1 antibodies to *Phleum pratense*

Compared to placebo treatment, all active treatment groups showed an increase in levels of specific total IgG, IgG_4 and IgG_1 antibodies to *Phleum pratense* and their absolute change from baseline (visit S1) to final visit was statistically significant ($p < 0.001$) which supported the immune stimulating effect of all dose levels of active treatment which was not seen in the placebo group.

Safety results:

During the trial, 22 patients in the [redacted] group, 18 patients in the [redacted] group, 19 patients in the [redacted] group, 22 patients in the 6-grasses group, and 20 patients in the placebo group had received at least one dose of study medication and were eligible for the SAF.

The median amounts (PNU and mL) of study medication and the number of injections were consistent with the study treatment plan. Over 90% of patients in all *Phleum pratense* groups reached the MTD without back dosing. Slightly fewer (81.8%) of the patients in the 6-grasses group reached the MTD without back dosing.

A total of 65 patients experienced at least one treatment-emergent AE during the trial. There was no large difference between active treatment groups and the placebo group. At least one AE occurred in 13 patients (65.0%) in the placebo group, 13 patients (59.1%) in the [redacted] group, 9 patients (50.0%) in the [redacted] group, 13 patients (68.4%) in the [redacted] group and 17 patients (77.3%) in the 6-grasses group.

When comparing AE frequencies based on system organ classes (SOCs) it turned out that patients most frequently reported AEs belonging to the SOC ‘General disorders and administration site conditions’. In this SOC the most frequently reported AEs belonged to the Preferred terms (PTs) ‘Injection site swelling’ and ‘Injection site pruritus’. Another SOC with frequently reported AEs was ‘Infections and Infestations’. In this SOC the most frequently reported PT in all treatment groups was ‘Nasopharyngitis’. Another SOC in which patients reported AEs was ‘Eye disorders’ and ‘Conjunctivitis allergic’ was the most frequently reported PT in all treatment groups.

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Summary and conclusions (continued):

For the majority of the patients who experienced at least one AE during the trial, the intensity of the AEs was mild and the time of onset was 30min to 48h after application of treatment. Differences were seen between the treatment groups in intensity of AEs reported. For 'Injection site swelling', more patients in the [redacted] group (15.8%) and the 6-grasses group (22.7%) reported at least one AE of moderate intensity whereas no 'Injection site swelling' of moderate intensity was reported in the [redacted] group and only 4.5% in the [redacted] group. For 'Nasopharyngitis', more patients in the [redacted] group (21.1%) reported at least one AE of moderate intensity whereas none of moderate intensity was reported in the [redacted] group, 9.1% in the [redacted] group, and 4.5% in the 6-grasses group.

No serious adverse events (SAEs) were reported during the double-blind treatment phase of the trial. One SAE occurred before first IMP administration.

At least one AE with reasonable possible causal relationship to study medication occurred in 34 patients; 6 patients (27.3%) in the [redacted] group, 4 patients (22.2%) in the [redacted] group, 10 patients (52.6%) in the [redacted] group, 13 patients (59.1%) in the 6-grasses group, and 1 patient (5.0%) in the placebo group.

AEs belonging to the SOC 'General disorders and administration site conditions' were the most common AEs reported as causally related to treatment and occurred only in the active treatment groups and not in the placebo group. 'Injection site swelling' which was the most commonly reported PT was reported at least once by 22.7% of the patients in the [redacted] group, 22.2% of the [redacted] group and in the [redacted] group by 36.8% and by 59.1% in the 6-grasses group. For the most commonly reported PTs, 'Injection site swelling' and 'Injection site pruritus', the AEs occurred most frequently between 30min and 48h after last application of medication. All local reactions reported by patients with at least one AE were also reported as related to study medication and belonged to the SOC 'General disorders and administration site conditions'. More patients in the [redacted] group (52.6%) and in the 6-grasses group (59.1%) than in the [redacted] group (27.3%) and the [redacted] group (22.2%) reported local reactions and the most commonly reported PTs were 'Injection site swelling' and 'Injection site pruritus'. No local reactions were reported in the placebo group.

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Summary and conclusions (continued):

The size of local reactions (diameter in mm) at the injection site 30min after drug administration was a safety endpoint in this trial. Median size of the local reactions (diameter in mm) at the injection site 30min after drug administration ranged from 0.0mm at T1 to 6.5mm at T9 in the [redacted] group, from 0.0mm at T1 to 2.0mm at T9 in the [redacted] group, from 0.0mm at T1 to 5.0mm at T9 in the [redacted] group, from 4.5mm at T1 to 5.0mm at T9 in the 6- grasses group and remained 0.0mm at T1 and T9 for the placebo group.

Only 4 patients experienced at least one systemic anaphylactic reaction that was related to study medication, This occurred in 1 patient (5.3%) in the [redacted] group ('Peak Exploratory Flow [PEF] decreased'), 2 patients (9.1%) in the 6-grasses group ('Eye lid oedema' and 'Oedema peripheral'), and 1 patient (5.0%) in the placebo group. Although on placebo, a patient in the placebo group reported at least one AE with at least a possible relationship to study medication. This patient had a decreased expiratory flow rate without showing any clinical symptoms.

Results from the close supervision of the patient after the drug administration showed that the mean and median values for the lowest PEF, lowest systolic blood pressure, lowest diastolic blood pressure, highest heart rate and highest respiratory rate for patients in all treatment groups were in normal range and showed no matter of concern for all dose levels.

Most patients had clinical chemistry, haematology, urinalysis, and vital sign values within the normal range both at baseline and final visit of the trial.

Overall conclusions:

This trial obtained confirmatory evidence for the superiority of each dose of *Phleum pratense* compared to placebo already at the interim analysis and the trial was stopped early for benefit since all trial objectives were met.

The primary endpoint for this trial was the change of the size of the swelling (area in mm²) 6h after intracutaneous testing (LPR) between baseline (visit S2) and after treatment (visit FU2).

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Summary and conclusions (continued):

Of note is the fact that the ICT was performed with a mixture of 6-grasses, results for efficacy showed that for all allergoid *Phleum pratense* dose groups the change of the LPR was significantly greater than placebo. Results for the individual dose groups showed that the efficacy in the [redacted] group was greater than in the [redacted] group and [redacted] did not show further increase in efficacy.

The change in LPR between baseline and after treatment was also statistically significantly greater in the 6-grasses group compared to placebo. The comparison of the 6-grasses group (with [redacted] showed comparable efficacy to the allergoid *Phleum pratense* [redacted] group.

When considering the change of the TNSS (measured in the ECC), an endpoint assessed at the target organ, the dose of [redacted] showed the largest treatment effect. The [redacted] group revealed no further clinical efficacy compared to the [redacted] group. Of note is the fact that the challenge was performed with *Dactylis glomerata*, a very common grass in Europe and treatment was performed with *Phleum pratense* or 6-grasses.

Safety analyses indicated that the [redacted] and [redacted] groups showed a comparable safety profile that was better than the safety profile of the [redacted] group. No new or unknown AEs were reported. The safety profile is in line with the safety seen after subcutaneous immunotherapy (SCIT). During the prolonged observation period the heart rate, respiratory rate, blood pressure, and PEF value were in normal range for all patients in all treatment groups and did not show any concern.

Taking into consideration all efficacy and safety data, the allergoid *Phleum pratense* dose of [redacted] showed the best risk / benefit profile and is at least as effective and safe as the 6-grasses therapy. Thus, the results of this trial reveal that allergoid *Phleum pratense* at an MTD of [redacted] is comparable to 6-grasses at the same MTD.

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