Name of Sponsor: HAL Allergy BV, Leiden, The Netherlands	
Name of Finished Product: PURETHAL Grasses	
Name of Active Ingredient: Suspension of glutaraldehyde-modified extract from 10 grass pollen (Agrostis stolonifera, Anthoxanthum odoratum, Dactylis glomerata, Lolium perenne, Arrhenatherum elatius, Festuca rubra, Poa pratensis, Holcus lanatus, Phleum pratense, Secale cereale)	
Title of Study: A prospective, randomized, open, multi-centre study to assess safety of PURETHAL Grasses given with a rush induction schedule to patients with allergic rhinoconjunctivitis (PURETHAL Grasses Rush study)	
Studied period (years): 2010 Date first enrolment: 17-02-2010 Date last completed: 26-08-2010	Phase of development: IV
Objective: The aim of the study is to show that a rush-in initial phase of three injections given in two weeks with PURETHAL Grasses is as safe as a conventional initial phase with six injections in five weeks	
Methodology: Open, randomized, parallel group, multi-centre	
Number of patients: 100-150 subjects planned analyzed: Safety population n=146; ITT population n=144, PP population n=97	
Diagnosis and main criteria for inclusion: Subjects with rhinitis or rhinoconjunctivitis due to grass pollen, who are selected to be treated with SCIT; age ≥ 18 years	
Test product, dose and mode of administration: Test product: PURETHAL Gräser, 20,000 AUM/ml Dose: Conventional: Initial treatment: 6 incremental weekly doses of 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5 ml (week 1, 2, 3, 4, 5, 6). Maintenance treatment: 0.5 ml in intervals according to registered scheme (week 8, 10, 12, 16). Rush: Initial treatment: 3 incremental weekly doses of 0.1, 0.3, and 0.5 ml (week 1, 2, 3). Maintenance treatment: 3 monthly doses of 0.5 ml (week 7, 11, 15). Mode of administration: Subcutaneous injection	
Duration of treatment: Conventional: 16 weeks per patient; Rush: 15 weeks per patient	
Criteria for evaluation: Primary: Proportion of patients, who successfully (without systemic reactions > grade I or too many additional injections) reached the maintenance dose Secondary: Early and late local reactions, systemic reactions within 24 hours, other AEs, serum specific Immunoglobulins Safety: Vital signs (blood pressure, pulse rate), physical examination	
Statistical methods: A noninferiority approach was chosen to compare the success rates between both treatment groups, the non-inferiority margin was set to 15%. For investigation of a difference in treatment success the following hypotheses were tested: H_0: $\pi_{rush} - \pi_{conventional} - 0.15$ vs. H1: $\pi_{rush} - \pi_{conventional} > - 0.15$, whereby π_{rush} and $\pi_{conventional}$ denote the proportion of patients who successfully reached the maintenance dose in the rush treatment group and in the conventional treatment group, respectively. The one-sided 97.5% confidence interval for the difference in proportions between the two treatment groups was determined. H_0 was rejected if the confidence interval lies above -0.15. In this case non-inferiority of the rush treatment in comparison to the conventional treatment could be concluded. Secondary parameters were tested with appropriate non-parametric tests to determine statistical differences. A difference with a p-level of less than 5% two-sided would be regarded as significant.	

Summary – Conclusions

Results: The proportion of subjects who successfully reached the maintenance dose was 92% vs. 92.75% (Difference: 0.75%, Confidence Interval: -7.91%,100.00%) in the ITT population for the conventional vs. the rush treatment regimen, respectively. Therefore, non-inferiority of the rush compared to the conventional regimen was demonstrated. In addition, no significant differences in secondary endpoints, such as early and late local reactions, grade of systemic reactions within 24 hours and other adverse events recorded during the study were observed. Evaluation of the immunologic response, showed that the rush treatment regimen induced statistically significant increases in grass-pollen allergen-specific immunoglobulin (IgG, IgG4, IgE) levels similar to the conventional regimen after 4 months of treatment.

Safety Results: In total, 78 subjects (conventional n=40, rush n=38) reported 237 treatment-emergent adverse events. Out of these AEs, 164 were considered to be related to the study medication, particularly 86 were associated with the rush regimen. The pattern and intensity of the AEs were similar for the rush and conventional treatment. No statistically significant differences in vital signs (blood pressure and pulse rate) between the treatment groups at baseline were observed.

Conclusion: Non-inferiority of the proportion of patients reaching the maintenance dose of 0.5 ml PURETHAL Grasses following a rush initial phase compared to a conventional initial phase was shown. Results on the safety analysis of the rush regimen are similar to the results of the conventional regimen. Treatment with PURETHAL Grasses according to a rush regimen is as safe and well tolerated as the conventional regimen.