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: 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 clinical trial for the immunological and histological evaluation of specific immunotherapy with an aluminium hydroxide-adsorbed recombinant hypoallergenic derivative of the major birch pollen allergen, rBet v 1-FV

Coordinating Investigator

[redacted]

Study centres

2 centres in Sweden [redacted]

Publication (reference)

Not applicable (n.a.)

Study period (years)		**Development phase**
AL0702rB DBP: Consent of AL0801rB patients		II
First patient in:	08-Oct-2007	
Last patient out of DBP (V III/16):	03-Jun-2010	
Last patient out of AL0801rB study:	26-Apr-2011	

Objectives

To assess 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

The AL0801rB study was planned as a study initiated by Prof. Rak at two Swedish study centres who were also participating in the AL0702rB study. Aim of the study was to evaluate immunological parameters in patients with allergy symptoms at the two centres who had been screened for the AL0702rB study but who had not met the inclusion/exclusion criteria of moderate to severe symptoms or were excluded from the AL0702rB study due to a cat allergy.

The study AL0801rB recruited patients who had been enrolled but not treated in the course of the AL0702rB trial. Study designs of AL0801rB and AL0702rB trials were similar except for the primary and secondary endpoints and that patients in the AL0702rB had moderate to severe allergy symptoms whereas patients in the AL0801rB demonstrated allergy symptoms of any severity. The study was performed as a randomised, double-blind, placebo-controlled phase II study with 2 parallel groups to evaluate safety and immunohistological changes of specific immunotherapy with an aluminium hydroxide-adsorbed recombinant hypoallergenic derivative of the major birch pollen allergen, rBet v 1-FV.

The trial was performed at two study centres which also participated in the AL0702rB study. Both the screening phase and the baseline phase covering one pollen season had been performed in the course of the AL0702rB trial. Treatment and documentation was conducted over two pollen seasons and ended at V III/16. Subjects then continued blinded medication until unblinding of the study and the decision on continuation with the open-label period or termination of the study (“bridging phase”).

Number of patients planned and analysed

20 patients were planned for the AL0801rB study of which 14 patients were enrolled and analysed. 25 patients from the AL0702rB study (15 active and 10 placebo patients) were added to the Full Analysis Set (FAS) of study AL0801rB so that a total of 39 patients were analysed in the pooled analyses of biologic specimens from nose and blood.

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Diagnosis and main criteria for inclusion

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, seasonal allergic rhinitis with or without controlled bronchial asthma (peak expiratory flow [PEF] and/or forced expiratory volume at one second [FEV1] 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 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 ≥ 5mm (demonstrated in a valid skin prick test: negative NaCl control wheal < 3mm, positive Histamine (0.1%) control wheal ≥ 3mm) *and*
- positive Enzyme-linked Allergosorbent Test (EAST) to birch pollen ≥ 1.5kU/L determined in the central laboratory.
- For female patients: Effective contraception and negative pregnancy test result.

At the beginning of the treatment phase (October 2008): Patients had to demonstrate 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 v 1-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

2 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

2 years

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Criteria for evaluation

Efficacy:

Primary endpoint

Changes in populations of inflammatory cells and subpopulations of immunologically active cells. The subpopulations which were evaluated are cells considered central in allergic inflammation. Numbers of positively stained cells: Eosinophils as stained with antibody against eosinophil peroxidase (EPO), mast cells stained with anti-tryptase, neutrophils with anti-HNL (human neutrophil lipocalin) and cluster of differentiation (CD)4+ T cells with anti CD4 antibody. All these cells were evaluated in nasal biopsies obtained before the start of treatment (outside the birch pollen season) and during immunotherapy (after one year of treatment with rBet v 1-FV) around the peak of the pollen season.

Secondary endpoint

Specific IgE, IgG_1 and IgG_4 were measured at four time points: At screening visit (V I/1), after uptitration (V II/10) and after birch pollen season in first and second treatment year (V II/19 and V III/16, respectively) as well as the absolute change from screening were analysed descriptively.

Safety

The safety analyses were performed for the following adverse event (AE) categories:

All AEs, systemic reactions, serious adverse events (SAEs), AEs with at least “possible” relationship to the study medication, and all systemic reactions as well as all AEs with at least possible relationship to study medication during the uptitration phase and during the maintenance phase, and all AEs with at least possible relationship to study medication by TRYBA classification ~~(27)~~.

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

Due to its exploratory character and the focus on immunological and histological findings, only descriptive statistics were performed in this study. Exploratory p-values (Mann-Whitney-U-Test) for the difference between the two treatment groups were calculated for each parameter/measurement and all definite time points separately. All further statistical considerations were descriptive and had exploratory character, only.

Summary conclusions

Efficacy results

The efficacy analyses aimed to obtain additional information on the mechanism of action of specific immunotherapy (SIT) with recombinant birch pollen allergen. Therefore, results are pooled from the studies AL0801rB and AL0702rB.

Nasal biopsies were performed to evaluate whether changes from before the start of treatment (outside the birch pollen season) and during immunotherapy (after one year of treatment with rBet v 1-FV) around the peak of the pollen season were detectable in the nasal mucosa produced by the body in response to allergens. The following immunological parameters were measured to document the outcome of specific immunotherapy: Numbers of positively stained cells: Eosinophils as stained with antibody against EPO, mast cells stained with anti-tryptase, neutrophils with anti-HNL, cluster of differentiation 3 (CD3)+ T cells with anti CD3 antibody, and CD4+ T cells with anti CD4 antibody.

A statistically significant reduction of CD4+ T cells in epithelium from before the start of treatment (outside the birch pollen season) to during immunotherapy (after one year of treatment with rBet v 1-FV) around the peak of the pollen season was observed in the active group compared to placebo ($p = 0.0308$). A statistically significant difference between active and placebo treatment groups was also observed for CD4+ T cells in subepithelium ($p = 0.0183$). Subepithelium and epithelium CD4+ T cells remained stable in the active treatment group but increased in the placebo treatment group.

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Summary conclusions (continued)

Efficacy results

Eosinophils stained with antibody against EPO and with the marker EG2 in epithelium showed no increase from before the start of treatment (outside the birch pollen season) to during immunotherapy (after one year of treatment with rBet v 1-FV) around the peak of the pollen season in the active treatment group but an increase in these cells was observed for the placebo treatment group. This difference was not statistically significant (EPO: $p = 0.0692$, EG2: $p = 0.0563$). Eosinophils stained with the same markers in the subepithelium showed only a slight increase in the active group but showed a marked increase in the placebo treatment group for this time period. These differences did not reach statistical significance for the EPO marker ($p = 0.0533$) and the EG2 marker ($p = 0.2869$).

Notable differences between treatment groups for mast cells stained with anti-tryptase, neutrophils with anti-HNL and CD3+ T cells with anti CD3 antibody were not observed in the nasal epithelium and subepithelium biopsies.

Nasal lavage samples were evaluated to determine if differences in the amount and content of immunological cells in the nose could have been detected. No significant differences between treatment groups were observed for changes from before the start of treatment (outside the birch pollen season) and during immunotherapy (after one year of treatment with rBet v 1-FV) around the peak of the pollen season for monocytes, lymphocytes, neutrophils, eosinophils and basophils in nasal lavage samples.

There was no statistically significant difference between treatment groups for the following cytokines: Interleukin (IL)-4, IL-5, IL-9, IL-10, IL-13, IL-17a, IL-22, interferon (IFN)-γ, and transforming growth factor (TGF)-β. However, there was a slight decrease in IL-22 in the active group which was not observed in the placebo treatment group. Changes in these directions would be expected for SIT.

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Summary conclusions (continued)

Efficacy results

Results for eosinophil cationic protein (ECP) indicated a smaller increase from before the start of treatment (outside the birch pollen season) and during immunotherapy (after one year of treatment with rBet v 1-FV) around the peak of the pollen season for the active treatment group than observed for the placebo treatment group. However, this trend to stronger increase of ECP in the placebo treatment group was not statistically significant ($p = 0.0723$). Differences between the treatment groups were also observed for human serum albumin (HSA), α2-makroglobulin and to a lesser extent for total protein. Higher HSA values were observed during the birch pollen season in the placebo treatment group than in the active treatment group but this change from before treatment to during treatment was not statistically significantly different between the groups ($p = 0.0975$). A similar but less clear trend in the same direction was observed for α2-makroglobulin ($p = 0.1124$) and total protein ($p = 0.1775$).

For the primary analyses in this exploratory study, the following laboratory parameters were measured in peripheral blood samples before treatment, after the maximum tolerated dose (MTD) was reached and during the birch pollen season of the first treatment year: IL-5, IL-6, IL-9, IL-10, IL-13, IL-17a, IL-22, IFN-γ, tumor necrosis factor (TNF)-α, and TGF-β.
No notable differences between active and placebo treatment groups in these immunologic response parameters in peripheral blood samples were observed.

Statistically significant differences in changes in the IL producing cells between treatment groups were not observed.

Specific IgE, IgG_1 and IgG_4 levels at screening visit, after uptitration and after the birch pollen season were analysed to evaluate immunological response to treatment. The median allergen specific IgE levels showed little variation from screening visit to end of the study for both treatment groups. The median changes of the allergen specific IgG_1 and IgG_4 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.

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Summary conclusions (continued)

Safety results

Out of the 39 patients for whom analysis of immunological parameters was performed, 25 patients were included in study AL0702rB. The safety data from these patients are reported in the clinical study report of study AL0702rB. The remaining 14 patients constituted the Safety Set in the present study AL0801rB. Thus, a total of 14 patients were evaluated in the Safety Set; 8 patients were treated with active treatment and six patients were treated with placebo. Median duration of administration of study medication up to V III/16 was 526.0 days in the active treatment group and 529.5 days in the placebo treatment group. Median duration of administration of study medication after maintenance dose was reached was 458.5 days in the active treatment group and 463.0 days in the placebo treatment group. Median duration of administration of study medication including the bridging phase was 799.5 days in the active treatment group and 696.0 days in the placebo treatment group The duration of administration of study medication after the maintenance dose was reached including the bridging phase was longer in the active group (739.5 days) than in the placebo treatment group (623.5 days).

The active treatment group received a median of 18 injections and the placebo received a median of 17 injections in the first year of treatment. Both treatment groups received a median of 9 injections in the second treatment year. The median number of injections before the first application of the individual maintenance dose was 7.5 in the active treatment group and 7.0 in the placebo treatment group. The median number of maintenance dose injections up to V III/16 was 11 in the active treatment group and 11.5 in the placebo treatment group. Overall, the median number of maintenance dose injections up to end of study was 16 in the active treatment group and 14.5 in the placebo treatment group.

In the first year of treatment, the median total amount of injected study medication was [redacted] in the active treatment group and [redacted] in the second year of treatment.

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Summary conclusions (continued)

Safety results

The median total amount of injected study medication in the second year of treatment including the bridging phase was [redacted] in the active treatment group. Median individual maintenance dose was [redacted].

The overall frequencies of AEs reported by patients in the two treatment groups were similar. All patients had at least one AE with onset during or after administration of the first study medication; this included the 8 patients in the active treatment group and the 6 patients 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 (8 active patients and 6 placebo patients). All patients in both treatment groups reported the AE preferred term (PT) nasopharyngitis. Patients with bronchitis (3 patients), influenza (3 patients) and viral gastroenteritis (2 patients) were only reported in the active treatment group.

AEs related to the SOC general disorders and administration site conditions were more frequently reported in the active treatment group (8 patients) than in the placebo treatment group (3 patients). Under this SOC, the PTs injection site pruritus (8 active patients and 2 placebo patients), injection site pain (5 active patients and 2 placebo patients), and injection site erythema (4 active patients and 1 placebo patient) were more frequently reported by patients in the active treatment group than in the placebo treatment group.

Respiratory, thoracic and mediastinal disorders were reported by 7 patients in the active treatment group and 4 patients in the placebo treatment group. The PT allergic rhinitis was reported more frequently by patients in the active treatment group (3 patients) compared to no patients in the placebo treatment group.

During the study, SAEs were reported for 2 patients in the active treatment group. The SAEs reported in these 2 patients were anaphylactic reaction in one patient in the second treatment year and dyspnoea and throat irritation in 1 patient during the bridging phase.

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Summary conclusions (continued)

Safety results

All patients in the active treatment group and 3 patients out of the 6 patients 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 reported by patients were general disorders and administration site conditions which occurred in all patients of the active treatment group and 3 out of 6 patients of the placebo treatment group. Administration site complications were more frequent reported by patients in the active treatment group than in the placebo treatment group. 8 active treatment patients and 2 placebo treatment patients reported injection site pruritus. Injection site pain was reported by 5 active treatment patients and 2 placebo treatment patients, and injection site erythema was reported by 4 active treatment patients and 1 placebo treatment patient.

Systemic reactions during the study which were by definition at least possibly related to study medication and were not considered as local reaction were reported more frequently in the active treatment group compared to the placebo treatment group. Seven patients in the active treatment group and 1 patient in the placebo treatment group experienced systemic reactions. Respiratory, thoracic and mediastinal disorders were the most frequently reported systemic reactions reported by patients (4 active patients vs. no placebo patient) and allergic rhinitis was the most frequent PT reported by patients (3 active patients vs. no placebo patient). Two of the systemic reactions reported by patients were reported as SAEs (anaphylactic reaction in one patient in the second treatment year and dyspnoea and throat irritation in one patient during the bridging phase).

The majority of patients had normal chemistry, haematology and urinalysis values at baseline and last visit. 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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Conclusion

This study showed a statistically significant reduction of CD4+ T cells in epithelium and subepithelium from pre-season to the birch pollen season. This was not accompanied by changes in immunological parameters from nasal lavage or peripheral blood.
For example: A decline in IL- 4, IL-5 and IFN-γ producing cells is expected due to tolerance induction in the early phase of SIT as well as during the pollen season along with a slight increase of IL-10 producing cells. Such a change was not detected in the present study. However, it has to be considered that it might be possible that the time point of evaluation after treatment in this study was too early to see the desired effects in the peripheral blood samples.

The evaluation of the safety data is in line with the safety data gained so far with specific immunotherapy with an aluminium hydroxide-adsorbed recombinant hypoallergenic derivative of the birch pollen allergen, rBet v 1-FV. No new or unexpected AEs were reported and no clinically relevant changes from baseline to last assessment were present for the other safety variables.

Date of the final report: 30-Sep-2013