2 SYNOPSIS

NAME OF COMPANY: Allergopharma GmbH & Co. KG	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: Not applicable (n.a.)		
NAME OF ACTIVE INGREDIENT: Aluminium hydroxide-adsorbed recombinant hypoallergenic derivative of the major birch pollen allergen, rBet v 1-FV		

Title of study
A multicentre randomised placebo-controlled double-blind pivotal clinical trial for the evaluation of safety and efficacy of specific immunotherapy with an aluminium hydroxide-adsorbed recombinant hypoallergenic derivative of the major birch pollen allergen, rBet v1-FV

Coordinating Investigator
[redacted]

Study centres
36centres: 16 in Germany, 14 in Poland, 2 in Finland and 4 in Sweden.
33 centres (13 in Germany, 14 in Poland, 2 in Finland and 4 in Sweden) randomised patients.

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

Study period (years)		**Development phase**
Double-blind phase:	First patient in: 08-Oct-2007 Last patient out: 18-Jun-2010	III

Objectives
This clinical trial was planned as a pivotal study. The aims of this clinical trial were

- to prove the hypothesis that efficacy of specific immunotherapy (SIT) with a recombinant major allergen preparation of birch pollen was statistically and clinically superior to placebo in a representative number of birch pollen allergic patients suffering from allergic rhinoconjunctivitis with or without asthma
- to evaluate the safety of the preparation of the folding variant of recombinant major allergen of birch pollen (Bet v1-FV) for perennial treatment
- to assess immunologic parameters during the course of the study in order to obtain evidence of the immunologic effects of the recombinant major allergen of birch pollen
- to assess additional immunological parameters (changes in populations of inflammatory cells and in subpopulations of immunologically active cells) during the course of the study in order to obtain additional information on the mechanism of action of the investigational product.

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Methodology

This clinical trial was performed as a randomised, double-blind, placebo-controlled phase III study with two parallel groups. The study was carried out over a period of about two and a half years reflecting two assessment birch pollen seasons and one previous baseline season. Before randomisation patients' severity of symptoms and intake of medication were scored daily in the baseline pollen season.

Symptoms and intake of antiallergic medication was documented by the patients in diaries for eight weeks during each pollen season in 2008, 2009 and 2010. Disease specific quality of life questionnaires (RQLQ) were completed at two-weekly intervals during each diary phase: the questionnaires following the peak pollen counts were analysed. Blood samples were taken at four time points for determination of allergen specific immunoglobulin (Ig) G_1, IgG_4 and immunoglobulin E (IgE). At each visit the patients were asked by the investigator for any changes in her/his state of health and any adverse events (AEs) were documented.

Analysis of the primary endpoint, the change of the area under the curve (AUC) of Symptom Medication Score (SMS) from the baseline season to the season after two years of double-blind treatment, was performed as soon as the data of all patients who finished the last visit and assessments were available for analysis. Treatments were continued unchanged until the time of unblinding at the finalisation of analysis. It was guaranteed that all patients would be offered an adequate treatment after the analysis of the study. This treatment would either consist of the recombinant preparation of birch pollen allergen for both treatment groups in case of proven efficacy in an open-label follow-up phase or an established marketed preparation for SIT in case of a negative study result. The respective treatment would in any event cover three years as recommended by the World Allergy Organisation (WAO).

Number of patients planned and analysed

Planned: 326 patients, analysed: 255 patients

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Diagnosis and main criteria for inclusion into controlled study

Patients with IgE-mediated allergic diseases including symptoms of allergic rhinoconjunctivitis, allergic bronchial asthma (Global Initiative for Asthma [GINA I and II]), triggered by birch pollen allergens.

Inclusion criteria

- Male and female outpatients, 18 - 60 years;
- Patients suffering from IgE-mediated, moderate to severe seasonal allergic rhinitis with or without controlled bronchial asthma (peak expiratory flow [PEF] and/or forced expiratory volume at one second [FEV_1] at least 80% predicted normal) attributable to birch pollen *and*
- in the course of the year: Major allergy symptoms during birch pollen season *and*
- symptoms of allergic rhinoconjunctivitis against birch pollen allergens requiring medication during the last birch pollen season *and*
- proven clinical relevance (clin. rel.) of birch pollen allergy by positive Conjunctival Provocation Test (CPT) result using natural birch pollen extract *and*
- positive Skin Prick Test reaction to natural birch pollen allergens demonstrated by birch pollen allergen wheal diameter $\geq$ 5mm (demonstrated in a valid Skin Prick Test: negative sodium chloride (NaCl) control wheal < 3mm, positive histamine (0.1%) control wheal $\geq$ 3mm) *and*
- positive Enzyme-linked Allergosorbent Test (EAST) to birch pollen ≥ 1.5 kilounits per litre of specific allergen (kU[A]/L) determined in the central laboratory.
- For female patients: Effective contraception and negative pregnancy test result. Highly effective methods of birth control were defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomised partner. No pharmacological interactions are known for hormonal contraceptives and specific immunotherapeutic preparations.

At the beginning of the treatment phase (September 2008): Patients had to demonstrated moderate to severe symptoms of allergic birch pollen disease during the baseline season.

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Test product, dose and mode of administration, batch number
Recombinant hypoallergenic folding variant of the major birch pollen allergen Bet v1-FV as sterile suspension for subcutaneous injection. *Dosage:* Strength A ([redacted]), Strength B ([redacted]). *Up-dosing phase:* Injection intervals of 7 (+7) days; maintenance treatment: injection intervals up to 4 + 2 weeks dose; during birch pollen season: 50% of the maximum individually tolerated dose.
Investigational product:
The following batch numbers were used during the study:
[redacted]

Duration of treatment
Two years

Reference therapy or comparator, dose and mode of administration, batch number
Placebo:
The following batch numbers were used during the study:
[redacted]

Duration of treatment
Two years

Criteria for evaluation
Efficacy:
Primary endpoint
- Changes of the AUC of the SMS from the baseline season to the season after two years of double-blind treatment

Secondary endpoints
- Changes of the AUC of Rhinoconjunctivitis SMS (RC-SMS) after one and two years of treatment
- Changes of rhinoconjunctivitis specific RQLQ overall scores and seven domain scores during each grass pollen season
- Changes in the specific CPT after approximately one year treatment (with the individual reactive allergen concentration) using three categories unchanged, partly improved and improved

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Criteria for evaluation (continued)

- Changes in the specific CPT after approximately one year treatment (with the individual reactive allergen concentration) using the three categories unchanged, partly improved and improved
- Change of AUC of Symptom Score and Medication Score after one and two years of treatment
- Changes of SMS after the first treatment year
- Immunologic changes in specific IgE, IgG_1, IgG_4 measured at screening visit (V) (V I/1), after uptitration (V II/10) and after birch pollen season in the first and second treatment year (V II/19 and V III/16, respectively)
- The number and percentage of patients with response defined as an at least 40% decrease of AUC of SMS from baseline to the end of each treatment year
- The absolute values as well as the change in number of well days defined as number of days with Symptom Score ≤ 4 and Medication Score = 0
- The absolute values as well as the change in number of rhinoconjunctivitis well days defined as number of days with rhinoconjunctivitis Symptom Score ≤ 3 and Medication Score = 0

The primary endpoint analyses as well as all other efficacy analyses were conducted also by the following subgroups: Gender, asthma (yes, no), duration of allergic rhinoconjunctivitis (< 10 years, ≥ 10 years), country (Germany, Poland, Sweden, and Finland), and severity of rhinoconjunctivitis symptoms (moderate, severe).

Safety:

The safety analysis was performed for the following AE categories:
All AEs, systemic reactions, serious adverse events (SAEs), AEs with at least "possible" relationship to the study medication, AEs with at least possible relationship to study medication during uptitration, AEs with at least possible relationship to study medication during maintenance phase, systemic reactions during maintenance phase, all AEs with at least possible relationship to study medication by TRYBA classification (23),

In addition clinical laboratory values (haematology with blood cell differential count, clinical chemistry and urinalysis), and vital signs were evaluated.

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Statistical methods

The primary endpoint of the study was the change of the AUC of SMS from the baseline season to the season after two years of double-blind treatment. Based on the actual pollen count in the respective year, the AUC of the daily SMS was calculated over a certain time period which was defined at the blind data review meeting (BDRM). The AUC of the daily SMS was calculated from score data collected from 21 days. The statistical null-hypothesis of no differences between the changes of AUC of SMS in both treatment groups was tested by a confirmatory two-sided Wilcoxon-Mann-Whitney U-Test with a significance level of 5%. All further statistical considerations were descriptive and had exploratory character, only.

Summary conclusions

Efficacy results

In the active treatment group, the median AUC of the SMS at baseline in 2008 was 279.5 but was reduced to 156.8 in 2010 after two years of active treatment. In the placebo treatment group, the median AUC of the SMS at baseline in 2008 was 288.0 and was reduced to 185.0 in 2010 after two years of placebo treatment. The median change of the AUC of the SMS from baseline to end of two years of treatment (2008 to 2010) was -75.3 for the active treatment group which was greater than the median change of -57.5 for the placebo treatment group. The difference between active treatment and placebo in the change to baseline of the AUC of the SMS after two years of double-blind treatment was not statistically significant (two-sided Wilcoxon-Mann-Whitney U-Test p-value = 0.1094). The Per-Protocol analyses were conducted as sensitivity analyses and confirmed the results from the Full Analysis Set (FAS) analyses. As a sensitivity analysis, 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 and was similar to the results for the primary endpoint analyses.

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Summary conclusions (continued)

A prospectively planned analysis of covariance (ANCOVA) of the AUC of SMS after two years of treatment was performed with treatment, AUC of SMS at baseline, country, gender, asthma (yes/no) and duration of allergic rhinoconjunctivitis (less than 10 years/more than 10 years) as explanatory variables. The ANCOVA results indicated a statistically significant difference in improvement mainly by, country ($p < 0.0001$) and baseline AUC of SMS in 2008 ($p < 0.0001$).However, after adjustment for these variables, the difference between active treatment and placebo in the change to baseline of the AUC of the SMS after two years of double-blind treatment was not statistically significant ($p = 0.1033$).

Post-hoc analyses were conducted using an ANCOVA model which included the variables asthma, centre (instead of country) and individual duration of allergy (not categorized) as well as the AUC of the SMS at baseline as covariates. Results from the post-hoc ANCOVA-model revealed a statistically significant treatment effect ($p = 0.0254$) in favour of active treatment with a lower AUC of the SMS in 2010 of 199.92 (LS-mean) for rBet v1-FV as compared to 233.79 for placebo.

When the same ANCOVA model was applied to the AUC of the RC-SMS in 2010, a statistically significant treatment effect in favour of rBet v1-FV was observed ($p = 0.0195$) with a mean AUC of the RC-SMS in 2010 of 179.04 for rBet v1-FV and 209.99 for placebo.

When the change to baseline of the AUC of the SMS from 2008 to 2010 was compared by severity of disease assessed either by symptoms (moderate, severe) or CPT, patients with moderate to severe symptoms who were treated with active treatment compared to placebo, showed a greater improvement in the AUC of the SMS after two years of treatment. In the post-hoc subgroup analyses among patients with an AUC of SMS◦≥ 120 at baseline, patients who were treated with active treatment compared to placebo, showed a greater improvement in the AUC of SMS after two years of treatment. An additional analysis among patients with a positive CPT < 5000 standard biological units (SBU)/mL at baseline, showed a greater improvement in the median AUC of the SMS for patients with two years of active treatment compared to patients treated with placebo.

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Summary conclusions (continued)

For all secondary endpoints (.e.g. RC-SMS, patient's response to the study medication, RQLQ) results were similar to the results observed for the overall AUC of the SMS.

Specific IgE, IgG_1 and IgG_4 levels at screening visit (V I/1), after uptitration (V II/10) and after the birch pollen season in the first and second treatment year (V II/19 and V III/16, respectively) were analysed to evaluate immunological response to treatment. The median allergen specific IgE levels showed little variation from screening visit (V I/1) to end of the study for both treatment groups. The median changes of the allergen specific IgG_4 and IgG_1 levels from baseline to last visit were greater in the active treatment group than for the placebo treatment group which confirmed the immunogenic stimulating effect of the active treatment.

Safety results

A total of 255 patients were evaluated in the Safety Set; 128 patients were treated with active treatment and 127 patients were treated with placebo. The duration of administration of study medications was similar between the treatment groups. Median duration of administration of study medication was 558 days in both, the active treatment group and the placebo treatment group. Median duration of administration of study medication after maintenance dose was reached was 488.5 days in the active treatment group and 499.0 days in the placebo treatment group. The median number of injections before the first application of the individual maintenance dose was seven in both treatment groups and the median number of maintenance dose injections in both treatment groups was 14 injections. Both treatment groups received a median of 19 injections in the first year of treatment, and received a median of eight injections in the second year. Thus, the median total amount of injected study medication in the active treatment group was [redacted] rBet v1 in the first year of treatment, and [redacted] in the second year of treatment.

The overall frequencies of AEs in the two treatment groups were similar. A total of 220 patients had at least one AE with onset during or after administration of the first study medication; this included 112 patients (87.5%) in the active treatment group and 108 patients (85.0%) in the placebo treatment group. AEs related to the system organ class (SOC) "infections and infestations" were the most frequent AEs in both treatment groups (active: 66.4%, placebo: 70.1%).

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Summary conclusions (continued)

Nasopharyngitis was the most frequently reported AE preferred term (PT) under this SOC in both groups with a frequency of 46.1% in the active treatment group and 44.9% in the placebo treatment group.

AEs related to the SOC "general disorders and administration site conditions" were more frequently reported in the active treatment group (64.1%) than in the placebo treatment group (57.5%). Under this SOC, the PTs injection site pruritus (47.7% active versus [vs.] 26.0% placebo), injection site swelling (39.8% active vs. 26.0% placebo) and injection site erythema (31.3% active vs. 22.8% placebo) were more frequently reported in the active treatment group than in the placebo treatment group. However, injection site pain was more frequently report in the placebo than in the active treatment group (19.5% active vs. 36.2% placebo).

"Respiratory, thoracic and mediastinal disorders" were more frequently reported in the active treatment group than in the placebo treatment group (41.4% of the active treatment group and 31.5% of the placebo treatment group). The PT allergic rhinitis was reported more frequently in the active treatment group (23.4%) compared to the placebo treatment group (15.7%).

Other notable differences in incidence of AEs between the two treatment groups included the more frequent occurrence of the SOC "eye disorders" in the active treatment group (23.4%) compared to the placebo treatment group (16.5%). Allergic conjunctivitis was the most frequently reported PT in this SOC and was reported by 16.4% of patients in the active treatment group and 11.0% of placebo patients. Under the SOC "skin and subcutaneous tissue disorders", the PT urticaria was reported by 9.4% of the patients in the active treatment group but only by 0.8% of the placebo treatment group.

During the study, SAEs were reported for 21 patients. For 17 patients, these SAEs were considered as treatment emergent, i.e. the SAE was reported after treatment was started. Of these, 11 patients in the active treatment group and six patients in the placebo treatment group reported SAEs (8.6% active vs. 4.7% placebo). No single SAE SOC or PT occurred in > 2% of patients in the treatment groups indicating that no specific SAE occurred with increased frequency in the treatment groups. For three patients each with one SAE in the active treatment group and one patient with three SAEs in the placebo treatment group, the SAEs were reported as at least possibly related to study medication.

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Summary conclusions (continued)

The incidences of AEs that were at least possibly related to study medication were of similar frequency for the two treatment groups. A total of 87 patients (68.0%) in the active treatment group and 77 patients (60.6%) in the placebo treatment group experienced at least one AE with at least possible relationship to study medication. The most common SOCs for AEs with at least possible relationship to study medication were "general disorders and administration site conditions" which occurred in 61.7% of the active treatment group and 55.9% of the placebo treatment group. "Respiratory, thoracic and mediastinal disorders" as potentially treatment related were more frequently reported in the active treatment group than in the placebo treatment group. Other notable differences between the two treatment groups in incidence of AEs with at least possible relationship to study medication included the PT urticaria which was reported by 7.8% of patients in the active treatment group but not in the placebo treatment group.

There were no noteworthy differences between the treatment groups in clinical chemistry, haematology and urinalysis parameter values or changes in values from baseline to last assessment on V III/16. There were also no clinically relevant changes from baseline to last assessment in systolic and diastolic blood pressure or heart and respiratory rates.

Conclusion

The result from the evaluation of efficacy suggested that patients treated with active treatment showed more improvement than patients with placebo treatment. However, the differences in improvement were not large and for the primary endpoint, change to baseline of the AUC of the SMS after two years of double-blind treatment, the difference between active treatment and placebo did not reach statistical significance.

A prospectively planned ANCOVA taking into account the covariates asthma, country, gender and duration of allergic disease (less than 10 years/more than 10 years) and the baseline values of AUC of the SMS as a covariate did not show a statistical relevance as well. On the other hand the post-hoc ANCOVA model accounting for asthma, centre and individual duration of allergy as well as the AUC of the SMS at baseline as a covariate revealed a statistically significant treatment effect. The same post-hoc ANCOVA model showed a statistically significant treatment effect when applied to RC-SMS.

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Conclusion (continued)

Additionally, the post-hoc subgroup analyses among patients with an AUC of SMS ≥ 120 at baseline or with a positive CPT < 5000SBU/mL at baseline, patients who were treated with active treatment compared to placebo, showed a greater improvement in the AUC of SMS after two years of treatment. This result indicates that in patients with moderate to severe disease the efficacy of active treatment could be shown.

In conclusion, the positive trends in the confirmatory analysis and the results from further post-hoc analyses and subgroup analysis support the efficacy of rBet v1-FV.

The evaluation of safety in this study showed moderate differences between treatment groups in incidence of AEs related to administration site conditions and allergic rhinitis: These differences were not large and have been reported in previous SIT studies.

An anaphylactic reaction was reported in two patients.

Date of the final report: 26-Feb-2013