Integrated Clinical Trial Report

A randomised, multiple dose, dose-escalation, double-blind, placebo-controlled phase I trial investigating the optimal safe dose of ALK Ragweed tablet *Ambrosia artemisiifolia* in adult subjects with seasonal rhinoconjunctivitis caused by ragweed pollen

Investigational Medicinal Product:

ALK Ragweed tablet

Clinical trial ID:	RT-01
BB-IND:	12970
Indication:	Seasonal allergic rhinoconjunctivitis induced by ragweed pollen
Development Phase:	I
First subject first visit:	12 June 2006
Last subject last visit:	30 March 2007
Investigator:	*Signatory Investigator*: [redacted] MD
Trial sites:	2 sites in the USA
Sponsor:	Group Clinical Development ALK-Abelló A/S DK-2970 Hørsholm, Denmark
Clinical Trial Manager:	[redacted] Ph.D., ALK-Abelló A/S
Report No. and date:	RT-01, 27 September 2007

This trial was conducted in compliance with the principles of *ICH Good Clinical Practice*.

Synopsis – Trial RT-01

Title of Trial A randomised, multiple-dose, dose-escalation, double-blind, placebo-controlled Phase I trial investigating the optimal safe dose of ALK Ragweed tablet (*Ambrosia artemisiifolia*) in adult subjects with seasonal rhinoconjunctivitis caused by ragweed pollen allergy.
Investigators *Site 1:* [redacted], MD. *Site 2:* [redacted] MD
Trial Sites Due to difficulty in enrolling allergic subjects the clinical trial site was changed from [redacted] (site 1) to [redacted] (site 2) after treatment of 7 subjects in the first treatment group (3 Amb a 1-U). The remaining 5 subjects in the first treatment group and the following treatment groups were treated a [redacted] (site 2). *Site 1 (first 7 subjects):* [redacted] TX, USA *Site 2 (remaining 46 subjects):* [redacted] IL, USA
Publication None
Trial Period *Site 1:* *First subject first visit* – 12 June 2006 *Last subject last visit* – 14 August 2006 *Site 2:* *First subject first visit* – 14 January 2007 *Last subject last visit* – 30 March 2007
Objectives This clinical trial seeks to identify a dose of the ALK Ragweed tablet that has a safety profile that will allow once daily intake (as self-medication) by the subject.
Methodology A randomised, multiple dose, dose-escalation, double-blind, placebo-controlled trial. It was planned to randomise six groups of 12 subjects to either active treatment or placebo treatment (3:1) resulting in 72 subjects totally. The dosage groups were staggered by intervals of approximately 7 days. This was to allow review by the data safety monitoring board (DSMB) of initial safety data in each group before dosing at the next dose level was commenced. The following doses were to be tested: 3 Amb a 1-U*, 6 Amb a 1-U, 12 Amb a 1-U, 24 Amb a 1-U, 50 Amb a 1-U and 100 Amb a 1-U given once daily as tablets with matching placebo to maintain the blinding. 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). The trial was conducted outside the ragweed pollen season. * Amb a 1-U relative to the reference provided by FDA.

Number of Subjects Planned and Analysed

It was planned to enrol a total of 72 subjects and 80 subjects were screened. 53 subjects were enrolled and randomised in the trial. 49 subjects completed the trial.

Subject disposition for the treatment phase are shown below:

Treatment Dose (Amb a 1-U)	Active 3 (N=9)	Active 6 (N=9)	Active 12 (N=9)	Active 24 (N=9)	Active 50 (N=4)	Active All (N=40)	Placebo All (N=13)
Full Analysis Set (FAS) *	9 (100%)	9 (100%)	9 (100%)	9 (100%)	4 (100%)	40 (100%)	13 (100%)
Subjects completed	8 (89%)	9 (100%)	9 (100%)	7 (78%)	3 (75%)	36 (90%)	13 (100%)
Withdrawn due to Adverse events	1 (11%)	0 (0%)	0 (0%)	2 (22%)	1 (25%)	4 (10%)	0 (0%)

*All subjects randomised were included in the Full Analysis Set. N=number of subjects; Active= ALK Ragweed tablet. Cross-reference: Table 1.

4 subjects withdrew (3 subjects due to adverse events, and 1 subject withdrew the informed consent due to experience of AEs and was regarded as an AE withdrawal).

It was decided by the DSMB to terminate further inclusion of subjects after treatment of 5 subjects (4 active and 1 placebo) in the 50 Amb a 1-U group. Treatment with 100 Amb a 1-U was not initiated.

Diagnosis and Main Inclusion Criteria

Male and female subjects 18-50 years of age with a clinical history of ragweed pollen induced allergic rhinitis or rhinoconjunctivitis of at least one year prior to trial entry either requiring treatment during the ragweed allergy season and/or causing restriction of activities. A positive skin prick test (*Site 1:* wheal diameter ≥ 3 mm; *Site 2:* wheal diameter ≥ 5 mm) and positive specific IgE against *Ambrosia artemisiifolia* (*Site 1:* ≥IgE Class 3; *Site 2:* ≥IgE Class 2*)*. No clinical history of significant asthma outside the ragweed pollen season. Finally, no clinical history of perennial allergic rhinitis caused by an allergen to which the subject is regularly exposed, no clinical history of significant symptomatic seasonal allergic rhinitis requiring medication due to grass pollen during the trial period, and no previous treatment by immunotherapy with ragweed pollen allergen or other allergens within the previous 5 years.

Inclusion criteria on skin prick test and specific IgE were changed from site 1 to site 2 to facilitate enrolling of subjects.

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number(s)

ALK Ragweed tablet 3 Amb a 1-U*; batch No. 461152

ALK Ragweed tablet 12 Amb a 1-U; batch No. 461154

ALK Ragweed tablet 50 Amb a 1-U; batch No. 461157

*Amb a 1-U relative to the reference provided by FDA

Doses:

Group 1: ALK Ragweed tablet 3 Amb a 1-U (1 x 3 Amb a 1-U)

Group 2: ALK Ragweed tablet 6 Amb a 1-U (2 x 3 Amb a 1-U)

Group 3: ALK Ragweed tablet 12 Amb a 1-U (1 x 12 Amb a 1-U)

Group 4: ALK Ragweed tablet 24 Amb a 1-U (2 x 12 Amb a 1-U)

Group 5: ALK Ragweed tablet 50 Amb a 1-U (1 x 50 Amb a 1-U)

Group 6✦: ALK Ragweed tablet 100 Amb a 1-U (2 x 50 Amb a 1-U)

✦ Treatment with 100 Amb a 1-U was not initiated.

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(s)

Placebo tablet: batch No. 271013

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. The groups commenced treatment in a staggered manner, at intervals of 7 days.

Immunological Assessments

The immunological parameters Amb a specific IgE and IgG_4 antibodies were evaluated to investigate if the treatment had an allergen specific effect on the immune system.

Safety Assessments

Adverse events monitoring and daily patient diary (adverse events, concomitant medication and time for intake of study medication). Clinical laboratory tests (haematology, blood chemistry, urinalysis and serology), vital signs, 12-lead ECG, physical examination, oral examination, spirometry (FEV_1).

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 only summary statistics were used.
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. Baseline changes in immunoglobulin levels (IgE and IgG_4) over the planned 28 day treatment period were subject to an exploratory statistical analysis and differences between treatment groups were tested by two-group (Exact) Wilcoxon Rank Sum Test.

Demography of Trial Population

Treatment dose N	**3 Amb a 1-U (N=9)**	**6 Amb a 1-U (N=9)**	**12 Amb a 1-U (N=9)**	**24 Amb a 1-U (N=9)**	**50 Amb a 1-U (N=4)**	**Active All (N=40)**	**Placebo (N=13)**
Age (years)							
Mean (SD)	35.9 (7.4)	33.5 (10 5)	30.6 (8.1)	25.6 (6.4)	38.8 (13.6)	32.1 (9.4)	28 1 (7.8)
Median	36.3	36.0	32.4	22.7	42 9	33.5	25.0
Min-Max	23 - 46	19 - 46	19 - 40	20 - 39	19 – 50	19 - 50	20 - 42
Height (cm)							
Mean (SD)	166 (7.7)	172 (9.3)	170 (10.4)	181 (9.6)	170 (2.9)	172 (10.0)	171 (10.7)
Median	165	170	168	185	170	170	170
Min-Max	152 - 180	157 - 185	157 - 188	163- 191	168 - 173	152 - 191	147 - 191
Weight (kg)*							
Mean (SD)	67.2 (12.6)	89.9 (29.2)	86.5 (21.6)	82.6 (20.8)	89 1 (23.7)	82.3 (22.6)	84.8 (18 1)
Median	66.2	77.1	97.5	73.5	88.0	72.8	81 2
Min-Max	47 - 86	59 - 138	50 - 113	59 - 123	66 - 115	47 - 138	64 – 134
BMI							
Mean (SD)	24.2 (3.5)	30.3 (8.9)	29.9 (6.9)	24.9 (4.5)	30.6 (7.1)	27.6 (6.7)	29.6 (8.3)
Median	24.3	27.4	28.2	23.1	30 2	25.0	27 5
Min-Max	20 - 32	19 - 43	19 - 39	21 - 34	23 - 38	19 - 43	21 - 48
Years with rhino-conjunctivitis	✦						¤
Mean (SD)	20.0 (13.5)	21.8 (12.9)	14.6 (6.2)	13.6 (7.5)	14.8 (14.7)	16.8 (10.5)	11.0 (5.7)
Median	21.0	19.0	13.0	12.0	14.0	13.5	12.0
Min-Max	6 - 33	7 - 41	8 - 25	5 - 28	0 – 31$	0 – 41	2 - 20
Sex							
Female (%)	7 (78%)	4 (44%)	5 (56%)	2 (22%)	3 (75%)	21 (53%)	6 (46%)
Male (%)	2 (22%)	5 (56%)	4 (44%)	7 (78%)	1 (25%)	19 (48%)	7 (54%)

*at screening, ✦ N= 4, ¤ N=11, **$** subject(s) with 0 years of rhinoconjunctivitis reported ≥ 1 year of rhinitis.
Cross-reference: Table 2 and Table 4 1

Immunological Results

Treatment with ALK Ragweed tablet for 28 days induced increases in *Ambrosia artemisiifolia* specific IgE and IgG_4 in all active treatment groups, and not in the placebo group.

Safety Results

- No related serious AEs were reported.
- 544 mild, 38 moderate and 10 severe treatment emergent AEs were reported by the 40 actively treated subjects compared to 19 mild and 1 moderate AEs reported by 13 placebo treated subjects.
- One subject (#16) in the 6 Amb a 1-U group experienced the same AEs (itching of ears, eyes, scalp, nose, and mouth) every day of the 28-day treatment period resulting in an extraordinary large number of AEs (141, all mild).
- Four subjects withdrew due to AEs. The events leading to withdrawal were all AEs that were expected from sublingual immunotherapy but with an intensity that was judged unacceptable:
    - 1 subject in 3 Amb a 1-U group due to 4 mild AEs (ear pruritus, chest discomfort, throat irritation, and oral pruritus
    - 2 subjects in 24 Amb a 1-U. 1 subject due to 3 moderate AEs (flushing, oedema mouth and swllen tongue) and 1 subject due to 3 severe AEs (dysphagia, chest discomfort and chest pain)
    - 1 subject in 50 Amb a 1-U group due to 1 severe AEs (periorbital oedema).
- The most frequently reported AEs when expressed by number of subjects experiencing the AE and number of AEs were pruritus related to the mouth, ears, eyes and skin; and nasal passage irritation.
- A dose-response was observed between doses and number and severity of observed AEs.
- The IMP related AEs occurred for a number of days. Generally, the most frequently reported treatment related AEs resolved within minutes to days.
- No major changes were identified upon reviewing the clinical laboratory parameters, vital signs, physical examination or lung function assessments.
- Oral examination revealed abnormal findings in three subjects in the 24 Amb a 1-U group (mild to moderate findings of conjunctivitis with facial urticaria and laryngospasm, oedema-erythema, oedema-erythema of the frenulum, angiooedema with erythema of the frenulum, oedema and swelling of the frenulum with angiooedema).
- Subjects judged doses ≤ 12 Amb a 1-U to be acceptable and >24 Amb a 1-U as unacceptable.
- No differences in safety parameters were observed between subjects with and without a medical history of ragweed induced asthma. Furthermore, no AEs that could be associated with asthma exacerbation were reported by these patients.

Conclusions

In adult subjects with seasonal rhinitis or rhinoconjunctivitis induced by ragweed pollen, doses of the ALK Ragweed tablet up to and inclusive 24 Amb a 1-U once daily for 28 days were tolerated. However doses below 24 Amb a 1-U are considered more appropriate based on the severity and number of AEs reported and the subjects' acceptance of the treatment.

No differences in safety parameters were observed between subjects with and without a medical history of ragweed induced asthma.

Based on the immunological evaluation the ALK Ragweed tablet has an effect on the immune system (*Ambrosia artemisiifolia* specific IgE and IgG_4 antibodies).

In conclusion, the ALK Ragweed tablet in doses below 24 Amb a 1-U are considered to be applicable for investigations in further clinical trials.

Date of the Report

27 September 2007

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