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: A randomized, double-blind, placebo-controlled study to determine safety, tolerability and the optimal effective dose of SUBLIVAC FIX Birch in patients with allergic rhinitis/rhinoconjunctivitis caused by birch pollen	
Studied period (years): 2012-2013 Date first enrolment: 02 July 2012 Date last completed: 28 March 2013	Phase of development: II
Objectives: <u>Primary Objective:</u> Determination of the optimal effective dose of SUBLIVAC FIX Birch (SB) based on reduction of upper airways reactivity assessed by Titrated Nasal Provocation Test (TNPT) after 5 months of treatment with different dosages of SB compared to placebo. <u>Co-primary Objective:</u> Difference in proportions of patients not reaching maintenance dose within 10 days due to related Adverse Events (AEs) of different dosages of SB compared to placebo.	
Methodology: <u>Randomized, double-blind, placebo-controlled, multi-centre, dose tolerability, dose-range-finding</u>	
Number of patients: Planned: 250 patients; Screened: 317 patients; Enrolled: 270 patients. <u>Analyzed: Safety population n= 269; ITT population n= 269; PP population n= 242</u>	
Diagnosis and main criteria for inclusion: birch pollen-induced allergic rhinitis/rhinoconjunctivitis with or without concomitant mild allergic asthma, age:18-60 years	
Test product, dose and mode of administration: <u>Test product:</u> SUBLIVAC FIX Birch3,333 AUN/ml; 10,000 AUN/ml; 20,000 AUN/ml; 40,000 AUN/ml Dose: Start with 1 drop daily of SUBLIVAC FIX Birch and increase by 1 drop daily, until the maintenance dose of 5 drops is reached. <u>Reference therapy:</u> SUBLIVAC Placebo Dose: Start with 1 drop daily of SUBLIVAC Placebo and increase by 1 drop daily, until the maintenance dose of 5 drops is reached. <u>Mode of administration</u>: Sublingual administration	
Duration of treatment: 5 months	
Criteria for evaluation: <u>Efficacy</u> Primary: The absolute difference in mean symptom score in the TNPT between 5 months of treatment and baseline in the different SB dose groups compared to placebo. Co-Primary: The proportions of patients not reaching maintenance dose within 10 days due to related AEs per dosage group. Secondary: Changes in serum specific immunoglobulin levels (IgE, IgG, IgG4) after 5 months of treatment with different dosages of SB compared to placebo. Changes in Peak Nasal Inspiratory Flow (PNIF) after 5 months of treatment with different dosages of SB compared to placebo. <u>Safety:</u> Safety and tolerability of different dosages of SB compared to placebo assessed by number and severity of local and systemic reactions, adverse events, safety laboratory blood parameters and ECG	
Statistical methods: The primary endpoint was the absolute difference in mean symptom score in the TNPT between 5 months of treatment and baseline was evaluated by means of analysis of covariance (ANCOVA). A two-sided p-value of less than 0.05 was considered to be statistically significant. In case the dose-response relationship was not linear, the shape of the dose response curve would be estimated using appropriate contrast tests, adjusting the p-values for multiple testing. The optimal dose we compared individual dose groups to placebo, controlling the overall type I error rate of 0.05 using a step-down procedure.	

Summary – Conclusions

Efficacy Results:

The current study was performed to evaluate the dose response and dose tolerability of SUBLIVAC FIX Birch. The primary efficacy results show a clear dose response curve: all active doses are better than placebo and the 40,000 AUN/ml dose proved to be the most effective dose. The secondary efficacy results support this conclusion: active doses result in a larger improvement in PNIF and serum IgG levels compared to placebo and the 40,000 AUN/ml dose shows the largest effect.

Safety Results:

All active doses result in more local and systemic adverse reactions compared to placebo. However, the occurring adverse reactions are mainly mild and well-controlled. Based on the co-primary endpoint these adverse reactions do not cause treatment discontinuation.

Conclusion:

Based on both the primary and secondary efficacy results, treatment with the 40,000 AUN/ml dose has the most pronounced effect on symptom scores and PNIF following TNPT, and induced the largest increase in birch- and Bet v 1-specific serum IgG/IgG4 levels. The results show that all SUBLIVAC FIX Birch doses are safe and well tolerated. The frequency and nature of the adverse reactions observed in this study are comparable to similar products.