2 Synopsis

Name of Sponsor/Company: ALLERGOPHARMA GmbH & Co. KG	**Individual Trial Table Referring to Part of this Dossier**	**(For National Authority Use only)**
Name of Finished Product: Allergovit® 6-grasses	**Volume: not applicable**	
Name of Active Ingredient: Aluminium hydroxide adsorbated allergoid of six grasses	**Page: not applicable**	

Title of Trial:

Open label phase II multicentre clinical trial to evaluate safety during shortened uptitration of an allergoid grass pollen preparation in adult patients with IgE mediated allergic rhinitis / rhinoconjunctivitis with or without controlled bronchial asthma (AL1201AV).

Investigator(s):

[redacted]

Trial Centre(s):

11 investigational sites in Germany screened and randomised patients.

Publication (reference):

Not applicable

Trial Period (years):	**Phase of Development:**
Date of first enrolment: 29-Oct-2012 Date of last completed: 08-May-2013	Phase II

Objectives:

The main objective was to evaluate the safety and tolerability of a shortened uptitration scheme with Allergovit® 6-grasses.

Methodology:

Multicentre, open label, randomised phase II trial with 2 parallel active treatment groups (Group I and Group II). Randomisation was based on a 1:1 ratio.

Patients randomised in Group I (shortened uptitration scheme with 4 injections) were treated over a period of up to 12 weeks; patients randomised in Group II (standard uptitration scheme with 7 injections) were treated for up to 15 weeks.

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Number of Patients (planned and analysed):

120 randomised patients were planned (60 in each treatment group).

A total of 123 patients were randomised, 122 patients (61 in each group) received at least 1 injection of the trial medication and thus were included for analysis in the Safety Set. Of these, 110 patients were included in the Per-Protocol set.

Diagnosis and Main Criteria for Inclusion:
Male or female outpatients aged 18 to 65 years suffering from IgE-mediated seasonal allergic rhinoconjunctivitis with or without asthma caused by grass pollen documented by skin prick test wheal for grass pollen ≥3mm in diameter, histamine wheal ≥3mm, NaCl control reaction <2mm, and with IgE result ≥0.70kU/L to grass pollen. Patients had to have main discomfort due to allergic rhinoconjunctivitis during the grass pollen exposure months. Diagnosed asthma was to be classified as being "controlled" according to GINA guidelines (GINA, 2006).

Test Product(s): Dose and Mode of Administration, Batch Number(s):

100% aluminium adsorbed allergoid mixture preparation of 6-grasses (Allergovit® 6-grasses) provided in two concentrations ([redacted] and [redacted])

In this trial only one batch of production of the test drug / investigational product [redacted]

The following batches of Allergovit® were administered during the Trial:

Group I: [redacted].

Group II: [redacted].

Injection schedule during uptitration:

The injections of gradually increasing doses were administered at 7-day intervals. The dose was to be increased progressively by one step at a time only, provided that the previous dose had been tolerated well.

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Maintenance Phase - Treatment with the Maximum Dose:

After the maximum dose was reached and tolerated, a maintenance treatment with 2 maximum dose injections was administered after 14 days and 28 days, respectively.

Dosage Modification and Adjustment:

Dose adjustments were needed if the injection intervals were not kept or in case the last applied dose was not tolerated.

Duration of Treatment:

Up to 12 weeks for patients randomised in Group I and up to 15 weeks for patients randomised in Group II.

Reference Therapy(ies), Dose and Mode of Administration, Batch Number(s):

Not applicable.

Criteria for Evaluation:

Efficacy:

As this was a safety and tolerability trial, no efficacy endpoints were evaluated.

Safety:

- Numbers, incidence, type and intensity of local adverse events (AEs) (local reactions at the injection site >5 cm), AEs and serious adverse events (SAEs) by MedDRA primary SOC and Preferred Term (PT),
- AEs as described above but considered to be related to trial medication by the investigator,
- Incidence and intensity of systemic anaphylactic reactions after injections according to the WAO grading system,
- Change of laboratory values (haematology, clinical chemistry and urinalysis) measured before and after the treatment phase,
- Change of vital signs and lung function measured before, during and after treatment,

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Criteria for Evaluation (continued):

- Number of local reactions at the injection site ≤5cm, and
- Assessment of the overall tolerability by the investigator and the patient using a 5 point Likert scale.

Statistical Methods:

- Analysis of safety and tolerability variables

Numbers and incidence rates of AEs, SAEs and anaphylactic systemic reactions (according to WAO grade) related to investigational product and differences between these numbers and incidence rates of the two treatment groups were reported. For incidence rates, 95%-confidence intervals (95%-CI) were reported. Laboratory values and vital signs were presented with mean ± standard deviation, 95%-CI, median, minimum, maximum for visit S1 (baseline) and the last injection visit (T1/9) and for the difference between these visits.

Treatment groups were compared with exploratory statistical tests.

Results of tolerability assessments were presented with numbers and percentages for each category as well as nonparametric statistical measures. Treatment groups were compared with exploratory statistical tests.

- Design and hypothesis

As this was a safety and tolerability trial, no hypotheses were formulated and data were analysed descriptively.

- Determination of sample size

This trial was performed to evaluate the safety and tolerability of 2 different uptitration schemes. Due to the exploratory design, there was no formal estimation of sample size accounting for type I error rate, power, standard deviation, and effect size. Overall, 120 patients, 60 patients per group were planned to be randomised to treatment. This sample size was considered sufficient to guarantee a probability of 95%, that AEs with a true incidence rate of 5 % in one treatment group occur at least once in this treatment group. Thus, a trial with this number of patients was considered to allow observing less frequently occurring AEs and to compare AE profiles as well as changes in vital signs and laboratory values.

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Demography of Trial Population and Baseline Characteristics:

Overall, 186 patients were screened and 123 were randomised to trial medication. Of these, 62 were randomised into Group I and 61 into Group II. Of those who were randomised, 8 patients terminated the study prematurely, 6 in Group I, 2 in Group II. The reasons for premature trial termination in Group I were occurrence of AEs (3 patients), withdrawal of consent (1 patient, before receiving trial medication) and other reasons (2 patients). 2 patients in Group II terminated the study due to other reasons. Both treatment groups were well balanced with regards to their demographic and all other baseline characteristics.

Summary and Conclusions:

The All-Patients Set comprised 186 patients, the Safety Set 122 patients, and the Per-Protocol Set 110 patients.

Efficacy results:

Not applicable. This was a safety and tolerability trial.

Safety results:

In Group I (shortened scheme), the planned number of injections was 6 (4 uptitration and 2 maintenance injections. A maximum of 8 injections could be administered regardless of the dose reached. In Group II (standard scheme), the planned number of injections was 9 (7 uptitration and 2 maintenance injections. A maximum of 11 injections could be administered regardless of the dose reached.

Mean treatment duration in treatment Group I was 68.8±18.7 days and 92.3±12.4 days in Group II. 75.4% of patients in Group I and 88.5% of patients in Group II reached the maintenance dose without backdosing.

During the entire trial duration, comprising the uptitration and maintenance phase, 78 (63.9%) patients reported 197 treatment- emergent adverse events (TEAE). The occurrence in both groups was similar. The majority (43.4%) of patients reported mild TEAEs only. 3 patients, all in Group I, withdrew from the trial due to AEs: 2 patients after swelling (>10cm) at the injection site at visit T1/1 and 1 patient due to a systemic reaction of WAO grade 1

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Summary and Conclusions (continued):

Safety results (continued):

One serious and severe TEAE (peritonsillar abscess), not related to the trial medication or procedure was reported during the uptitration phase in a patient in Group II receiving strength A at 0.1 mL.

81 of 197 of the reported TEAEs were related to the trial medication with overall 37 (30.3%) of patients reporting 81 TEAEs. In Group I, 22 patients (36.1%) reported a related TEAE compared to 15 (24.6%) patients in Group II. Most events reported were mild in intensity.

For TEAEs, the most frequent reported SO in Group I (29.5% of patients) and Group II (19.7% of patients) was 'General disorders and administration site conditions' (injection site swelling, erythema, pruritus, warmth, discomfort, reaction, and urticaria).

Local reactions comprising swelling and erythema at the injection site occurred in 18 Group I patients (29.5%) vs. 11 patients in Group II (18.0%). On average, during the whole study, the mean maximum diameter of local reactions per visit was well comparable between both treatment groups with an average maximal size of 2.1±1.6cm in Group I and 2.0±1.7cm in Group II.

Anaphylactic systemic reactions (MedDRA PT 'Anaphylactic reaction') were more frequently reported in Group I compared to Group II (Group I: 13.1% vs. Group II: 6.6%). Most of these reactions were graded with WAO grade 1. 5 reactions overall were of grade 2 and none was graded with grade 3, 4, or 5. Except for 1 patient with an abnormal platelet count at final visit, no clinically significant changes from baseline, for any other laboratory parameters tested were reported.

Vital signs at final visit did not show any clinically significant change from baseline.

The lung function tests and measurements of vital signs performed after the injections did not show any systematic change of any parameter in any treatment group.

Tolerability was assessed as good or very good in both groups, with investigators and patients rating treatment with 7 injections (Group II) better tolerated than the proposed treatment with 4 injections (Group I). The difference was statistically significant in favour of Group II (p=0.032) for the investigator rating.

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Summary and Conclusions (continued):

Overall conclusion

The main objective of the present trial was to evaluate the safety and tolerability of a shortened uptitration scheme with Allergovit® 6-grasses in adult patients with rhinoconjunctivitis caused by grass pollen with/without controlled asthma (according to GINA 2006).

A total of 123 patients were randomised to receive either 4 (Group I) or 7 (Group II) injections during the uptitration phase. Of these, 122 patients received at least 1 injection of trial medication.

Both treatment groups were well balanced with regards to their demographic and all other baseline characteristics.

The mean treatment duration in treatment per patient in Group I was 68.8±18.7 days and 92.3±12.4 days in Group II, thus reflecting the lower number of planned injections and the shorter scheduled treatment duration in Group I. The shortened uptitration scheme showed less protocol violations regarding the trial medication application.

There was no death and no serious related TEAE reported during the trial. One serious and severe TEAE (peritonsillar abscess), not related to the trial medication or procedure was reported after the first injection.

Overall, 78 patients reported 197 treatment-emergent adverse events (TEAE). The incidence in both groups was similar and the majority of TEAEs reported was mild.

The shorter uptitration scheme was associated with more TEAEs related to study medication, WAO systemic reactions and local reactions. In most cases, these reactions were of mild intensity. At the lowest dose of Group I ([redacted]), which was injected as second injection in Group II, the same number of patients reported at least one AE related to trial medication. It can be recommended to omit the first injection (Strength A, 0.1mL) in the uptitration scheme of Group II.

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Overall conclusion (continued):

All TEAEs related to study medication were suspected events that are already listed in the Summary of Product Characteristics (SmPC) as known side effects.

In conclusion, the shortened uptitration scheme with only 4 injections investigated in this study is faster than the standard scheme, tends to be easier in handling and can be added as possible scheme for patients with limited time who are willing to accept eventually some more mild side effects compared to the standard uptitration scheme.

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