2 SYNOPSIS

NAME OF COMPANY: Allergopharma GmbH & Co. KG	INDIVIDUAL STUDY TABLE REFERRING TO PART V OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AllerSlit® forte 6-Grasses		
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).

Coordinating Investigator:
[redacted]

Study centre(s):
26 centres: 23 centres in Germany and 3 centres in Italy
(19 centres with randomised patients)

Publication (reference):
Not applicable (n.a.)

Study period (years):		**Development phase:**
DBP:	22-Feb-2008 to 05-Nov-2009	III
Bridging phase:	06-Nov-2009 to 21-Feb-2010	
OLP:	21-Dec-2009 to 20-Oct-2011	

Objectives:
To obtain evidence for the safety and efficacy of sublingual specific immunotherapy (SLIT) 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 - after two and three treatment years in the active group and after one and two years in the former placebo group.

To assess immunological parameters during the course of the study to obtain evidence of immunological effects of the therapeutic vaccine.

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Methodology:

This clinical trial was carried out as a multicentre, multinational, phase III study in patients with rhinoconjunctivitis with/without controlled asthma caused by grass pollen. The study was carried out in a double-blind, placebo-controlled parallel group design over a period of one year with perennial treatments. The study continued in an open-label design for two additional years for patients in the active treatment group (called in this report active-active group). Patients in the placebo treatment group were offered an open-label treatment with SLIT regimen (called in this report placebo-active group) applied in this study for the full recommended period of three additional years of which two years were reported in this report.

For assessment of efficacy, the change of the area under the curve (AUC) of the Symptom and Medication Score (SMS) from the baseline season to after two and three years of treatment was calculated. Tolerability of the study medication intake was assessed via a visual analogue scale (VAS) assessment by the patient and the investigator.

For the assessment of safety, adverse events (AEs) by Medicinal Dictionary for Drug Regulatory Activities (MedDRA) primary system organ class (SOC) and preferred term (PT), dose of study drug used and the intake of medication were evaluated.

Number of patients planned and analysed:

In total, 126 patients were randomised in the AL0703st DBP study (63 patients to active treatment and 63 patients to placebo treatment) ~~(see section 10.1 of the clinical study report [CSR] AL0703st DBP)~~.

OLP:

Planned: All patients treated with the sublingual specific grass pollen extract immunotherapy or with placebo were offered to participate in the open-label treatment phase for descriptive analysis of efficacy and safety.

Analysed: 92 patients: 51 patients previously treated with SLIT and 46 patients who were previously treated with placebo in the DBP. Forty-seven (92.2%) of the active-active patients and 45 (97.8%) of the placebo-active patients received at least one dose of active study medication in the OLP and were eligible for the OLP Safety Set. Forty-four patients (86.3%) of the active-active patients and 38 (82.6%) of the placebo-active patients for whom any efficacy assessment in the OLP was available were included in the OLP Full Analysis Set (OLP FAS).

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2 SYNOPSIS (continued)

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Diagnosis and main criteria for inclusion:

Diagnosis: Immunoglobulin (Ig) E-mediated allergic disease manifested as symptoms of allergic rhinoconjunctivitis with or without controlled asthma caused by grass pollen.

~~See section 9.3.1 of the CSR AL0703st DBP for inclusion criteria.~~

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

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

The batch numbers of the active treatment were as follows:

[redacted]

Duration of treatment:

After one year DBP and a bridging phase until unblinding patients previously treated with AllerSlit® forte 6-Grasses were treated for two additional years until October 2011.

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 number of the placebo treatment during the bridging phase was as follows:

[redacted]

Duration of treatment:

After one year DBP and a bridging phase patients of the previous placebo treatment group received active treatment after unblinding until October 2011 for two years within the study.

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Criteria of evaluation - Efficacy:

In this OLP of the study only secondary endpoints after two years and after the full course of three years of treatment were evaluated; these endpoints included:

- Change of the AUC of the SMS
- Change of AUC of the Symptom Score
- Change of AUC of the Medication Score
- Change of AUC of rhinoconjunctivitis (RC) SMS
- Immunological profile (specific IgE, IgG_1 and IgG_4)
- Number of well days
- Number of RC well days
- Response (at least 40% improvement of AUC of SMS)
- Changes in specific Conjunctival Provocation Test (CPT)
- All efficacy analyses (except for Symptom Score and Medication Score) were performed also by age group (≤50, >50), gender (male, female), asthma status (yes, no) and region (north, south).

Criteria of evaluation - Safety:

~~See section 9.5.1.1 of the CSR AL0703st DBP.~~ The endpoints for the assessment of safety during the entire study were:

- All AEs
- Systemic reactions
- Serious adverse events (SAEs)
- AEs with at least “possible” relationship to the study medication
- Treatment-emergent adverse events (TEAEs) by severity (mild, moderate and severe)
- AEs with at least possible relationship to study medication by TRYBA classification (3)
- Change from baseline in vital signs
- Change from baseline in clinical laboratory parameters
- Urinalysis

The following endpoint for the assessment of safety was only performed during the OLP of the study:

- Patient’s and investigator’s assessment of tolerability (VAS)

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Statistical methods:

~~See appendix 16.1.9.1~~ "Amendment to SAP dated 08-Feb-2011" ~~of this CSR and section 9.7.5 of the CSR AL0703st DBP~~.

Summary and conclusions:

Efficacy results:

In this open-label part of the study, results from 51 of the 63 randomised patients of the active treatment group who were eligible to be treated for two additional years (2010 - 2011) after the DBP (active-active group) and 46 of the 63 randomised patients in the placebo treatment group who were eligible for active treatment for three additional years after the DBP (placebo-active group) are reported. Results for the 46 placebo-active patients were evaluated from 2009 to 2011. Forty-seven (92.2%) of the active-active patients and 45 (97.8%) of the placebo-active patients received at least one dose of active study medication in the OLP and were eligible for the OLP Safety Set. Forty-four patients (86.3%) of the active-active patients and 38 (82.6%) of the placebo-active patients for whom any efficacy assessment in the OLP was available were included in the OLP FAS.

At baseline, the majority of patients (over 50%) showed CPT responses at the 500 - 1600 standardised biological units (SBU)/mL titre levels.

The median AUC of the SMS for the active-active treatment group in the 2011 pollen season after three years of treatment was 130.0 which indicated an improvement over the baseline scores of 501.0 in the 2008 season. The median change of the AUC of the SMS from 2008 to 2011 was -315.0. During the DBP, the median change of the AUC of the SMS was -240.0. Therefore, the median change in the AUC of the SMS from active-active group after three years of treatment indicated further improvement in the SMS over that observed during the DBP and pointed out that the specific immunotherapy (SIT) therapy continued to be an effective therapy for these patients with allergic rhinitis attributable to grass pollen allergens.

The median AUC of the SMS for the placebo-active treatment group in the 2011 pollen season after two years of treatment was 119.5 which indicated improvement over the baseline scores of 565.5 in the 2008 season. The median change of the AUC of the SMS from 2008 to 2011 was -352.0.

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Summary and conclusions (continued):

Patients in both treatment groups showed an improvement in the median AUC of the RC-SMS under active treatment. The median change of the AUC of the RC-SMS from 2008 to 2011 for the active-active treatment group was -287.0 and for the placebo-active treatment group the median change from 2008 to 2011 was -334.8.

The median number of well days for the active-active treatment group in the 2011 pollen season was 28.0 days which indicated an improvement over the median number of 5.0 well days in the 2008 season. The median change of well days for the active-active treatment group from 2008 to 2011 was an increase of 18.0 days. For the patients in the placebo-active treatment group the median number of well days increased from 5.5 days in 2008 to 30.0 well days in 2011 which was a median increase of 21.0 days.

Response rates defined as an at least 40% decrease of AUC of SMS from baseline to after each year of treatment showed a steady increase from 2008 to 2011 in both treatment groups. In 2011, the response rate was 75.7% for patients of the active-active treatment group and 80.6% for patients in the placebo-active treatment group.

The specific CPT results from baseline to the end of each treatment year were evaluated only in the active-active treatment group and indicated a shift from a positive allergic reaction to a negative test result for the majority of patients at the visit after the end of the pollen season. A positive to negative shift was seen for 84.1% of the patients in the active-active treatment group indicating an improvement in their grass pollen allergy.

Immunologic changes in IgG_1 and IgG_4 antibody levels were evaluated from screening visit (Visit [V] I/-1) to after last year of study at the end of the grass pollen season (V IV/6). The allergen specific IgG_1 levels from screening visit to end of the study showed a median increase of 755µg/L in the active-active treatment group and 706µg/L in the placebo-active treatment group. The allergen specific IgG_4 levels from screening visit to end of the study showed a median increase of 343µg/L in the active-active treatment group and 732µg/L in the placebo-active treatment group. These results support the immunogenic stimulating effect of active treatment.

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Summary and conclusions (continued):

Safety results:

For reasons of comprehensibility the safety results described in this section will focus only on the data from the OLP (OLP Safety Set) and the data from the active-active patients who were treated for a full course of three years. Patients in the placebo-active treatment group showed a comparable safety profile as patients in the active-active treatment group. Thus, for reason of shortness and to avoid redundancies, only data of the active-active treatment group will be presented.

Extent of exposure

OLP: Forty-seven (92.2%) of the active-active patients and 45 (97.8%) of the placebo-active patients received at least one dose of active study medication in the OLP and were evaluated in the OLP Safety Set. Median duration of intake of study medication was 564.0 days in the active-active treatment group and 604.0 days in the placebo-active treatment group. The median total amount of study medication was 2240 drops in the active-active treatment group and 2271 drops in the placebo-active treatment 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 559.0 days in the active-active treatment group and 565.5 days in the placebo-active treatment group. The median number of days with no medication intake was low in both treatment groups (2.0 active-active, 0.5 placebo-active).

Complete study (active-active treatment only): Patients treated with active treatment during the DBP of the study and who had received at least one dose of active study medication in the OLP were evaluated in the OLP Safety Set (active-active treatment patients only) analyses. Median duration of intake of active medication was 1021.0 days and the median total amount of active medication was 4003 drops in the active-active treatment group.

Patients in the active treatment group had 100% of the maintenance dose on most of the treatment days. The median number of days with 100% maintenance dose was 998.0 days and the median number of days with no medication intake was 7.0 days.

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Summary and conclusions (continued):

Overview of AEs

OLP: Among the 92 patients evaluated in the OLP Safety Set, 79 patients (85.9%) experienced at least one AE during the study. Thirty-eight patients (80.9%) in the active-active treatment group and 41 patients (91.1%) in the placebo-active treatment group experienced at least one AE.

During the OLP, 21.3% of the patients in the active-active treatment group and 88.9% of the placebo-active treatment group experienced “General disorders and administration site condition” related AEs. Patients most frequently reported oral administration complications (19.1% active-active and 88.9% placebo-active). The higher rate of oral administration complications, an expected complication related to study medication, in the placebo-active treatment group was due to their first exposure to AllerSlit® forte 6-Grasses during the OLP. AEs related to the SOC “Infections and infestations” were frequently reported by patients in both treatment groups. The incidence of infections was slightly higher in the active-active treatment group (66.0%) than in the placebo-active treatment group (57.8%). Under this SOC, nasopharyngitis was the most frequently reported AE PT reported by patients in both groups (53.2% active-active and 35.6% placebo-active).

Complete study (active-active treatment only): Among the 47 active-active treatment patients evaluated in the OLP Safety Set, all patients (100%) experienced at least one AE during the complete study.

Patients under active treatment reported AEs related to the SOC “General disorders and administration site conditions” most frequently. During the complete study, 85.1% of the patients of the active-active treatment group experienced “General disorders and administration site condition” related AEs. Patients most frequently reported oral administration complications (85.1% of active-active patients). AEs related to the SOC “Infections and infestations” were also frequently reported by patients (80.9%).

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Summary and conclusions (continued):

Under this SOC, the most frequently reported PT was nasopharyngitis which was reported by 78.7% of the patients. “Respiratory, thoracic and mediastinal disorders” were reported as AEs by 53.2% of the active-active treatment group patients. “Eye disorders” AEs were reported by 46.8% of the active-active treatment group patients and conjunctivitis allergic was the PT most frequently reported by patients (23.4%). “Gastrointestinal disorders” AEs (SOC) were reported by 38.3% of the active-active treatment group patients. AEs related to the SOC “Injury, poisoning and procedural complications” were reported by 29.8% of patients in the active-active treatment group.

Severity of AEs

OLP: In both treatment groups, for the majority of patients with at least one AE, the severity of the AE was reported as mild. Sixty-six percent of the patients in the active-active treatment group and 82.2% of the patients in the placebo-active treatment group had AEs of mild intensity. The *AE of mild intensity* most frequently reported by patients was nasopharyngitis (48.9% active-active, 24.4% placebo-active). Oral administration complications of mild intensity were reported by 2.1% of patients in the active-active treatment group and by 62.2% of patients in the placebo-active treatment group. An *AE of moderate intensity* was reported for 53.2% of patients in the active-active treatment group and 66.7% of the patients in the placebo-active treatment group. Nasopharyngitis was the most common AE of moderate intensity reported by patients in both treatment groups (19.1% active-active, 15.6% placebo-active). Oral administration complications of moderate intensity were only reported more frequently by patients in the placebo-active treatment group (17.8%) compared to 0.0% of the active-active treatment group. *AEs of severe intensity* were reported by 8.5% of the patients in the active-active treatment group and by 13.3% of the patients in the placebo-active treatment group, but no PT was reported by more than one patient.

Complete study (active-active treatment only): The majority (91.5%) of active-active treatment patients with at least one AE reported the severity of the AE as mild. The *AE of mild intensity* most frequently reported by patients was nasopharyngitis (74.5% of active-active patients). Oral administration complications of mild intensity were reported by 40.4% of patients in the active-active treatment group.

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2 SYNOPSIS (continued)

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Summary and conclusions (continued):

An *AE of moderate intensity* was reported for 74.5% of patients in the active-active treatment group. Nasopharyngitis was the most common AE of moderate intensity reported by patients (36.2% of active-active patients). Oral administration complications of moderate intensity were reported by 17.0% of the active-active treatment group. *AEs of severe intensity* were reported by 6 patients (12.8%) in the active-active treatment group but no PT except for nasopharyngitis (n=2 patients) was reported by more than one patient.

Serious AEs (SAEs)

OLP: Three patients (6.4%) in the active-active treatment group and 6 patients (13.3%) in the placebo-active group experienced an SAE during the OLP of the study. All SAEs reported by patients were considered as unrelated to study medication.

Complete study (active-active treatment only): Five patients (10.6%) experienced SAEs during the complete study. All SAEs reported by patients were considered as unlikely to be related or unrelated to study medication.

Related AEs

OLP: During the OLP of this study, 23.4% of patients in the active-active treatment group and 88.9% of the patient in the placebo-active treatment group had AEs with at least possible relationship to study medication. The most common SOC for AEs with at least possible relationship to study medication reported by patients was “General disorders and administration site conditions” which reported by 17.0% of the patients in the active-active treatment group and by 88.9% of the patients in the placebo-active treatment group. The largest proportion of patients in both groups reported oral administration complications as at least possibly being related to study medication (17.0% active-active, 88.9% placebo-active).

Complete study (active-active treatment only): During the complete study, 41 patients (87.2%) in the active-active treatment group experienced at least one AE with at least possible relationship to study medication.

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Summary and conclusions (continued):

The most common SOC for AEs with at least possible relationship to study medication reported by patients was "General disorders and administration site conditions" which was reported by 85.1% of the patients in the active-active treatment group. Oral administration complications as at least possibly being related to study medication were reported by 85.1% of the active-active patients.

Systemic reactions

OLP: Systemic reactions were defined as AEs with at least possible relationship to study medication and occurring apart from the administration site. These reactions were reported by 12.8% of patients in the active-active treatment group and 26.7% of patients in the placebo-active treatment group. Conjunctivitis allergic was the most commonly reported systemic reaction among patients in both treatment groups and was reported by 8.5% of patients in the active-active treatment group and 11.1% of patients in the placebo-active treatment group.

Complete study (active-active treatment only): Systemic reactions were reported by 20 active-active treatment patients (42.6%) during the complete study. Conjunctivitis allergic was the most commonly reported systemic reaction but was reported by only 5 patients in the active-active treatment group (10.6%).

Discontinuations due to AEs

OLP: During the OLP, 4 patients discontinued the study early due to AEs; this included one patient (2.1%) in the active-active treatment group and 3 patients (6.7%) in the placebo-active treatment group.

Complete study (active-active treatment only): During the complete study, 9 patients in the active-active treatment group discontinued the study early due to AEs (14.3%).

Clinical laboratory and vital signs

OLP: During the OLP, most patients had clinical laboratory values which were normal or assessed as being not clinically relevant. Clinically relevant abnormalities for thyroid stimulating hormone (TSH), total bilirubin and glucose that were not previously reported in the DBP where reported for one patient each during the OLP. Also, 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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Summary and conclusions (continued):

Complete study (active-active treatment only): During the complete study, most patients in the active-active treatment group had clinical chemistry values which were normal or assessed as being not clinically relevant. One active-active patient had a clinically relevant abnormal basal TSH value at V III/6. One active-active patient had a clinically relevant abnormal glucose value at V II/7.

Assessment of tolerability

Patient and investigator global assessment of tolerability as measured with a VAS assessment indicated that active treatment was well tolerated by end of study. For the active-active treatment group, the median Patient VAS Score was 98 and the median Investigator VAS Score was 99. In the placebo-active treatment group, the median VAS Score was assessed as 90 by patients and investigators.

In summary, during the bridging phase and the OLP no new safety signals were detected and the VAS showed that there was a continuing improvement in tolerability.

Summary and conclusions:

Conclusions:

This open-label part of study AL0703st confirmed the efficacy of AllerSlit® forte 6-Grasses in patients suffering from allergic rhinoconjunctivitis with or without controlled asthma caused by grass pollen. A further decrease in the SMS was seen when comparing the results after the double-blind period with the results of the 3rd treatment year in the active-active treatment group of the open-label period. Furthermore, the placebo-active treatment group also showed improvements when switched from placebo to active treatment.

Patients treated with AllerSlit® forte 6-Grasses experienced the expected AEs 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. Thus, the safety profile seen in the OLP is in line with the safety profile seen in the DBP of the study.

Date of the final report: 02-Jul-2013