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 Tolerability Study	
Studied period (years): 2009-2010 Date first enrolment: 14-09-2009 Date last completed: 24-08-2010	Phase of development: II

Objectives:
To establish the maximum tolerated dose of PURETHAL Mites that is achieved by 90% of the patients with less than 20% of the injections giving rise to a swelling of > 5 cm and to determine the optimal regimen to reach this maximum dose.

Methodology:
Open label, parallel treatment groups, multicenter phase II tolerability

Number of patients: 48

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

Test product, dose and mode of administration:
Test product: PURETHAL® Mites, 20,000 AUeq/ml
Group 1: slow regimen (12+2 injections)
Initial treatment: incremental weekly dose of 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.8, 1.0, 1.2*, 1.6* and 2.0* ml
Additional maintenance: 2 two-weekly injections 2.0* ml
Group 2: intermediate regimen (9+2 injections)
Initial treatment: incremental weekly dose of 0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2*, 1.6* and 2.0* ml.
Additional maintenance: 2 two-weekly injections 2.0* ml
Group 3: fast initial treatment (6+2 injections)
Initial treatment: incremental weekly dose of 0.2, 0.4, 0.8, 1.2*, 1.6* and 2.0*ml.
Additional maintenance: 2 two-weekly injections 2.0* ml

*Injection volumes larger than 1 ml were given as 2 separate injections of equal volume within an area of 1 cm.
Mode of administration: Subcutaneous injection

Duration of treatment:
11-17 weeks per subject depending on the group

Criteria for evaluation:
Primary:
The maximum tolerated dose was defined as the highest dose that 90% of the patients can reach as maintenance dose. Within these patients less than 20% of the injections should give rise to an early local reaction (ELR) defined as a swelling with a diameter of more than 5 cm occurring 15 minutes after the injection.
Secondary:
Early local reactions (ELR) within 15 minutes after injection, late local reactions (LLR) within 24 hours after injection, early systemic reactions (ESR) within 30 minutes after injection, late systemic reactions (LSR) within 24 hours after injection, Clinical Index Score (CIS), titrated conjunctival provocation tests (CPT) one week after reaching 10,000 AUeq, 20,000 AUeq, or 40,000 AUeq for the respective groups compared to baseline and 2 weeks after the patients had received two maintenance dosages for all groups compared to baseline score, serum concentrations of specific immunoglobulins.
Safety:
Adverse events, vital signs (blood pressure), physical examination, ECG, general safety laboratory parameters from blood

Summary – Conclusion

Results:

Efficacy:

The maximum tolerated dose was calculated to be 1.2 ml. In the PP population, no early local reactions of > 5 cm and less than 20% (namely 12% overall) of the injections gave rise to a late local reaction of > 5 cm within 24 hours after an injection. In addition, only Grade I systemic reactions (7% overall) were observed and no systemic reactions with Grade II or higher. Therefore, considering the mild safety profile at the calculated maximum tolerated dose of 1.2. mL PURETHAL Mites for this study, it cannot be excluded that the true maximum tolerated dose is higher. In 59% (n=23) of the subjects from the PP population late local reactions with swellings > 5 cm were observed. In the PP population 2 subjects had an early systemic reaction and 14 subjects had late systemic reactions. The systemic reactions were all Grade I. Following treatment, CIS improved in all dosing regimens. After 6 injections, 30 of the 39 patients in the PP population were less sensitive to the CPT. At the end of the study, an improvement in the CPT was observed in 32 patients. Evaluation of the immunologic response, showed that all PURETHAL Mites treatment regimens induced statistically significant increases in house dust mite allergen-specific immunoglobulin (IgG, IgG_4, IgE) serum levels.

Safety:

In total, 293 treatment-emergent adverse event episodes were reported by 48 patients. Out of these AEs, 211 were considered to be related to the study medication (slow regimen n=29, intermediate regimen n=96, fast regimen n=86). The pattern and intensity of the AEs were similar for the 3 dosing regimens. No statistical significant differences in vital signs (blood pressure and pulse rate) between the treatment groups at baseline were observed. No relevant safety aspects appeared regarding physical examination, ECG, and general safety laboratory parameters from blood.

Conclusion:

PURETHAL Mites doses up to 40,000 AUeq as being used in the 3 dose regimens is well tolerated and safe.