135 Safety and Tolerability of Escalating Doses of House Dust Mite- Peptide Antigen Desensitization (HDM-PAD)

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RATIONALE: House Dust Mite (HDM) accounts for 20-25% of the allergic rhinoconjunctivitis disease burden worldwide. This study used peptide antigen desensitization (PAD) consisting of T-cell epitopes from major HDM-allergens and evaluated its safety and efficacy.

METHODS: T-cell epitopes were identified by algorithm, manufactured, and screened in ex vivo blood samples from HDM-allergic subjects. A second group of HDM-allergic subjects attended Baseline Challenge where Early and Late Phase Skin Responses (EPSR) (LPSR), and Conjunctival Provocation Test (CPT) response were measured. Subjects were randomised to 5 cohorts comprising 8 subjects receiving HDM-PAD (also known as ToleroMune® HDM) and 2 subjects receiving placebo. Successive cohorts received 4 administrations 4-weeks apart of 0.03, 0.3, 1.0, 3.0 and 12nmol, respectively. EPSR, LPSR and CPT were re-measured 18-22 weeks after first administration.

RESULTS: HDM-PAD was safe and well tolerated. There were no Serious Adverse Events. The most commonly reported TEAEs were nasopharyngitis, influenza, gastroenteritis and nausea. HDM-PAD did not induce changes in mean FEV1 post-dose. Four HDM-PAD treatment arms resulted in CPT score changes between -16.7% to -41.4% (placebo no change). Median % change in CPT score of -36.7% ($p=0.0257$ vs. placebo) and the largest change in EPSR (median % change -39.19%) and LPSR (median % change -51.19%) was observed after 3nmol HDM-PAD.

CONCLUSIONS: HDM-PAD is safe and well tolerated when given as four intradermal injections 4-weeks apart. Reductions in the EPSR, LPSR and CPT indicate that the identified T-cell epitopes have biological activity and merit further evaluation for treatment of HDM allergy.

136 Non-Detectable IgE Binding of an Amb a 1 Derived, Contiguous Overlapping Peptide Based, SIT Product Candidate Against Ragweed Allergy

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RATIONALE: A novel approach to SIT based on Contiguous Overlapping Peptides (COPs) derived from the major birch pollen allergen Bet v 1 (AllerT™, Anergis SA, Switzerland) , has been tested successfully in a phase I/IIa clinical trial. The same technology has been applied to ragweed allergy.

METHODS: Long synthetic peptides were devised based on the 3D structure and IgE epitopes of the Amb a 1. Competition ELISA, RBL and Basotests^{R} degranulation tests were used to test IgE binding capacity of the COPs. Immunogenicity of the COPs was tested in naive mice, allergy signs and body temperature were scored in mice sensitized to Amb a 1.

RESULTS: A mix of seven COPs, AllerR, showed no detectable IgE binding in competition ELISA tests from over 20 donors. AllerR does not induce degranulation of human basophils or "humanized" RBL basophils (RBL-703/21, Vogel et al.). Mice sensitized to Amb a 1 showed no reactivity to AllerR, no anaphylactic symptoms or body temperature change. Finally the immunogenicity of AllerR was tested in mice with addition of either Freund or Aluminum hydroxide adjuvants. Each peptide composing AllerR elicited an IgG response in naïve mice which recognized natural Amb a 1. The same result was essentially obtained using Aluminum hydroxide with more variable IgG levels.

CONCLUSIONS: Low IgE binding and tests in mice indicate the hypoallergenicity of AllerR, while immunizations showed recognition of natural Amb a 1. AllerR represents thus a good candidate for ultra-fast and safe SIT to be tested in a phase I/IIa study in human.

137 Efficacy of House Dust Mite Sublingual Immunotherapy in Adults with Allergic Rhinitis: Results of an Environmental Exposure Chamber Study

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RATIONALE: Efficacy of house dust mite (HDM) sublingual immunotherapy (SLIT) tablets was evaluated in an environmental exposure chamber (EEC) study. Here we report the results of the 6 month allergen challenge over the 2-4h period. This interval mimics real life exposure and provides an assessment of the sustained effect of treatment.

METHODS: In this double-blind study, adults (18–55 years) were randomized to receive placebo or SLIT tablets at a daily dose of 500IR, 300IR or 100IR. Rhinitis symptom severity was recorded every 15-30 minutes during a 4-hour exposure to HDM allergens. The change from baseline after 6 months of treatment in the area under the curve (ChBL_AUC) of the rhinitis total symptom scores over the full 4 hours (ChBL_AUC_0-4h) and the last 2 hours (ChBL_AUC_2-4h), served as primary and secondary endpoints, respectively. Differences between placebo and active groups were analyzed by ANCOVA.

RESULTS: 355 patients were randomized: 500IR (n=93), 300IR (n=86), 100IR (n=89) and placebo (n=87). The least square mean values of ChBL_AUC_2-4h for these groups were −424.77, −421.39, −390.34, and −299.16, respectively. This represented a statistically significant difference versus placebo for the 500IR and 300IR groups (42% and 41%, $p<0.05$), but not for the 100IR group (31%, $p=0.11$). The dose response was consistent with that observed over the full 4 hours of exposure.

CONCLUSIONS: The efficacy of HDM SLIT tablets observed in natural field studies was confirmed in an environmental exposure chamber. Results over the 2 final hours of exposure demonstrate the robustness of the effect over time.

138 Onset of Action of Sublingual Tablets of House Dust Mite Allergen Extracts in Adults

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RATIONALE: The efficacy and safety of house dust mite (HDM) sublingual immunotherapy tablets have been demonstrated. Here, we determined the time to onset of the treatment effect.

METHODS: In a double-blind study, adults with HDM-induced allergic rhinitis were randomized to receive a daily dose of either 500IR or 300IR of sublingual tablets of HDM (*Dermatophagoides pteronyssinus* and *D. farinae*) allergen extracts or placebo for one year, and were followed-up during the subsequent treatment-free year. Patients scored their rhinitis symptoms and use of symptomatic medications. The primary efficacy variable was the average adjusted symptom score (AASS), which adjusts symptom scores for rescue medication use. To determine the onset of action, the AASS was calculated over 2 weeks every 2 months during the treatment period, and analyzed by repeated measures ANCOVA mixed model.

RESULTS: A total of 509 patients were randomized: 500IR (n=169), 300IR (n=170) or placebo (n=170). The difference versus placebo in the least-square means AASS was statistically significant starting from month 4 of the treatment period, for both the 500IR and 300IR groups ($p < 0.05$). This represented an improvement relative to placebo for the 500IR group of 18% (−0.80) at month 4 and of 19% (−0.77) at month 12, and for the 300IR group of 22% (−0.99) at month 4 and of 17% (−0.67) at month 12.

CONCLUSIONS: Efficacy of 500IR and 300IR sublingual tablets of HDM allergen extracts was demonstrated beginning four months after treatment initiation.