Synopsis

TITLE OF TRIAL A Phase I Trial investigating the Clinical Safety of a New Concept for Specific Immunotherapy: Grass Pollen Extract given sublingually to Healthy Subjects allergic to Grass Pollen	
INVESTIGATOR Principal Investigator: [redacted], M.D.	
TRIAL SITE Rigshospitalet (Copenhagen University Hospital), Allergy Clinic, Blegdamsvej 9, DK-2100 Ø, Denmark	
PUBLICATIONS None	
TRIAL PERIOD 15 November 2001 – 27 September 2002	**DEVELOPMENT PHASE** Phase I

OBJECTIVES

The objectives of the trial were specified for each of the Periods 1-4:

- Period 1: To evaluate the clinical safety (the "therapeutic window") of a single sublingual administration of ALK Grass Tablet *Phleum pratense* in the dose range 2.500 SQ-U – 1.125.000 SQ-U grass pollen allergen extract (outside grass pollen season).

- Period 2: To evaluate the safety and efficacy of 8-week specific immunotherapy treatment with ALK Grass Tablet *Phleum pratense* as a daily sublingual administration of three different dosages (2.500 SQ-U, 25.000 SQ-U and 75.000 SQ-U grass pollen allergen extract) and placebo during 8 weeks outside the grass pollen season.

- Period 3: To evaluate the safety and efficacy of specific immunotherapy treatment with ALK Grass Tablet *Phleum pratense* as a daily sublingual administration of three different dosages (2.500 SQ-U, 25.000 SQ-U and 75.000 SQ-U grass pollen allergen extract) and placebo, approximately 4 weeks prior to the grass pollen season and during the grass pollen season (approximately 10 weeks).

- Period 4: To record any changes in the subjects immunological status based on clinical observations and laboratory analysis of serum, saliva and nasal secretion.

The evaluation of immunological markers, which are considered efficacy endpoints, are not included in this trial report, but will be described in a separate report.

METHODOLOGY

This was a phase I trial consisting of three succeeding treatment periods and a follow-up visit:

- Period 1: A single dose treatment period.
- Period 2: An 8-week multiple dose treatment period conducted prior to the grass pollen season year 2002.
- Period 3: A 15-week multiple dose treatment period conducted approximately 4 weeks prior to the grass pollen season and during the grass pollen season year 2002.
- Period 4: A follow up visit, planned to take place 3 months after the last visit of period 3.

Each of the treatment periods had a randomised, double-blind, placebo-controlled design, with dosing in a stepwise dose-escalation fashion during the single dose treatment period (Period 1), and with daily dosing in parallel groups during the two multiple dose treatment periods (Periods 2 and 3).

During Period 1 the subject reported any adverse events experienced immediately after administration of the trial medication and since last visit. In addition the subject assessed how he/she had tolerated the trial medication by use of a VAS score and whether he/she had taken any concomitant medication since last visit.

During Periods 2 and 3 the subject evaluated on a daily basis pre-defined symptoms by use of a diary. At visit any additional adverse events experienced since last visit were recorded and the subject assessed how he/she had tolerated the trial medication since last visit. This assessment was performed by use of a VAS score. In addition it was recorded if the subject had taken any concomitant medication.
A conjunctival provocation test was performed during Period 2 in order to evaluate whether the subject's sensitivity towards the grass pollen allergen had changed.
Blood, saliva and nasal secretion was collected during Period 2 and 3 for later assessment of various immunological markers.

Period 4 was a follow-up visit, where blood, saliva and nasal secretion was collected for later assessment of various immunological markers. At this visit adverse events, clinical symptoms and medical treatment for the follow-up period were also recorded and a conjunctival provocation test was performed.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

A total of 59 subjects were screened, of whom 54 were found eligible to enter the trial.
In all, 52 subjects entered the trial:
Forty-seven subjects were randomised to receive trial drug in Period 1. Fourty-three subjects continuing from Period 1 and five additional subjects were randomised to receive trial drug in Period 2. Of 44 subjects completing Period 2, a total of 32 subjects entered Period 3. Twenty-eight subjects completed Period 3 and attended the follow-up visit (Period 4).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Male and female subjects aged 18-65 years with *Phleum pratense* induced seasonal moderate to severe rhinoconjunctivitis, and with a positive skin prick test and specific IgE to *Phleum pratense*.
No clinical history of significant rhinitis, sinusitis and/or asthma outside the grass pollen season.

TRIAL PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Trial products
ALK Grass Tablet *Phleum pratense* 2.500 SQ-U:
Batch Nos. 0000040914, 0000043409, 0000047951, 0000047955, 0000049201 and 0000049205

ALK Grass Tablet *Phleum pratense* 25.000 SQ-U:
Batch Nos. 0000040915, 0000043885, 0000047952, 0000047956, 0000049202 and 0000049206

ALK Grass Tablet *Phleum pratense* 125.000 SQ-U:
Batch No. 0000040916

Doses
Period 1: Placebo, 2.500, 25.000, 75.000, 125.000 and 375.000 SQ-U
Period 2: Placebo, 2.500, 25.000 or 75.000 SQ-U
Period 3: Placebo, 2.500, 25.000 or 75.000 SQ-U

Mode of administration
Sublingual

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Trial product

Placebo ALK Grass Tablet *Phleum pratense*:
Batch Nos. 0000040917, 0000043889, 0000047953 and 0000049203

Mode of administration

Sublingual

DURATION OF TREATMENT

Period 1: One, two or three single doses of ALK Grass Tablet *Phleum pratense* or placebo.
Period 2: Once daily dosing in the morning of ALK Grass Tablet *Phleum pratense* or placebo for 8 weeks.
Period 3: Once daily dosing in the morning of ALK Grass Tablet *Phleum pratense* or placebo for approximately 15 weeks.

CRITERIA FOR EVALUATION – SAFETY

The primary safety variables:

- Adverse events including SAEs. For Periods 2 and 3 severe symptoms and symptoms categorized as "other" are registered as adverse events.
- Symptoms with the intensity mild or moderate (for Periods 2 and 3 only).

The symptoms were pre-defined in the diary and assessed on a daily basis during Periods 2 and 3 by the subject (see sec. 5.8.)

Other safety variables:

- Vital signs
- VAS score
- If required ECG, PEF/FEV_1 and blood parameters

CRITERIA FOR EVALUATION – EFFICACY

Efficacy variables:

- Conjuntival Provocation Test (CPT)

Immunological efficacy variables:

- Immunological markers measured in serum (IgG, IgE and lymphocyte proliferation), nasal secretion (IgA, IgE and IgG) and saliva (IgA, IgE and IgG)

STATISTICAL METHODS

One analysis set (the ITT analysis set) was used when performing the descriptive analysis.

Primary safety endpoint

Frequency tables were provided for adverse events and subject diary recordings of symptoms. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA)

Other safety endpoints

Summary tables presenting changes from baseline were provided for blood pressure, pulse, body mass index and VAS, displaying mean, standard deviation (SD), median and range within each treatment group.

Efficacy endpoints

Summary tables presenting change from baseline were provided for log-transformed conjunctival provocation test (log-CPT), displaying mean, standard deviation, median and range within each treatment group. Log-CPT profiles were presented graphically per subject per treatment group to identify possible changes in log-CPT over time.
The methods used upon evaluating the immunological markers will be described in a separate report.

DEMOGRAPHY OF TRIAL POPULATION

A total of 31 male and 21 female subjects entered the trial. Mean age was 32 years (range 20 – 57 years), all subjects were Caucasian and had a clinical history with moderate to severe grass pollen induced rhinoconjunctivitis..

SAFETY RESULTS

One serious adverse event (haemorrhage per rectum) was reported in Period 3 in the treatment group receiving ALK Grass Tablet *Phleum pratense* 25.000 SQ-U.
Two subjects discontinued treatment due to adverse events:
One subject receiving ALK Grass Tablet 75.000 SQ-U was withdrawn in Period 2 due to sting and blisters in the mouth, and one subject receiving placebo was withdrawn during Period 3 due to itching in the mouth.

Period 1:
During Period 1 of the trial 44 of 68 subjects (64.7%) reported at least 1 adverse event. In total 73 adverse events were reported and most of these adverse events were caused by local reactions in the throat and mouth. The most frequently reported were “itching mouth” (reported in 41.2% of the subjects) and “itchy throat” (reported in 16.2% of the subjects).
The majorities of adverse events (82.2%) were mild in severity and resolved spontaneously within 1 day.
Based on two events of “constriction throat” in the 375.000 SQ-U group (1 severe and 1 moderate) the dose escalation was stopped. The highest dose chosen for the following Periods was 75.000 SQ-U.

Period 2:
During Period 2 of the trial 36 of 47 subjects (76.6%) reported at least 1 adverse event. In total 150 adverse events were reported and most of these were caused by local reactions in or around the mouth. The most frequently reported adverse event was “itching mouth” (reported in 46.8% of the subjects). In addition to this adverse event 17% of the subjects reported “itching eyes” and 10.6% reported “itchy throat”. “Itching mouth”, “itchy throat” and “itching eyes” were reported more frequently with increased dosage.
The majorities of adverse events (86.0%) were mild in severity and resolved within 1 day.
In addition to the adverse events reported, 87.2% of the subjects reported 1229 symptoms. The majority of symptoms were due to “local allergic reactions in or around the areas of the mouth” (60.4%) and “runny nose, sneezing and itching nose” (27.6%). The majority of symptoms (86%) were mild and resolved within the first hour after administration.

Period 3-4:
During Period 3 of the trial 17 of 32 subjects (53.1%) reported at least one adverse event. In total 67 adverse events were reported and most of these were hay-fever symptoms. Of these the most frequently reported were “itching eyes” and “rhinitis” both reported in 18.8% of the subjects.
The severity of the adverse events was rated as follows: 53.7% were reported as being mild, 11.9% were reported as being moderate and 34.3% were reported as being severe. Almost all events of “rhinitis” and “itching eyes” were severe, while the majority of remaining adverse events were mild.
More than half of the adverse events (59.7%) resolved within 1 day.
There was no clear dose response with respect to severity and duration of adverse events.
In addition to the adverse events reported, 84.4% of the subjects reported 1924 symptoms. The number of symptoms reported increased with dose. The majority of symptoms were due to “local allergic reactions in or around the areas of the mouth” (24.6%) and “runny nose, sneezing and itching nose” (43.2%). However, “itching eyes” were also a frequently reported symptom (26.7%).
Most symptoms were scored as being mild in severity and for “local allergic reactions in or around

areas of the mouth" the majority was resolved within the first hour after administration.
The "runny nose, sneezing, itching nose" and "itching eyes" symptoms however, had duration of up to 24 hours.

EFFICACY RESULTS

- No change in CPT was observed for any of the treatment groups.
- Immunological markers will be described in a separate report.

CONCLUSIONS

Period 1: The 75.000 SQ-U dose-level was tolerated without problems and therefore this dose was chosen as the highest dosage for the following periods.

Period 2: The adverse events and symptoms seen outside the grass pollen-season were mainly related to local reactions in or around the mouth. Hay-fever like symptoms was however also reported. The majority of adverse events and symptoms were mild in severity and disappeared spontaneously within hours after tablet intake.

Period 3-4: During the grass pollen-season hay-fever symptoms were most predominant. However, reactions related to the areas in or around the mouth were also reported. The majority of adverse events and symptoms were mild in severity and disappeared spontaneously within hours after tablet intake.

In summary, the doses administered on a daily basis outside and during the grass pollen season (2.500 SQ-U, 25.000 SQ-U and 75.000 SQ-U) are considered safe for further investigation in future clinical trials with the ALK Grass Tablet *Phleum pratense*..

The trial was conducted in accordance with Good Clinical Practice.