Name of Sponsor: HAL Allergy BV, Leiden, The Netherlands		
Name of Finished Product: SUBLIVAC FIX Birch		
Name of Active Ingredient: allergen extract of birch pollen (*Betula verrucosa*)		

Title of Study: SUBLIVAC® Birch PROBE study

Studied period (years): 2009-2010 Date first enrolment: 13-07-2009 Date last completed: 02-03-2010	Phase of development: II

Objectives: To show, on an exploratory basis, that treatment with SUBLIVAC Birch is also effective compared to treatment with Staloral Birch by means of reduction in allergic symptoms during nasal provocation in subjects suffering from IgE mediated allergic complaints triggered by birch pollen.

Methodology: Prospective, Randomized, Open, Blinded Endpoint (PROBE), controlled, single-centre, parallel groups

Number of patients: 60-80 planned, analyzed: 74

Diagnosis and main criteria for inclusion: Seasonal rhinitis and/or rhinoconjunctivitis with or without mild asthma (FEV1 > 70%) related to birch pollen, age 18 years and older.

Test product, dose and mode of administration:
Test product: SUBLIVAC® Birch, 10,000 AUN/ml
Dose: Started with 1 drop daily of SUBLIVAC Birch and increased by 1 drop daily, until the maintenance dose of 5 drops was reached.
Mode of administration: Sublingual administration

Duration of treatment: 16-20 weeks per subject (at least 12 weeks for subjects with hazel or alder allergy)

Reference therapy, dose and mode of administration:
Reference therapy: Staloral Birch 10 I.R./ml and Staloral Birch 300 I.R./ml
Dose: Started with 1 puff of Staloral Birch 10 I.R./ml on day one, 2 puffs on day two and increase by 2 puffs until at day six 10 puffs were reached. At day seven 1 puff of Staloral Birch 300 I.R./ml was taken, at day eight 2 puffs and day nine 4 puffs. From then on 4 puffs daily were taken.

Criteria for evaluation:

Primary:	Difference in change of the titrated nasal provocation test (TNPT) between the two treatment groups
Secondary:	Immunoglobulins, other variables derived from TNPT
Safety:	Local and systemic reactions, adverse events, safety laboratory blood parameters and ECG

Statistical methods: For the primary analysis the proportion of subjects, having a beneficial result in the second TNPT, were compared between the two treatment groups. A non-inferiority approach was chosen, the non-inferiority margin was set to 30%. For investigation of a difference in treatment success the following hypotheses were tested: $H_0: \pi_{Stal} - \pi_{Subl} \geq 0.3$ vs. $H_1: \pi_{Stal} - \pi_{Subl} < 0.3$,
whereby π_{Subl} and π_{Stal} denote the proportion of change in TNPT after SUBLIVAC Birch and Staloral Birch treatment, i.e. the response rate due to a beneficial treatment effect. The one-sided 97.5% confidence interval for the difference in proportions between the two treatment groups was determined.
Analysis of the secondary efficacy parameters was performed in an explorative way using the appropriate parametric and non-parametric tests

Summary - Conclusions

Efficacy: The percentage of subjects showing a beneficial treatment effect was 45.8% vs. 35.0% in the PP population and 33.3% vs. 31.4% in the ITT population following SUBLIVAC and Staloral treatment, respectively. For all subjects for whom the first and the second TNPT were positive at the same dose, TNPT derived variables (changes in flow and in symptom score) were investigated. No differences in TNPT derived variables or symptoms were demonstrated between treatment with SUBLIVAC and Staloral. Evaluation of the immunologic response, showed that treatment with SUBLIVAC and Staloral induced a similar increase in IgG and IgG4 specific for Bet v and Bet v1 (approximately 2 times).

Safety: In total, 56 subjects reported 164 adverse events (SUBLIVAC n=88, Staloral n=76). Out of these, 145 were considered to be related to the medication; particularly 80 were associated to the use of SUBLIVAC birch. The majority of the adverse drug reactions was of mild intensity. The same pattern of AEs was observed for SUBLIVAC Birch and Staloral. No clinically relevant changes in other safety parameters, such as safety laboratory parameters, vital signs, physical examination and ECGs were observed.

Conclusion: Treatment with SUBLIVAC Birch was effective compared to treatment with Staloral Birch by means of reduction in allergic symptoms during nasal provocation in subjects suffering from IgE mediated allergic complaints triggered by birch pollen. No differences in TNPT derived variables or symptoms were demonstrated between treatment with SUBLIVAC and Staloral. Evaluation of the immunologic response, showed that treatment with SUBLIVAC and Staloral induced a similar increase in IgG and IgG4 specific for birch major allergens. Moreover, non-inferiority of SUBLIVAC was shown for both the primary parameter and secondary efficacy parameters. In addition, results on the safety analysis showed that SUBLIVAC Birch is safe and well tolerated and its safety profile does not differ from that of Staloral.