Name of Sponsor: HAL Allergy BV, Leiden, The Netherlands		
Name of Finished Product: PURETHAL Mites		
Name of Active Ingredient: A mixture of 50% *Dermatophagoides pteronyssinus* adsorbed modified extract and 50% *Dermatophagoides farinae* adsorbed modified extract.		

Title of Study: PURETHAL® Mites Dose Range Finding Study

Studied period (years): 2011-2013 Date first enrolment: 06-10-2011 Date last completed: 15-05-2013	Phase of development: II

Objectives: The objective of the present study is to characterize the dose-response relationship of PURETHAL® Mites (PM) with a nasal provocation test in order to identify the optimal dose in terms of highest clinical efficacy and safety.

Methodology: double-blind, parallel treatment groups, multicenter phase II tolerability

Number of patients: 420 screened, 290 enrolled, 236 completed

Diagnosis and main criteria for inclusion: Persistent rhinitis or rhinoconjunctivitis, with or without concomitant asthma, related to house dust mites, age ≥ 18 years and ≤ 60 years.

Test product, dose and mode of administration:
Test product: PURETHAL® Mites, 6,667 AUeq/mL, 20,000 AUeq/mL, 50,000 AUeq/mL, 100,000 AUeq/mL
Dose: Weekly up-dosing of 0.05 mL, 0.1 mL, 0.2 mL, 0.3 mL, 0.4 mL, 0.5 mL. Followed by monthly maintenance dose of 0.5 mL.
Mode of administration: Subcutaneous injections

Duration of treatment: Approximately 1 year

Criteria for evaluation:
Primary:
The primary endpoint was the absolute difference in mean symptom score in the TNPT between one year of treatment and baseline, among the different PM dose groups *versus* placebo.

Secondary:

- Absolute difference in mean symptom score in the TNPT between 22-30 weeks of treatment and baseline, among the different PM dose groups *versus* placebo.
- Peak Nasal Inspiratory Flow (PNIF) measurements during the entire study period, among the different PM dose groups *versus* placebo
- Serum immunoglobulin levels measured at baseline, between 22 and 30 weeks and after approximately 1 year of treatment, among the different PM dose groups *versus* placebo
- Average Adjusted Symptom Score (AAdSS) measured during the last 8 weeks of treatment, among the different PM dose groups *versus* placebo *(EMA Guideline, 2008; Grouin, 2011)*

Safety evaluation: Safety and tolerability among different PM dose groups *versus* placebo were assessed during the entire study period by determination of PM related AEs and by local and systemic reactions (reporting according to the Medical Dictionary for Regulatory Affairs (MedDRA) *(Cox, 2010)*
Statistical methods:
All measured variables as well as the (derived) safety and efficacy parameters were listed individually and, if appropriate, tabulated by descriptive statistics. For continuous variables descriptive statistics were provided including number of observations, mean, standard deviation, median, minimum, maximum and number of missing data. For categorical data frequency counts were presented.

Primary endpoint

The primary endpoint was the change from baseline in mean symptom score in the TNPT after one year of treatment. This change from baseline was defined as follows:

Mean Lebel score at end-of-study visit MINUS Mean Lebel score* at screening*

The primary endpoint was the change from baseline of the mean symptom score in the TNPT after one year of treatment. The primary treatment comparisons were active treatment versus placebo. The analysis of the change from baseline was carried out using an analysis of covariance (ANCOVA) approach, including the treatment (dose groups) as a factor and baseline TNPT score as a covariate in the model. Testing the treatment differences in the mean symptom score for the 4 active doses versus placebo was performed using a step-down procedure

starting with the highest dose. The presence of a linear dose-response relationship was tested using the corresponding contrast.

Secondary endpoints

The statistical analysis of the secondary efficacy endpoints was carried out descriptive and/or ANCOVA. Estimates of Treatment differences along with standard errors were provided for each active dose versus placebo.

Summary – Conclusions

Efficacy Results:

The primary endpoint was met, i.e. the results of the primary parameter demonstrate significant improvement after one year of treatment with a dose of 20,000 AUeq/mL and higher. Specific immunoglobulin levels IgG and IgG4 were increased in all dose groups, supporting the immunogenic effect of PM treatment. In the secondary parameters: TNPT after 6 months of treatment, PNIF, and AAdSS no significant differences were observed. In post-hoc analyses of subgroups with increased symptom scores at baseline a treatment effect could be observed in the dose groups of 20,000 AUeq/mL and higher.

Safety Results:

During the study 2501 AEs were reported by 261 patients (90%). The majority was assessed as related and being of mild intensity. The most common reported event was injection site swelling, which occurred in 37.9% of patients. The frequency of all injection site related events appeared dose dependent.

Early systemic reactions were reported in 2.1% of patients and 21.4% reported a late systemic reaction after injection. Most systemic reactions were Grade I, only one Grade III early reaction and four Grade II late reactions occurred; one occurred in the 6,667 AUeq/mL dose group and three in the 100,000 AUeq/mL dose group. Early local reactions were reported 1592 times by 190 patients (65.5%). Of these reactions, 84.6% were swellings between 0-5 cm. Late local reactions were reported in 2721 injections (63.1% of injections, in 222 patients). Swellings of more than 5 cm were more frequently reported in the higher dose groups. In the 100,000 AUeq/mL dose group, 17 swellings > 12 cm were reported by 11 patients.

During the study 18 SAEs were reported in 11 patients, 11 were assessed as not related. The causality of 7 SAEs was assessed as related to the study medication. Next to these, 5 special situations of which 4 pregnancies and one drug administration error were reported as SAE during the study. Laboratory values, urinalysis, vital signs, and ECG measurements over time did not show any signs of safety concern with regard to the treatment with different dosages of PURETHAL Mites.

Conclusion:

Efficacy was demonstrated after one year of treatment with a dose of 20,000 AUeq/mL and higher. Specific immunoglobulin levels IgG and IgG4 were increased in all dose groups, supporting the immunogenic effect of PM treatment. Reviewing the safety data, it is concluded that doses up to 50,000 AUeq/mL of PURETHAL Mites are well tolerated and safe. The dose of 100,000 AUeq/mL, on the other hand, did induce more local and systemic reactions after injection and more TEAEs occurred in the 100,000 AUeq/mL dose group. Since a dose of 100,000 AUeq/mL was less tolerated, we conclude that the risk-benefit ratio favours the use of 20,000 AUeq/mL and 50,000 AUeq/mL.