2 Synopsis

Name of Sponsor/Company: Allergopharma GmbH & Co. KG	**Individual Study Table Referring to Part of this Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Allergovit©		
Name of Active Ingredient: Birch pollen allergoid preparation		

Title of study:

A multicentre, randomised, placebo-controlled, double-blind clinical trial for evaluation of safety and efficacy of specific immunotherapy with an aluminium hydroxide-adsorbed allergoid preparation of birch pollen allergens

Coordinating investigator(s):

[redacted]

Study centre(s):

19 sites with randomised patients (Germany 10, Poland 3, Finland 2, Sweden 4).

Publication (reference) (see appendix 16.1.11):

Oral presentation at satellite symposium Allergopharma "Benefits of High-Dose-SIT the Choice for the European Allergists", 07-11 June 2008, XXVII Congress of the European Academy of Allergology and Clinical Immunology (EAACI), Barcelona, Spain.

Rak S, Valovirta E, Rudert M, Tribanek M, Haefner D, Narkus A, Meyer W. High-dose hypoallergenic birch pollen preparation is effective in Finland and Sweden. Allergy 67[S96], 526. 2012. Geneva, EAACI-Congress.

Haefner D, Meyer H, Weber B, Kettner J, Narkus A. Immunogenic activity of pollen allergoids. Allergy 68[S97], 471. 2013.

Kettner J, Häfner D, Meyer H, Weber B, Narkus A. Immunogenität der subkutanen spezifischen Immuntherapie (SCIT) mit hochdosierten hypoallergenen Pollenpräparaten. Allergo Journal 22[6], 402. 2013.

Rak S, Valovirta E. High-dose hypoallergenic Allergovit Birch is effective in Finland and Sweden. Allergo Journal 20[S1], S42. 2011.

2. Synopsis (continued)

Name of Sponsor/Company: Allergopharma GmbH & Co. KG	**Individual Study Table Referring to Part of this Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Allergovit©		
Name of Active Ingredient: Birch pollen allergoid preparation		

Study period (years): • June 2005 - June 2007 double-blind • June 2007 - January 2008 bridging • November 2007 - August 2010 open label	**Phase of development:** III/IV

Objectives:

To evaluate efficacy and tolerability of specific immunotherapy with an aluminium hydroxide-adsorbed allergoid preparation of birch pollen allergens.

Methodology:

This clinical study was designed as an international, multicentre, randomised, double-blind, placebo-controlled (DBPC) phase III/IV study in two parallel groups to assess efficacy and safety of specific immunotherapy with an aluminium hydroxide-adsorbed allergoid preparation of birch pollen allergens. Safety evaluation was continued until the first visit of the open label phase (bridging phase).

Open label phase (OLP): Treatment of patients in the active group was completed in open label design in year three to evaluate safety and efficacy for the overall course of immunotherapy *(3rd year active group).* The study was further continued in years three to five to evaluate safety during active open label treatment of the patients previously randomised to placebo *(3rd to 5th year placebo-active group).*

Number of patients (planned and analysed):

Planned: 420 patients to be screened to achieve 252 patients randomised

Analysed:

DBPC phase (1st and 2nd study year)

All Patient Set: 403 patients screened, 253 patients randomised (active: 124; placebo: 129). Four randomised patients withdrew before first application of study medication.

Safety Set (SAF): 249 patients (active: 122; placebo: 127)

Full Analysis Set (FAS): 227 patients (active: 113; placebo: 114)

(continued)

2. Synopsis (continued)

Name of Sponsor/Company: Allergopharma GmbH & Co. KG	**Individual Study Table Referring to Part of this Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Allergovit©		
Name of Active Ingredient: Birch pollen allergoid preparation		

Number of patients (planned and analysed, continued):

Per Protocol Set (PP): 206 patients (active: 107; placebo: 109)

Safety Set Bridging phase: 215 patients (active: 106; placebo: 99)

Open label phase (3rd year active group)

Active randomised patients:

Safety Set Follow-up (FU1 SAF): 85 patients

Full Analysis Set Follow-up (FU1 FAS): 73 patients

Per-Protocol Set Follow-up (FU1 PP): 69 patients

Open label phase (placebo-active group 3rd to 5th study year):

Active treatment of initial placebo randomised patients:

Safety Set Follow-up (FU3 SAF): 67 patients

Diagnosis and main criteria for inclusion:

Male or female outpatients between 18 and 60 years of age with immunoglobulin (Ig) E-mediated moderate to severe seasonal allergic rhinitis/rhinoconjunctivitis with or without bronchial asthma (Global Initiative for Asthma [GINA] grade I or II), attributable to birch pollen allergens, documented by

- Symptoms of allergic rhinitis/rhinoconjunctivitis against birch pollen allergens requiring medication during birch pollen season 2005.
- Positive Enzyme Allergo Sorbent Test /CAPACITY SYSTEM (EAST/CAP) to birch pollen class ≥ 2.

(continued)

2. Synopsis (continued)

Name of Sponsor/Company: Allergopharma GmbH & Co. KG	**Individual Study Table Referring to Part of this Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Allergovit©		
Name of Active Ingredient: Birch pollen allergoid preparation		

Diagnosis and main criteria for inclusion (continued):

- Positive Prick Test reaction to natural birch pollen allergens demonstrated by allergen wheal at least as large as histamine control reaction (histamine-dihydrochloride of 0.1% = 1 mg/mL) and a negative control test (saline solution). A positive histamine control reaction demonstrated by wheal diameter ≥ 3 mm, a negative control test demonstrated by wheal diameter < 3 mm.
- Proven clinical relevance of birch pollen allergy by positive Conjunctival Provocation Test (CPT) result using natural birch pollen extract.
- For female patients: effective contraception and negative pregnancy test result.

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

Investigational product:

Suspension of aluminium hydroxide-adsorbed allergoid preparation of birch pollen allergens.

Mode of administration:

Subcutaneous injection in the following strengths:

Strength A ([redacted]); strength B ([redacted])

Batch numbers:

Double-blind, placebo-controlled (DBPC) phase:

- [redacted]

Open label phase:

- [redacted]

Duration of treatment: Active: three years; placebo: two years (annual preseasonal treatment courses).

2. Synopsis (continued)

Name of Sponsor/Company: Allergopharma GmbH & Co. KG	**Individual Study Table Referring to Part of this Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Allergovit©		
Name of Active Ingredient: Birch pollen allergoid preparation		

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

Placebo: Comparative compound: Sterile aluminium hydroxide suspension.

Batch numbers: [redacted]; [redacted]

Vials with strength A ([redacted]) and strength B ([redacted]) histamine-dihydrochloride.

Criteria for evaluation:

Efficacy:

Primary endpoint:

- The change of the area under the curve (AUC) of the daily sum of the Symptom Medication Score (SMS) after two years of double-blind treatment.

Key secondary endpoints:

Efficacy:

- Number of "well days" (Symptom Score ≤ 4, Medication Score = 0)
- Changes in allergen specific CPT reactivity
- Immunologic changes: Allergen specific IgE, IgG_1 and IgG_4

Open label phase (3rd year active group):

- AUC of the SMS
- Number of "well days" (Symptom Score ≤ 4, Medication Score = 0)
- Immunologic changes: Allergen specific IgE, IgG_1 and IgG_4

Safety (during the entire study):

- Occurrence of adverse events (AEs)
- Change from screening in vital signs and laboratory parameters

2. Synopsis (continued)

Name of Sponsor/Company: Allergopharma GmbH & Co. KG	**Individual Study Table Referring to Part of this Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Allergovit©		
Name of Active Ingredient: Birch pollen allergoid preparation		

Statistical methods:

Primary analysis

The primary endpoint was tested in a confirmatory sense within the FAS with an analysis of covariance (ANCOVA) model adjusting for asthma status at randomisation and centre; the treatment effect was tested at a two-sided significance level of 0.025. All further statistical tests were performed in an exploratory sense only.

Demography of study population and baseline characteristics:

SAF

Mean age was 37.6 (SD 12.2) years in the active treatment group and 35.5 (SD 11.2) years in the placebo treatment group. Males were slightly less frequent in the active group (43.4%) than in the placebo group (52.8%). Mean height and weight were similar in both groups.

Over 98.8% of patients (active: 98.4%; placebo: 99.2%) were Caucasian. At baseline, all patients with asthma were classified according to the GINA classification. GINA grade I was recorded for 83.3% in the active treatment group and 86.1% in the placebo group. The percentage of patients with GINA grade II was 16.7% in the active group and 13.9% in the placebo group.

Overall, demographic and screening characteristics were similar between the active and placebo treatment group.

FAS

Demographic and baseline characteristics were similar to SAF of the DBPC phase and between groups.

2. Synopsis (continued)

Name of Sponsor/Company: Allergopharma GmbH & Co. KG	**Individual Study Table Referring to Part of this Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Allergovit©		
Name of Active Ingredient: Birch pollen allergoid preparation		

Summary and conclusions:

Efficacy results:

DBPC phase

The primary endpoint was the AUC of the SMS after two years of therapy (2007). The AUC of the SMS was 207.6 (PP: 206.5) in the active treatment group and 238.9 (PP: 239.3) in the placebo group.

The results for the primary efficacy analysis AUC of the SMS adjusted (ANCOVA) for asthma status and centre did not reach statistical significance for the overall patient set of all four countries ($p = 0.0710$ [FAS: $n = 227$]). For the PP set ($n = 216$), a p-value of 0.0523 was observed.

Exploratory subgroup analyses including the population of the more northern and eastern European regions (Scandinavia and Poland without the most southern located centre 12; $n = 102$) with similar birch pollen load but less interference of other tree pollen showed a clinically relevant and statistically significant improvement ($p = 0.0034$) of the mean AUC of SMS for the active (136.1) compared to the placebo group (205.7). Thus, the proof of efficacy of active treatment in this study was dependent on geographic and climatic regions.

The difference in percentage of median "well days" between active and placebo (61.9% vs. 28.6%) for the subgroup of patients of the northern and eastern centres was statistically significant ($p = 0.0232$).

The percentage of patients of the FAS showing an improvement in allergen specific CPT after the second treatment course was higher in the active treatment group (67.5%) than in the placebo group (56.0%).

In the immunological analyses of serum antibodies clear increases were noted for the median IgG_1 and IgG_4 levels in the active treatment group after the first treatment course. A further increase of the median IgG_4 level was noted after the second course, indicating a booster-effect in the immunogenic activity of the active treatment.

(continued)

2. Synopsis (continued)

Name of Sponsor/Company: Allergopharma GmbH & Co. KG	**Individual Study Table Referring to Part of this Dossier**	**(For National Authority Use only)**
Name of Finished Product: Allergovit©	**Volume:**	
Name of Active Ingredient: Birch pollen allergoid preparation	**Page:**	

Summary and conclusions (continued):

Open label phase (3rd year active group)

After three years (2008) of active SIT the mean AUC of the SMS further decreased (2006: 279.7; 2007: 197.7; 2008: 128.5). Among the patients who participated in the third year of active treatment, the median number and percentage of "well days" continued to increase from 14.3% in 2006, to 42.9% in 2007 and to 61.9% in 2008.

IgG_1 and IgG_4 antibody levels after the third active treatment course followed the same trend observed during the first and second courses.

Safety results:

DBPC phase

Patients in both treatment groups received a median number of ten injections in the first (2006) and second treatment year (2007).

101 patients (82.8%) of the active treatment group and 102 patients (80.3%) of the placebo group reported at least one AE. Nasopharyngitis was the most frequently reported AE preferred term (PT) under the system organ class (SOC) "infections and infestations" and was similar in occurrence for both groups (46.7% active vs. 45.7% placebo). Injection site reaction (42.6% active vs. 23.6% placebo), injection site pruritus (34.4% active vs. 13.4% placebo) and injection site swelling (26.2% active vs. 7.9% placebo) were the most common PTs under the SOC "general disorders and administration site conditions" and were more frequent in the active group (50.8%) vs. 35.4% in the placebo group. Under the SOC "respiratory, thoracic and mediastinal disorders", asthma (8.2% active vs. 15.0% placebo) and cough (10.7% active vs. 10.2% placebo) were the most frequently reported PTs.

The number of patients with at least possibly treatment related AEs was higher in the active than in the placebo group (50.0% vs. 29.1%), primarily caused by AEs reported under the SOC "general disorders and administration site conditions" (active: 50.0%; placebo: 29.1%). This was primarily due to the PTs injection site reaction (active: 42.6%; placebo: 22.8%), injection site pruritus (active: 34.4%; placebo 12.6%), injection site swelling (active: 26.2%; placebo: 7.9%), adverse drug reaction (active: 13.9%; placebo: 16.5%) and injection site pain (active: 11.5%; placebo: 6.3%).

(continued)

2. Synopsis (continued)

Name of Sponsor/Company: Allergopharma GmbH & Co. KG	**Individual Study Table Referring to Part of this Dossier**	**(For National Authority Use only)**
Name of Finished Product: Allergovit©	**Volume:**	
Name of Active Ingredient: Birch pollen allergoid preparation	**Page:**	

Summary and conclusions (continued):

Safety results (continued):

The difference between active and placebo treatment group reflects higher incidences in local reactions (42.6% vs. 23.6%) typically seen in association with allergen SIT such as itching and local swelling at the injection site. Patients with systemic reactions were similar between the two treatment groups (active: 13.9% vs. placebo: 16.5%).

The SOCs "general disorders and administration site conditions", "respiratory, thoracic and mediastinal disorders", "infections and infestations" and "eye disorders" included the most common systemic reactions in both treatment groups.

Fourteen patients had 18 serious adverse events (SAEs) after start of treatment. None of these SAEs was considered to be treatment related.

In general, the SIT was well tolerated. Vital signs and safety laboratory parameters did not indicate any safety concerns associated with the study medication.

3 years active group

Among the 85 patients who continued treatment in the open label period, 73 patients (85.9%) had at least one AE during their three years treatment course. Seven of these patients (8.2%) had at least one SAE. None of these SAEs was related to study medication.

45 patients (52.9%) had an AE that was considered at least possibly related to study medication. This frequency was similar to that reported during the double-blind study phase (52.9% FU1 vs. 50.0% first two years). Injection site disorders continued to be the most commonly reported PTs for AEs that were at least possibly related to treatment. Also the frequency of local and systemic reactions was similar to that reported for patients with two years of active treatment. Local reactions were reported in 44.7% of patients and systemic reactions in 14.1% of the patients in the FU1 active group.

The most frequent AE SOCs were "infections and infestations" (64.7%) "general disorders and administration site conditions" (54.1%), "respiratory and thoracic and mediastinal disorders" (36.5%), "nervous system disorders" (28.2%).

(continued)

2. Synopsis (continued)

Name of Sponsor/Company: Allergopharma GmbH & Co. KG	**Individual Study Table Referring to Part of this Dossier**	**(For National Authority Use only)**
Name of Finished Product: Allergovit©	**Volume:**	
Name of Active Ingredient: Birch pollen allergoid preparation	**Page:**	

Summary and conclusions (continued):

Safety results (continued):

The results from the third year and the entire three years of active treatment were consistent with those observed during the first two years of treatment. No new safety issues were identified.

Placebo-active group

Patients in the FU3 SAF received a median total number of injections that ranged between 10 and 11 injections.

During the OLP active treatment phase 35 patients (52.2%) had at least one AE. In 19 patients (28.4%) at least one local reaction and in five patients (7.5%) at least one systemic reaction had been observed.

Four patients (6.0%) with SAEs were reported. None of the SAEs was related to study medication.

Injection site disorders were the most commonly reported PTs for AEs that were at least possibly related to treatment. These AEs included injection site reaction in 19 patients (28.4%), injection site pruritus in 16 patients (23.9%), injection site erythema in nine patients (13.4%) and injection site swelling in eight patients (11.9%).

During the three years of active treatment, no clinically relevant haematological, clinical chemistry or urinalysis abnormalities were observed and there was little change in mean vital sign values in the FU3 SAF patients.

Conclusions:

Although a lower AUC of the SMS for the active treatment group compared to the placebo group was determined, a statistically significant difference in the primary analysis of efficacy for the overall patient population could not be demonstrated. However, the study results showed large differences in the AUC of SMS for patients from the different climatic/geographic regions.

(continued)

2. Synopsis (continued)

Name of Sponsor/Company: Allergopharma GmbH & Co. KG	**Individual Study Table Referring to Part of this Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Allergovit©		
Name of Active Ingredient: Birch pollen allergoid preparation		

Summary and conclusions (continued):

Conclusions (continued):

In exploratory analyses, a statistically significant difference was found between active and placebo treatment when the mean AUC of SMS of the patients from the northeastern European located centres was considered separately in a subgroup (n = 102, p = 0.0034).

Since the exposure to birch pollen in the investigated geographic regions in 2007 showed comparable peaks in Germany, Poland, Finland and Sweden, the differences in mean AUC of SMS depending on geographic regions indicate additional influencing factors like interfering allergens beside birch pollen. In the northern regions like Scandinavia, interfering allergens play only a minor or no role.

The regional differences in the primary variable were also observed in the subgroup analyses of the secondary variable "well days". The difference in percentage of median "well days" between active and placebo for the subgroup of patients from the northern and eastern European centres (Scandinavia and Poland without the most southern located centre 12) was statistically significant (61.9% vs. 28.6%; p = 0.0232).

In the immunological analyses of serum parameters marked increases were noted for the median IgG_1 and IgG_4 levels in the active treatment group after the first treatment year and a further increase of median IgG_4 levels after the second year, indicating a clear immunogenic effect of the active treatment.

There were no clinically relevant abnormal findings in vital signs and laboratory parameters which were considered to be related to the study medication.

Overall, SIT with a marketed aluminium hydroxide-adsorbed allergoid preparation of birch pollen allergens, was well tolerated and efficacy could be shown at least in regions with less interfering pollen flow. The safety profile was within the range known for SIT.

Date of report / Version no.:

10-Dec-2015 / Revised final version of the CSR dated 23-Aug-2012