# Synopsis – Trial MT-01

**Title of Trial**

A randomised, multiple dose, dose-escalation, double-blind, placebo-controlled Phase I Trial investigating the safety of ALK HDM tablet in adult subjects with house dust mite induced asthma (with/without rhinoconjunctivitis)

**Investigator**

[redacted] MD, PhD

**Trial Centre**

[redacted], Copenhagen, Denmark

**Publication(s)**

None

**Trial Period**

*First subject first visit* – 10 August 2005

*Last subject last visit* – 07 November 2005

**Objectives**

To identify a dose range of ALK House Dust Mite (HDM) tablet that has a safety profile that will allow once-daily intake (as self-medication) by the subject.

**Methodology**

This was a randomised, multiple dose, dose-escalation, double-blind, placebo-controlled, single-centre trial. Six treatment groups commenced treatment in a staggered manner, at intervals of 7 days. This was to allow review by the safety committee of initial safety data in each group before administration of a higher dose to the next dosage group. Each of the 6 treatment groups was planned to consist of 12 subjects randomised to either active treatment or placebo (3:1). The doses were 1 DU*, 2 DU, 4 DU, 8 DU, 16 DU and 32 DU given once daily as tablets with matching placebo to maintain the blind. Subjects received treatment for 28 days and attended a follow-up visit 1-2 weeks after the last day of treatment (i.e. on days 35-42).

*DU = Development Unit. 1 DU equals 0.5 µg major allergen Der p 2 + 0.5 µg major allergen Der f 2

**Number of Subjects Planned and Analysed**

It was planned to enrol a total of 72 subjects and 138 subjects were screened. 71 subjects were enrolled in the trial as one subject did not attend the first visit. 58 subjects completed the trial. Subject disposition for the treatment phase are shown below:

| Treatment Dose (DU) | 1 DU (N=9) | 2 DU (N=9) | 4 DU (N=9) | 8 DU (N=9) | 16 DU (N=9) | 32 DU (N=9) | Active All (N=54) | Placebo All (N=17) |
|---|---|---|---|---|---|---|---|---|
| Full Analysis Set (FAS)* | 9 (100%) | 9 (100%) | 9 (100%) | 9 (100%) | 9 (100%) | 9 (100%) | 54 (100%) | 17 (100%) |
| Subjects completed | 9 (100%) | 9 (100%) | 9 (100%) | 9 (100%) | 8 (89%) | 0 (0%) | 44 (81%) | 14 (82%) |

*All subjects randomised are included in the Full Analysis Set

N=number of subjects

Active= ALK HDM tablet

1 withdrawn – due to oedema mouth (2 adverse events (AEs)) and throat tightness (1 AE) (16 DU group)

Treatment of all subjects (9 active, 3 placebo) in the 32 DU group was discontinued after 2 days of dosing as 1 subject suffered from a severe allergic reaction (vomiting immediately after intake of the tablet).

**Diagnosis and Main Inclusion Criteria**

Male and female subjects 18-65 years of age with a clinical history of house dust mite induced mild to moderate asthma (with or without concurrent rhinoconjunctivitis) of at least one year prior to trial entry and with use of appropriate medication (in accordance with the GINA Guidelines)(1) for the control of the mild to moderate asthma symptoms during the past 3 months. A positive skin prick test (wheal diameter ≥ 3 mm) and positive specific IgE against *Der p* or *Der f* (≥IgE Class 3), no clinical history of severe asthma within the last two years, and forced expiratory volume in 1 second ($FEV_1 \geq 70\%$) of predicted value with appropriate medication were required. Finally, no clinical history of perennial allergic asthma and/or rhinitis caused by an allergen to which the subject is regularly exposed, and sensitised (except house dust mites), no current severe atopic dermatitis and no previous treatment by immunotherapy with house dust mite allergen or within the previous 5 years with any other allergen.

**Investigational Medicinal Product, Dose and Mode of Administration, Batch Number**

ALK HDM tablet 1 DU (0.5 µg Der p 2 and 0.5 µg Der f 2 major allergen extract); batch No. 261863

ALK HDM tablet 4 DU (2.0 µg Der p 2 and 2.0 µg Der f 2 major allergen extract); batch No. 261864

ALK HDM tablet 16 DU (8.0 µg Der p 2 and 8.0 µg Der f 2 major allergen extract); batch No. 261865

*Doses:*

Group 1: ALK HDM tablet 1 DU (1 x 1 DU)

Group 2: ALK HDM tablets 2 DU (2 x 1 DU)

Group 3: ALK HDM tablet 4 DU (1 x 4 DU)

Group 4: ALK HDM tablets 8 DU (2 x 4 DU)

Group 5: ALK HDM tablet 16 DU (1 x 16 DU)

Group 6: ALK HDM tablets 32 DU (2 x 16 DU)

*Mode of administration:*

Once daily, sublingually. The tablet was placed under the tongue and kept there for one minute before swallowing.

**Reference Therapy, Dose and Mode of Administration, Batch Number**

ALK HDM tablet (Placebo): batch No. 141332

*Doses:*

Group 1+3+5: 1 Placebo tablet

Group 2+4+6: 2 Placebo tablets

*Mode of administration:*

Once daily, sublingually. The tablet was placed under the tongue and kept there for one minute before swallowing.

**Duration of Treatment**

The duration of treatment was 28 days for all groups except the 32 DU group. The groups commenced treatment in a staggered manner, at intervals of 7 days.

**Criteria for Evaluation – Immunology**

The immunological parameters specific IgE antibodies and the inhibitory components to IgE-allergen binding (IgX) were evaluated for the two species *Der p* and *Der f*.

**Criteria for Evaluation – Safety**

Adverse events (AEs), safety laboratory tests (haematology, urinalysis and biochemistry), vital signs, 12-lead electrocardiograms (ECG), physical examination, oral examination, spirometry to measure $FEV_1$, daily peak flow measurements

**Statistical Methods**

The sample size for this Phase I trial followed empirical considerations. No formal sample size estimation was performed. Only one analysis set, the full-analysis set (FAS), was considered for the trial. The FAS consisted of all randomised subjects. All randomised subjects received trial medication. No formal statistical comparison of treatment groups at baseline was performed. For numeric data the following summary statistics were used:

N = number of observations (subjects)
Mean = mean (average) of the observations
SD = standard deviation
Median = median (50 percentile)
P25% = lower 25 percentile
P75% = upper 75 percentile
Min = lowest value
Max = highest value

All assessments were summarised by dose level, pooled placebo and pooled active. For categorical data frequencies and percentages were used in the presentation of data. AEs were summarised by treatment according to MedDRA System Organ Class and Preferred term. Changes in abnormal laboratory data were tabulated in frequency tables. Immunological data (IgE and IgX) were subject to a post-hoc exploratory statistical analysis. Differences between treatment groups in changes from baseline to follow-up visit were tested.

**Demography of Trial Population**

| **Treatment Dose (DU) N** | **1 DU (N=9 )** | **2 DU (N=9)** | **4 DU (N=9)** | **8 DU (N=9)** | **16 DU (N=9)** | **32 DU (N=9)** | **Active All (N=54** | **Placebo (N=17)** |
|---|---|---|---|---|---|---|---|---|
| **Age (years)** | | | | | | | | |
| Mean (SD) | 30.7 (10.4) | 32.4 (14.1) | 25.9 (5.3) | 30.0 (11.2) | 27.9 (6.0) | 25.2 (7.6) | 28.7 (9.5) | 29.0 (9.7) |
| Median | 29 | 26.0 | 25.0 | 27.0 | 27.0 | 22.0 | 26.0 | 25.0 |
| Min-Max | 18-51 | 19-63 | 18-32 | 21-50 | 22-39 | 18-42 | 18-63 | 21-55 |
| **Height (cm)** | | | | | | | | |
| Mean (SD) | 172 (9.2) | 171 (11.1) | 172 (7.2) | 177 (8.0) | 175 (6.3) | 172 (8.2) | 173 (8.3) | 176 (10 1) |
| Median | 169 | 169 | 172 | 180 | 175 | 170 | 174 | 179 |
| Min-Max | 161-186 | 158-190 | 160-185 | 163-188 | 165-184 | 162-189 | 158-190 | 156-191 |
| **Weight (kg)** | | | | | | | | |
| Mean (SD) | 83.3 (19.5) | 72.2 (18.4) | 70.1 (7.4) | 77.7 (12.0) | 79.7 (19.3) | 71.9 (13.8) | 75.8 (15.7) | 75.9 (14.2) |
| Median | 83.7 | 66.6 | 69.2 | 73.0 | 82.0 | 67.9 | 73.5 | 74.0 |
| Min-Max | 57-115 | 48-97 | 60-82 | 62-97 | 53-108 | 53-92 | 48-115 | 54-114 |
| **Years with allergy** | | | | | | | | |
| Mean (SD) | 16.3 (13.4) | 8.3 (3.9) | 12.4 (4.5) | 14.8 (7.4) | 15.6 (6.5) | 17.1 (8.5) | 14.3 (7.9) | 14.9 (6.6) |
| Median | 14.5 | 10.0 | 11.0 | 13.0 | 15.0 | 17.0 | 13.0 | 15.0 |
| Min-Max | 3-41 | 2-12 | 7-21 | 9-27 | 4-25 | 5-31 | 2-41 | 0-26 |
| **Years with asthma** | | | | | | | | |
| Mean (SD) | 13.8 (9.4) | 14.8 (11.4) | 13.0 (6.9) | 17.1 (6.4) | 16.1 (6.6) | 15.8 (8.9) | 15.1 (8.2) | 14.2 (6.0) |
| Median | 13.0 | 12.0 | 13.0 | 19.0 | 15.0 | 17.0 | 14.0 | 15.0 |
| Min-Max | 3-33 | 2-39 | 2-25 | 9-27 | 4-25 | 5-31 | 2-39 | 1-22 |
| Female (%) | 6 (67%) | 7 (78%) | 6 (67%) | 3 (33%) | 5 (56%) | 7 (78%) | 34 (63%) | 9 (53%) |
| Male (%) | 3 (33%) | 2 (22%) | 3 (33%) | 6 (67%) | 4 (44%) | 2 (22%) | 20 (37%) | 8 (47%) |

**Immunological Results**

Treatment with ALK HDM Tablet for 28 days induced statistically significant increases from pre-treatment to post-treatment in allergen specific IgE levels in all active treatment groups compared to placebo.

The induction of changes from pre-treatment to post-treatment in blocking antibody activity (IgX) remained non statistical significant until the intermediate doses. Then some of the IgX changes became significant, but not in a consistent pattern.

**Safety Results**

- No serious AEs were reported. One subject from group 16 DU was withdrawn from the trial due to 3 AEs (2 oedema mouth and 1 throat tightness). Treatment of the subjects in the 32 DU group was discontinued after 2 days of dosing as 1 subject suffered from a severe allergic reaction (vomiting immediately after intake of the tablet).
- 1267 mild, 103 moderate and 6 severe (5 treatment related) treatment emergent AEs were reported by the 53 actively treated subjects compared to 42 mild and 7 moderate AEs reported by 13 placebo treated subjects.
- The most frequently reported AEs were related to the mouth and throat, primarily oral pruritus and throat irritation. The total number of AEs was dose related. The total number of AEs was distinctly lower in the 1 DU and 2 DU groups compared to the 4 DU, 8 DU and 16 DU groups.
- The treatment related AEs occurred for a number of days. Generally, the most frequent treatment related AEs resolved within minutes to hours.
- No major changes were identified upon reviewing the clinical laboratory parameters, vital signs, physical examination or lung function assessments.
- The treatment caused 5 events of asthma exacerbations (2 events in the 2 DU group, 2 events in the 16 DU group and 1 event in the placebo group).
- The oral examination revealed objective findings. The number of subjects with abnormal findings and the total number of abnormal findings were distinctly lower in the 1 DU and 2 DU groups compared to the 4 DU, 8 DU and 16 DU groups.

**Conclusions**

The ALK HDM tablet in doses up to 16 DU given once daily for 28 days was tolerated in subjects with house dust mite induced asthma (with/without rhinoconjunctivitis). The ALK HDM tablet in doses up to 16 DU is considered to have a safety profile that allows investigations in further clinical trials.

**Date of the Report**

Final version 26 April 2006

This trial was conducted in compliance with the Declaration of Helsinki and the principles of *Good Clinical Practice*.