2 SYNOPSIS

NAME OF COMPANY: Allergopharma Joachim Ganzer KG	INDIVIDUAL STUDY TABLE REFERRING TO PART V OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AllerSlit forte Grass pollen		
NAME OF ACTIVE INGREDIENT: Aqueous extract of grass pollen from *Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense* and *Poa pratensis*		

Title of study:

A multicentre, multinational, placebo-controlled, double-blind, randomised study to evaluate efficacy and safety of a perennial, sublingual, specific immunotherapy in patients with rhinoconjunctivitis with/without controlled asthma caused by grass pollen (ALLEGRA6).

Investigator(s):

[redacted]

Study centre(s)

26 centres in Germany (19 centres with randomised patients)and 3 centres in Italy

Publication (reference):

None

Study period:	**Development phase:**
Double-blind phase: First patient entered – 22/02/2008 Last patient last visit – 05/11/2009	Phase III

Objectives:

The objectives of the placebo-controlled study were as follows:

- To demonstrate that the grass pollen allergen extract solution is safe and suitable for SLIT treatment of grass pollen allergic patients.
- To obtain evidence for the safety and efficacy of sublingual specific immunotherapy with a liquid formulation of a grass pollen extract in comparison to placebo in a representative number of grass pollen allergic patients suffering from rhinoconjunctivitis with/without controlled asthma caused by grass pollen.
- To assess immunologic parameters during the course of the study to obtain evidence of immunologic effects of the therapeutic vaccine.

2 SYNOPSIS (continued)

NAME OF COMPANY: Allergopharma Joachim Ganzer KG	INDIVIDUAL STUDY TABLE REFERRING TO PART V OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AllerSlit forte Grass pollen		
NAME OF ACTIVE INGREDIENT: Aqueous extract of grass pollen from *Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense* and *Poa pratensis*		

Methodology:

This clinical trial was carried out as a multicentre, multinational, placebo-controlled, double-blind, randomised, phase III study with parallel groups in patients with rhinoconjunctivitis with/ without controlled asthma caused by grass pollen.

The objectives of the study were evaluated by the following endpoints:

The primary endpoint of this study was the difference between active treatment and placebo in the change of the area under the curve of the symptom and medication score (SMS) from the baseline season to the season after 1 year of treatment (double-blind phase). The SMS was calculated by the daily sum of symptoms and use of anti-allergic medication documented in patients' diaries during the grass pollen season. Following a baseline assessment of the primary and secondary endpoints before treatment in the grass pollen season of the year 2008, the study was carried out in a placebo-controlled design over a period of one year with perennial treatments.

An analysis of the primary endpoint was to be carried out after completion of one year of treatment and the documentation of symptoms and medication use, in the grass pollen season 2009. Adverse Events, dose of study drug used and the intake of medication were collected. The analysis of the primary endpoint was to be performed as soon as possible after the end of the grass pollen season 2009 when all data were available at Allergopharma Joachim Ganzer KG.

If efficacy was demonstrated for the active treatment group in the analysis of the primary endpoint after one year, active treatment it was planned that the study continued in an open design for two additional years for patients in the active treatment group. Results and conclusions from this part of the study will be reported separately. Patients in the placebo group were to be offered an open treatment with the sublingual specific immunotherapy regimen applied in this study for the full-recommended period of three (additional) years (the last year with the commercial available product).

If superiority of active treatment could not be demonstrated after one year of the double-blind placebo-controlled phase, the study was to be discontinued and reported. In this case all patients were to be treated individually at the investigators discretion.

2 SYNOPSIS (continued)

NAME OF COMPANY: Allergopharma Joachim Ganzer KG	INDIVIDUAL STUDY TABLE REFERRING TO PART V OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AllerSlit forte Grass pollen		
NAME OF ACTIVE INGREDIENT: Aqueous extract of grass pollen from *Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense* and *Poa pratensis*		

Number of patients planned and analysed:

The study drug was planned to be tested in 148 patients. In total, 126 patients were randomised in the study; 63 patients to active treatment and 63 patients to placebo treatment. 125 patients (63 active and 62 placebo) were evaluated in the safety analyses and 102 patients (52 active and 50 placebo) were evaluated in the efficacy analyses.

Diagnosis and main criteria for inclusion:

Diagnosis: IgE-mediated allergic disease manifested as symptoms of allergic rhinoconjunctivitis with or without controlled asthma caused by grass pollen

Inclusion criteria:

- Provision of informed consent before initiation of any study related procedures at Screening
- Male and female outpatients
- Age18 - 65 years
- IgE-mediated seasonal allergic rhinoconjunctivitis with or without controlled asthma caused by grass pollen documented by
  - Positive Skin Prick Test wheal for grass pollen ≥ 5mm in diameter **and**
  - Positive histamine (0.1% histamine free base) wheal ≥ 3mm and a negative NaCl control reaction < 3mm
  - Positive EAST ≥ 1.5 kU/L to grass pollens **and**
  - Proven clinical relevance of grass pollen allergy by positive Conjunctival Provocation Testing with grass pollen allergens **and**
  - Main discomfort in the months May, June, July of the year
- For female patients with childbearing potential: must have had a negative serum pregnancy test before the baseline phase.
- Female patients must have had a negative serum pregnancy test at enrolment and had to be willing to use a reliable method of birth control during the study, as judged by the investigator.

2 SYNOPSIS (continued)

NAME OF COMPANY: Allergopharma Joachim Ganzer KG	INDIVIDUAL STUDY TABLE REFERRING TO PART V OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AllerSlit forte Grass pollen		
NAME OF ACTIVE INGREDIENT: Aqueous extract of grass pollen from *Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense* and *Poa pratensis*		

Inclusion criteria (continued):

- For patients with bronchial asthma at entry: confirmed diagnosis and asthma classification as controlled "according" GINA guidelines (version 2006).

At the Beginning of the treatment phase:

- Rhinoconjunctivitis symptoms documented in the patients diary during the baseline season
- Patients must have demonstrated a symptom score of at least 4 every day during the week following the peak pollen count in the baseline season.

Test product, dose and mode of administration, batch number:

Sublingual specific immunotherapy (SIT) preparation of a grass pollen allergen extract in a water/glycerol solution with phosphate buffered saline. The 100% maintenance dose was 4 drops daily, standardized to contain a major allergen content of [redacted] grasses group 5.

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

Duration of treatment:

1 year (double-blind phase)

Reference therapy, dose and mode of administration, batch number:

Placebo drops (water/glycerol solution with phosphate buffered saline).
The 100% maintenance dose was 4 drops daily, sublingually administered.

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

2 SYNOPSIS (continued)

NAME OF COMPANY: Allergopharma Joachim Ganzer KG	INDIVIDUAL STUDY TABLE REFERRING TO PART V OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AllerSlit forte Grass pollen		
NAME OF ACTIVE INGREDIENT: Aqueous extract of grass pollen from *Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense* and *Poa pratensis*		

Criteria of evaluation
Efficacy

- The absolute values as well as the change of the AUC of SMS after 1 year of treatment
- Specific IgE, IgG_1 and IgG_4 at screening visit (V I/-1), 3 month after start of pollen season (V I/5), and every study year at the end of grass pollen season as well as the absolute change from screening to the end of study years
- The change in specific Conjunctival Provocation Test from baseline to the end of first treatment year
- The absolute values as well as the change of number of well days from baseline to the end of first treatment year
- The AUC of rhinoconjunctivitis SMS after one year of treatment as well as the number of rhinoconjunctivitis well days
- Patient's response to the study medication defined as an at least 40% decrease of AUC of SMS from baseline to after 1 year of treatment
- All analyses were evaluated in the Full Analysis Set (FAS), as well as for subgroups by age (≤ 50, > 50), gender (male, female) and region (north, south).

Criteria of evaluation:
Safety:

- The safety analysis was performed for the following adverse event categories:
- All adverse events
- Systemic reactions
- Serious adverse events
- Adverse events with at least "possible" relationship to the study medication
- All adverse events with at least possible relationship to study medication with onset on visit V I/7 (first day of study medication) by MedDRA primary system organ class (SOC) and preferred term (PT)
- All adverse events with at least possible relationship to study medication by TRYBA classification SOC and PT
- Clinical laboratory values (haematology with blood cell differential count, clinical chemistry, hormone, and urinalysis), and vital signs

2 SYNOPSIS (continued)

NAME OF COMPANY: Allergopharma Joachim Ganzer KG	INDIVIDUAL STUDY TABLE REFERRING TO PART V OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AllerSlit forte Grass pollen		
NAME OF ACTIVE INGREDIENT: Aqueous extract of grass pollen from *Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense* and *Poa pratensis*		

Statistical methods:

The primary endpoint of this study was the difference between active treatment and placebo in the change of the area under the curve (AUC) of the SMS. The primary analysis compared the change of the AUC from the measurement at baseline to the measurement after 1 year of treatment. Based on the actual pollen count, the AUC of the daily SMS was calculated over a 42-days time period defined at the Blind Data Review Meeting.
The statistical null-hypothesis of no difference between the AUC of both treatment groups was tested in a confirmatory sense. The Null hypothesis “No treatment difference between the two study arms after one-year sublingual SIT” was tested by using two-sided Wilcoxon-Mann-Whitney-U-Test.
The Null hypothesis was to be rejected and the superiority of a treatment (placebo or active) was assumed for a p-value below the significance level of 5%.
Absolute and relative frequencies (percentages) were calculated for categorical variables. Percentages for categorical variables were based on all non-missing values (= 100%).
Continuous variables were summarized with number of observations, mean, standard deviation, median, minimum, maximum and the 5%, 25%, 75% and 95% quantiles.
These descriptive statistics were calculated for absolute values and for absolute differences to baseline, where appropriate.

Demography of study population:

Demographic and other baseline characteristics were similar between the active and placebo treatment groups. Median age at baseline in the Safety Set (n = 63 patients in the active treatment and n = 62 patients in the placebo group) was 37 years in the active group and 35 years in the placebo group. Males (54.0% active, 55.6% placebo) were more frequent in both treatment groups than females (46.0% active, 44.4% placebo). Controlled bronchial asthma was reported by 33.3% of the active treatment patients and 30.6% of the placebo patients. Medical history of allergic conditions and history of allergic symptoms were similar between the treatment groups. Fewer females in the active group had no household pet than females in the placebo group (Safety Set: 27.6% active vs. 63.0% placebo). In addition, more females in the placebo group were non-smokers than females in the active group (Safety Set: 55.2% active vs. 67.9% placebo) However, more males in the active group were non-smokers than males in the placebo group (Safety Set: 52.9% active vs. 42.9% placebo).

2 SYNOPSIS (continued)

NAME OF COMPANY: Allergopharma Joachim Ganzer KG	INDIVIDUAL STUDY TABLE REFERRING TO PART V OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AllerSlit forte Grass pollen		
NAME OF ACTIVE INGREDIENT: Aqueous extract of grass pollen from *Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense* and *Poa pratensis*		

Demography of study population (continued):

The peak pollen counts at the designated stations near each study site in 2008 were generally higher than the peak pollen counts in 2009 and there were more days in 2008 than in 2009 with measures of ≥ 20 particles per cubic meter.

However, this trend was not seen for the three Italian and two German stations. This might have markedly influenced the results for the symptom medication score, because less pollen exposure may lead to reduced symptoms reported by the patients.

Summary and conclusions:

Efficacy results:

The Full Analysis Set consisted of 52 patients in the active treatment group and 50 patients in the placebo group. The primary analysis compared the change of the AUC from the measurement at baseline in 2008 to the measurement after 1 year of treatment in 2009. In the active treatment group, the median AUC of the SMS at baseline in 2008 was 518.5 but was reduced to 254.0 in 2009 after one year of treatment. The median AUC of the SMS at baseline in 2008 was slightly lower (512.0) in the placebo group and was reduced to 330.0 in 2009 after one year of placebo treatment. The median change of the AUC of the SMS from baseline to end of one year of treatment was -201.3 for the active treatment group and -143.0 for the placebo group.

The null hypothesis “No treatment difference between the two study arms after one-year sublingual SIT” was tested using the two-sided Wilcoxon-Mann-Whitney U-Test. Although the change in the median AUC of the SMS was greater in the active treatment group compared to the placebo group this difference was not statistically significant ($p = 0.3564$).

For sensitivity analyses, missing SMS values were replaced by the patient’s highest value of the defined time period (if not more than 25% of the values were missing). This SMS was called the worst case SMS. Results from the worst case analyses were similar to the primary analyses. In the active treatment group, the median AUC of the worst case SMS at baseline in 2008 was 518.5 but was reduced to 280.0 in 2009 after one year of treatment. The median AUC of the worst case SMS at baseline in 2008 in the placebo group was similar (515.5) to the active group but the median value (341.0) in 2009 after one year of placebo treatment was higher than in the active group.

2 SYNOPSIS (continued)

NAME OF COMPANY: Allergopharma Joachim Ganzer KG	INDIVIDUAL STUDY TABLE REFERRING TO PART V OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AllerSlit forte Grass pollen		
NAME OF ACTIVE INGREDIENT: Aqueous extract of grass pollen from *Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense* and *Poa pratensis*		

Summary and conclusions:

Efficacy results (continued):

Thus, the median change of the AUC of the SMS from baseline to end of one year of treatment was -191.3 for the active treatment group which was greater than the median change of -143.0 for the placebo group. Although the change in the median AUC of the SMS was greater in the active treatment group compared to the placebo group this difference was not statistically significant (p = 0.3755).

Results from the AUC of rhinoconjunctivitis SMS after one year of treatment were similar to the overall AUC of the SMS results. Patients in the active treatment group showed a greater change in the median AUC of the rhinoconjunctivitis SMS after one year of treatment.

The median AUC of the rhinoconjunctivitis SMS at baseline was 497.5 but declined to 235.5 after one year of treatment in the active treatment group.

For the placebo treatment group, the median AUC of the rhinoconjunctivitis SMS at baseline was 443.5 which declined to 295.0 after one year of placebo treatment. The median change from baseline to end of 1 year of treatment was greater in the active group (-176.5) than in the placebo group (-135.0). There were no consistent differences observed between the subgroups except for the similar differences by asthma status that were described previously in the primary analyses. The median number of well days at baseline was the same in both treatment groups (4.5 days).

After 1 year of treatment, there was a greater increase in wells day among patients in the active treatment group (20.0 days) compared to patients in the placebo group (15.0 days). The median change in number of wells days from 2008 to 2009 was 8.5 days for the active group compared to 4.0 days for the placebo group indicating that patients receiving active treatment had a median of 4.5 additional days in which they had less symptoms and used less medication compared to the placebo patients.

A positive response to the study medication was defined as an at least 40% decrease of AUC of SMS from baseline to after 1 year of treatment. The responder rate was 53.8% for patients in the active treatment group which was greater than the responder rate of 37.8% for patients in the placebo group.

2 SYNOPSIS (continued)

NAME OF COMPANY: Allergopharma Joachim Ganzer KG	INDIVIDUAL STUDY TABLE REFERRING TO PART V OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AllerSlit forte Grass pollen		
NAME OF ACTIVE INGREDIENT: Aqueous extract of grass pollen from *Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense* and *Poa pratensis*		

Summary and conclusions:

Efficacy results (continued):

It was required that all patients had to have a positive Conjunctival Provocation Test to grass pollen allergens at baseline. When changes in the specific Conjunctival Provocation Test from baseline to the end of first treatment year were evaluated, more patients in the active treatment group were negative after one year of active treatment (positive to negative shift 66.0%). In comparison, only 50.0% of patients in the placebo group were negative after one year of treatment.

The median levels of allergen specific IgG_1 in the active treatment group increased from 78.0µg/L at baseline to 394.0µg/L after one year. During this same time period there was no increase in IgG_1 observed in the placebo group. These results support the immunogenic stimulating effect of the active treatment.

Immunologic changes in IgE, IgG_1 and IgG_4 antibody levels were also evaluated by age, gender, asthma status and region subgroups. Immunologic results in the subgroup analyses were similar to the results from the overall analysis (~~see section 14, tables 14.2.2.7-10~~). However, the change from baseline to end of study for median IgG_1 levels was greater in females and younger patients.

Summary and conclusions:

Safety results:

The extent of exposure to study medications was similar between the active and placebo treatment groups. Median duration of intake of study medication was 339.0 days in the active treatment group and 334.5 in the placebo treatment group. The median total amount of study medication was 1295 drops in the active treatment group and 1298 drops in the placebo group. In both treatment groups, patients had 100% of the maintenance dose on most of the treatment days. The median number of days with 100% maintenance dose was 323.5 days in the active treatment group and 323.0 days in the placebo group. The median number of days with no medication intake was low in both treatment groups (1.0 active, 0.0 placebo). The median number of days with oral allergic syndrome, an expected side effect that may occur with SLIT, was markedly higher in the active group (13.5 days) than in the placebo group (0 days).

2 SYNOPSIS (continued)

NAME OF COMPANY: Allergopharma Joachim Ganzer KG	INDIVIDUAL STUDY TABLE REFERRING TO PART V OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AllerSlit forte Grass pollen		
NAME OF ACTIVE INGREDIENT: Aqueous extract of grass pollen from *Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense* and *Poa pratensis*		

Summary and conclusions:

Safety results (continued):

Among the 125 patients evaluated in the Safety Set, 104 patients (83.2%) experienced at least one adverse event (AE) during the study. AEs were reported slightly more frequently in the active treatment group compared to the placebo group. Sixty patients (95.2%) in the active treatment group and 44 patients (71.0%) in the placebo group experienced at least one AE.

Systemic reactions were reported more frequently among patients in the active treatment group than in the placebo group. Twenty-four patients (38.1%) in the active group reported at least one adverse event with systemic reactions compared to 5 patients (8.1%) in the placebo group. Rates of serious adverse events (SAEs) were similar between the treatment groups and were uncommon during the study. There were a total of 6 patients with reported SAEs during the study. Three patients (4.8%) in the active treatment group and 3 patients (4.8%) in the placebo group experienced a serious adverse event. All SAEs were reported as unlikely or unrelated to study medication. AEs that were at least possibly related to study medication were reported more frequently among patients in the active treatment group than in the placebo group. A total of 54 patients (85.7%) in the active treatment group compared to 13 patients (21.0%) in the placebo group experienced at least one AE with at least possible relationship to study medication. Eleven patients discontinued the study early due to adverse events; this included 8 patients (12.7%) in the active group and 3 patients (4.8%) in the placebo group. In both treatment groups, for the majority of patients with at least one adverse event, the severity of this AE was reported as mild. Eighty-one percent of the patients in the active treatment group and 64.5% of patients in the placebo group had AEs of mild intensity.

The most frequently reported AE of mild intensity was nasopharyngitis (50.8% active, 33.9% placebo). Oral administration complications of mild intensity occurred in 39.7% of the active group compared to 8.1% of the placebo group. AEs of moderate intensity were reported for 57.1% of the active treatment group and 40.3% of the placebo group. Nasopharyngitis was the most common AE of moderate intensity and occurred with similar frequency in both treatment groups (17.5% active, 17.7% placebo). Oral administration complications of moderate intensity occurred more frequently in the active group (15.9%) compared to 1.6% of the placebo group.

2 SYNOPSIS (continued)

NAME OF COMPANY: Allergopharma Joachim Ganzer KG	INDIVIDUAL STUDY TABLE REFERRING TO PART V OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AllerSlit forte Grass pollen		
NAME OF ACTIVE INGREDIENT: Aqueous extract of grass pollen from *Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense* and *Poa pratensis*		

Summary and conclusions:
Safety results (continued):
AEs of severe intensity occurred in 6.3% of the patients in the active group and in 4.8% of the patients in the placebo group. In the active treatment group, the AEs of severe intensity were upper abdominal pain, nasopharyngitis, otitis media, peritoneal infection and migraine (1 patient for each term). In the placebo group, one patient each had an allergic conjunctivitis, rotator cuff syndrome and a cerebrovascular accident. Serious adverse events (SAEs) were reported in only 6 patients during the treatment period. Three patients (4.8%) in the active treatment group and 3 patients (4.8%) in the placebo group experienced an SAE. The following SAE preferred terms were reported in one patient each in the active treatment group: inguinal hernia, diverticulitis, and otitis media. For the placebo group the following preferred terms were reported in one patient each: tendon rupture and rotator cuff syndrome, cerebrovascular accident and depression. All SAEs were reported as unlikely or unrelated to study medication.
Adverse events with at least possible relationship to study medication was reported more frequently (85.7%) in the active treatment as in the placebo treatment group (21.0%). The most common SOCs for AEs with at least possible relationship to study medication were general disorders and administration site conditions which occurred in 81.0% of the active treatment group compared to 19.4% of the placebo group and eye disorders which occurred in 25.4% of the active treatment group compared to 4.8% of the placebo group. Administration site conditions were primarily due to oral administration complications. Eye disorders were primarily due to conjunctivitis allergic and eye pruritus. Respiratory disorders, primarily cough, sneezing and throat irritation occurred more frequently in the active treatment group (23.8%) than in the placebo group (8.1%). Gastrointestinal disorders occurred more frequently in the active treatment group (7.9%) than in the placebo group (0.0%). The most common preferred term was dysphagia which occurred in 3.2% of the active group and 0.0% of the placebo group. There were no noteworthy differences between the treatment groups in clinical chemistry and haematology absolute values or for absolute changes from baseline to last assessment on Visit II/7. Most of the patients in both treatment groups had normal urinalysis parameters at baseline (Visit I/-1) and at end of study (Visit II/7). There were no clinically relevant changes from baseline to last assessment in systolic and diastolic blood pressure or heart and respiratory rates.

2 SYNOPSIS (continued)

NAME OF COMPANY: Allergopharma Joachim Ganzer KG	INDIVIDUAL STUDY TABLE REFERRING TO PART V OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AllerSlit forte Grass pollen		
NAME OF ACTIVE INGREDIENT: Aqueous extract of grass pollen from *Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense* and *Poa pratensis*		

Summary and conclusions:

Conclusions:

One year of treatment with AllerSlit forte Grass pollen, a perennial, sublingual, specific immunotherapy in patients with rhinoconjunctivitis with/without controlled asthma caused by grass pollen, resulted in a decrease in symptoms and need for medication as well as an increase in the number of well days. This effect was seen even though the peak pollen counts at the designated stations near each study site were generally lower in 2009 than the peak pollen counts in 2008 and there were fewer days in 2009 than in 2008 with measures of ≥ 20 particles. This might have markedly influenced the results for the symptom medication score, because less pollen exposure may lead to reduced symptoms reported by the patients. Therefore, an unspecific effect in the placebo group may be present in the data.

Overall, AllerSlit forte Grass pollen is safe and suitable for SLIT treatment of grass pollen allergic patients.

After one year of treatment with AllerSlit forte Grass pollen, more patients in the active treatment group had a negative Conjunctival Provocation Test compared to patients in the placebo group. Furthermore, substantial changes in the immunological profile were seen in the active treatment group but not in the placebo group, i.e. the specific IgG_1 and IgG_4 levels increased after treatment demonstrating the immunological effect of the active treatment. Patients treated with AllerSlit forte Grass pollen experienced the expected adverse events related to the administration of a sublingual therapy but severity for the majority of patients was mild. No drug related SAEs were reported. No clinically relevant changes on blood chemistry, haematology or urinalyses and vital signs were observed.

Overall, AllerSlit forte Grass pollen is safe and suitable for SLIT treatment of grass pollen allergic patients.

2 SYNOPSIS (continued)

NAME OF COMPANY: Allergopharma Joachim Ganzer KG	INDIVIDUAL STUDY TABLE REFERRING TO PART V OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AllerSlit forte Grass pollen		
NAME OF ACTIVE INGREDIENT: Aqueous extract of grass pollen from *Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense* and *Poa pratensis*		

Summary and conclusions:

Conclusions (continued):

No statistically significant differences could be detected for the primary endpoint. Therefore, the null hypothesis could not be rejected and statistical superiority could not be confirmed. However clinical superiority of active treatment was shown and all secondary variables as well showed superiority of active treatment. A pooled analysis of efficacy with the previously completed study AL0102st together with the present study showed statistically significance for the primary endpoint SMS. Considering all these information, it was decided to continue the study in an open design for patients in the active treatment group and to start with active treatment in the former placebo group.

Date of report: 26/07/2010 / final 1.0

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.