Synopsis

TITLE OF TRIAL

A randomised, multiple dose, dose-escalation, double-blind, placebo-controlled phase I trial to investigate the safety of ALK Grass tablet *Phleum pratense* in subjects with seasonal grass pollen induced rhinoconjunctivitis and mild to moderate asthma

INVESTIGATOR

Dr. [redacted] (Belfast, GB) was principal investigator.

TRIAL SITE

MDS Pharma Services Inc.
22-24 Lisburn Road
Belfast, NI, BT9 6AD
Great Britain

PUBLICATIONS

None

TRIAL PERIOD	**DEVELOPMENT PHASE**
14 March 2004 – 26 May 2004	Phase I

OBJECTIVES

To identify a dose range of ALK Grass tablet *Phleum pratense* 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. Four treatment groups commenced treatment in a staggered manner, at intervals of approximately one week, to allow review by the safety committee of initial safety data in each group before dosing began at the next (higher) dose level. Each of the four treatment groups was planned to consist of 12 subjects randomised to either active treatment or placebo (3:1). Planned doses were 75,000, 150,000, 300,000 and 500,000 SQ-T, given once daily as tablets of various strengths with matching placebo to maintain the blind.
Subjects received treatment for 28 days (up to day 28, inclusive) and attended a follow-up visit 1–2 weeks after the last day of treatment (i.e. on day 35–42). The trial was conducted outside the grass pollen season in the spring 2004.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

It was planned to enrol a total of 48 subjects and 116 subjects were screened. Only 43 subjects complied with the protocol criteria and were enrolled in the trial. Subject disposition and treatment groups for the treatment phase are shown below:

Treatment Dose (SQ-T)	75,000 SQ-T (N=9)	150,000 SQ-T (N=9)	300,000 SQ-T (N=9)	500,000 SQ-T (N=5)	Active All (N=32)	Placebo All (N=11)
Full Analysis Set (ITT) *	9 (100%)	9 (100%)	9 (100%)	5 (100%)	32 (100%)	11 (100%)
Subjects completed	9 (100%)	9 (100%)	9 (100%)	5 (100%)	32 (100%)	11 (100%)

*All subjects randomised are included in the Full Analysis Set
N=number of subjects
Active= ALK Grass tablet

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Male or female subjects 18-65 years of age with a clinical history of mild to moderate, well-controlled asthma within the last two years, and a clinical history of significant grass pollen induced allergic rhinoconjunctivitis of two years or more either requiring treatment during the grass pollen season or causing significant restrictions of activities. A positive skin prick test and positive specific IgE against *Phleum pratense* and no clinical history of severe asthma was required. Finally, no clinical history of significant symptomatic seasonal allergic rhinitis requiring medication due to tree pollen or weed pollen during the planned treatment period and no clinical history of significant active perennial allergic rhinitis symptoms caused by an allergen to which the subject is regularly exposed.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

ALK Grass tablets *Phleum pratense* 25,000 SQ-T (40 µg grass allergen extract). Batch no. 68300
ALK Grass tablets *Phleum pratense* 75,000 SQ-T (120 µg grass allergen extract). Batch no. 68304

Doses:
Group 1: ALK Grass tablets 75,000 SQ-T (3 x 25,000 SQ-T + 1 x placebo) or placebo x 4
Group 2: ALK Grass tablets 150,000 SQ-T (2 x 75,000 SQ-T + 2 x placebo) or placebo x 4
Group 3: ALK Grass tablets 300,000 SQ-T (4 x 75,000 SQ-T) or placebo x 4
Group 4: ALK Grass tablets 500,000 SQ-T (2 x 25,000 SQ-T + 6 x 75,000 SQ-T) or placebo x 8

Mode of administration:
Once daily, sublingually.

DURATION OF TREATMENT

The duration of treatment was 28 days for all groups. The groups commenced treatment in a staggered manner, at intervals of approximately one week

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

ALK Grass tablets Placebo. Batch no. 68296
Doses:
Group 1: placebo x 4
Group 2: placebo x 4
Group 3: placebo x 4
Group 4: placebo x 8

Mode of administration:
Once daily, sublingually.

Rescue medication:
As appropriate, subjects were equipped with a $ß_2$-agonist inhaler to alleviate potential asthmatic symptoms.

CRITERIA FOR EVALUATION – EFFICACY

Not applicable

CRITERIA FOR EVALUATION – SAFETY

Adverse events, safety laboratory assessments (haematology, urinalysis and chemistry), physical examination, vital signs, electrocardiogram (ECG), oral examination, spirometry to measure forced expiratory volume in one second (FEV_1), daily peak flow measurements (PEF).

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 Analyses Set (FA Set) was considered for this trial. The FA Set consisted of all the randomised subjects. The FA Set was previously referred to as the Intent-to-Treat (ITT) Population and is in accordance with the ICH guidelines. 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 had safety endpoints and safety data was summarised by treatment (placebo, dose level). Pre-dose to post-dose changes were calculated and summarised. Adverse events were summarised by treatment and for any cases of withdrawal, reasons was to be documented individually.

DEMOGRAPHY OF TRIAL POPULATION

Baseline characteristics for all subjects exposed are shown below:

Treatment Dose (SQ-T) N		Active 75,000 9	Active 150,000 9	Active 300,000 9	Active 500,000 5	Active all 32	Placebo 11
Age (years)	Mean (SD)	22.1 (3.2)	23.2 (2.8)	28.0 (9.5)	25.8 (5 5)	24.7 (6.2)	24.5 (5.5)
	Median	20.0	23.0	23.0	25.0	23.0	22.0
	Min-Max	20 - 29	18 - 28	19 - 42	21 - 35	18 - 42	21 - 40
Height (cm)	Mean (SD)	175 (11.1)	170 (10.3)	172 (8.5)	174 (7 3)	173 (9.4)	172 (6.5)
	Median	175	170	171	179	173	170
	Min-Max	157 - 192	151 - 185	160 - 192	166 - 180	151 - 192	164 - 183
Weight at screening (kg)	Mean (SD)	70.9 (13.3)	77.6 (18.7)	80.4 (22.0)	84.4 (19.6)	77.6 (18.2)	83.6 (14.3)
	Median	70.4	76.2	76.0	72.2	72.3	82.6
	Min-Max	53 - 99	48 - 110	58 - 112	68 - 109	48 - 112	54 - 105
Years with allergy*	Mean (SD)	13.7 (6.3)	8.8 (6.1)	21.1 (10.7)	21.4 (10.1)	15.6 (9.6)	13.7 (9.2)
	Median	12.0	5.0	20.0	20.0	13.5	15.0
	Min-Max	4 - 25	4 - 20	7 - 42	10 - 36	4 - 42	3 - 29
Years with asthma*	Mean (SD)	12.9 (4.5)	15.7 (5.3)	22.2 (10.2)	19.4 (11.0)	17.3 (8.3)	15.4 (7.2)
	Median	15.0	18.0	20.0	20.0	16.0	15.0
	Min-Max	5 - 18	7 - 20	9 - 42	8 - 36	5 - 42	2 - 27
Gender	Female (%)	3 (33)	3 (33)	3 (33)	2 (40)	11 (34)	5 (45)
	Male (%)	6 (67)	6 (67)	6 (67)	3 (60)	21 (66)	6 (55)

N=number of subjects
* Calculated from medical history records

EFFICACY RESULTS

None

SAFETY RESULTS

- No serious or severe AEs were reported and no subjects withdrew due to AEs.
- 598 mild and 10 moderate treatment emergent AEs were reported by the 32 actively treated subjects, compared to 57 mild and 3 moderate AEs reported by the 11 subjects receiving placebo.
- Most frequently reported AEs were related to the mouth and throat, primarily oral pruritus. The number of AEs seemed dose related, but the dose relation was mainly caused by dose relation in number of oral pruritus events.
- The treatment related AEs often occurred in relation to first intake of trial medication. Generally the most frequent treatment related AEs resolved within minutes or hours.
- No safety concerns were identified upon reviewing the clinical laboratory parameters, vital signs, physical examination or lung function assessments.
- The treatment caused no asthma exacerbations.

CONCLUSIONS

- Treatment with the ALK Grass tablet in doses up to 500,000 SQ-T, given once daily for 28 days, were well tolerated by subjects suffering from grass pollen induced rhinoconjunctivitis and mild to moderate asthma. No safety concerns were identified with regard to treatment of asthmatic patients.

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.