Name of Sponsor: HAL Allergy B.V., Leiden, The Netherlands		
Name of Finished Product: SUBLIVAC FIX *Phleum pratense*		
Name of Active Ingredient: *Phleum pratense*		

Title of Study: A randomized, double-blind, placebo-controlled study to determine safety, tolerability and the optimal effective dose of SUBLIVAC FIX *Phleum pratense* in patients with allergic rhinitis/rhinoconjunctivitis caused by grass pollen

Studied period (years): 2012-2013 Date first enrolment: 11-SEP-2012 Date last completed: 15-MAY-2013	Phase of development: II

Objectives:
Primary Objective:
Determination of the optimal effective dose of SUBLIVAC FIX *Phleum pratense* based on reduction of upper airways reactivity assessed by TNPT after 5 months of treatment with different dosages of SUBLIVAC FIX *Phleum pratense* compared to placebo.
Co-primary Objective:
Difference in proportions of patients not reaching maintenance dose within 10 days due to related AEs of different dosages of SUBLIVAC FIX *Phleum pratense* compared to placebo.

Methodology:
Randomized, double-blind, placebo-controlled, multi-centre, multi-country (Germany and Poland), 5-arm, staggered start.

Number of patients:
Planned: 250 patients; Screened: 316 patients; Enrolled: 266 patients.

Diagnosis and main criteria for inclusion: Allergic rhinitis/rhinoconjunctivitis related to grass pollen with or without concomitant mild to moderate persistent asthma, age:18-60 years

Test product: SUBLIVAC FIX *Phleum pratense* 3,333 AUN/ml; 10,000 AUN/ml; 20,000 AUN/ml; 40,000 AUN/ml
Reference therapy: SUBLIVAC Placebo
Dose: Start with 1 drop daily and increase by 1 drop daily, until the maintenance dose of 5 drops is reached.

Duration of treatment: 5 months

Criteria for evaluation:

Primary:	The absolute difference in mean symptom score in the TNPT between 5 months of treatment and baseline in the different SUBLIVAC FIX *Phleum pratense* 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 SUBLIVAC FIX *Phleum pratense* compared to placebo. Changes in PNIF after 5 months of treatment with different dosages of SUBLIVAC FIX *Phleum* pratense compared to placebo.
Safety:	Safety and tolerability of different dosages of SUBLIVAC FIX *Phleum pratense* 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 by means of analysis of covariance (ANCOVA) with the baseline total symptom score used as a covariate.

Results and conclusions:
No statistically different changes in mean TNPT nor PNIF scores could be demonstrated between the different SUBLIVAC FIX *Phleum pratense* dose groups and placebo compared to placebo after 5 months of treatment. However, post-hoc analyses indicated a significant decrease in symptom scores combined with an improvement in PNIF following TNPT in the 10,000, 20,000 and 40,000 AUN/ml SUBLIVAC FIX Phleum pratense groups compared to placebo for the subgroup of patients randomized in Germany, while no differences were observed in the Polsish population.Furthermore, a significant increase in *Phleum*, Phl p 1 and Phl p 5b specific immunoglobulin levels was observed. All active doses resulted in more local and systemic adverse reactions compared to placebo. The adverse reactions were mainly mild and well-controlled and did not lead to treatment discontinuation (co-primary endpoint).