Title of Trial	A randomised, parallel-group, double-blind, placebo-controlled Phase II trial assessing the safety and efficacy of ALK Grass tablet *Phleum pratense* in subjects with seasonal grass pollen induced rhinoconjunctivitis and mild to moderate grass pollen induced asthma
Trial ID	GT-07
Development Phase	Phase II
IND Number (US only)	
Compound Name	ALK Grass tablet *Phleum pratense*
Indication	Seasonal allergic rhinoconjunctivitis caused by grass pollen
Investigators	In total 15 investigators. Professor [redacted] and Professor [redacted] were appointed signatory investigators
Trial Sites	A total of 15 sites participated: 11 in Denmark, and 4 in Sweden
Trial Initiated	3 February 2004
Trial Completed	6 September 2004
Sponsor	ALK-Abelló A/S Group Clinical Development Bøge Allé 6-8 DK-2970 Hørsholm Denmark
International Medical Officer	[redacted]
International Trial Manager	[redacted]
Data manager	[redacted]
Statistician	[redacted]
Medical Writer	[redacted]
Report Date	4 February 2005

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

Synopsis

TITLE OF TRIAL

A randomised, parallel-group, double-blind, placebo-controlled Phase II trial assessing the safety and efficacy of ALK Grass tablet *Phleum pratense* in subjects with seasonal grass pollen induced rhinoconjunctivitis and mild to moderate grass pollen induced asthma.

INVESTIGATOR(S)

Signatory investigator SE: Professor [redacted], Sahlgrenska University Hospital, Sweden
Signatory investigator DK: Professor [redacted], Aarhus University Hospital, Denmark

TRIAL SITE(S)

A total of 15 sites participated: 11 in Denmark, and 4 in Sweden.

PUBLICATIONS

None

TRIAL PERIOD	**DEVELOPMENT PHASE**
3 February - 6 September 2004	Phase II

OBJECTIVES

Primary objective:

- To evaluate the safety profile of the ALK Grass tablet in a dosage of 75,000 SQ-T as compared to placebo in subjects diagnosed with mild to moderate grass pollen induced asthma as well as grass pollen induced rhinoconjunctivitis.

Secondary objective:

- To evaluate the efficacy of the ALK Grass tablet in a dosage of 75,000 SQ-T as compared to placebo in subjects diagnosed with mild to moderate grass pollen induced asthma as well as grass pollen induced rhinoconjunctivitis.

METHODOLOGY

This was a multi-centre, double-blind, randomised, parallel group, placebo-controlled trial. The trial was conducted 12±2 weeks prior to and during the grass pollen season 2004. A total of 105 subjects diagnosed with mild to moderate grass pollen induced asthma as well as grass pollen induced rhinoconjunctivitis were randomised (2:1) to either 75,000 SQ-T ALK Grass tablets or placebo. The trial consisted of 6 visits and a telephone follow-up. During the treatment phase subjects received double-blind medication once daily.
Each day the subjects rated their asthma and rhinoconjunctivitis symptoms on a scale from 0 to 3 (0 = no symptoms, 1 = slight symptoms, 2 = moderate symptoms, 3 = severe symptoms). The rated asthma symptoms were: Cough, wheeze, chest tightness (dyspnoea) and exercise induced symptoms. The rated rhinoconjunctivitis symptoms were nose symptoms: Runny nose, blocked nose, sneezing, itchy nose; and eye symptoms: Gritty feeling/red/itchy eyes, watery eyes.
In case of continuing symptoms of allergic asthma or rhinoconjunctivitis, subjects received additional rescue medication in a stepwise fashion depending on the persistency and severity of their symptoms. Steps 1, 2 and 3 for rhinoconjunctivitis symptoms and Steps A, B and C for asthma symptoms (see below).

Medication Step		Score
	Rhinoconjunctivitis	
1	Loratadine 10 mg tablets once daily	6 (per tablet)
1	Levocabastine eye drops (0,5 mg/ml one drop in each eye twice daily)	2 (per drop)
2	Budesonide nasal spray (up to 32 µg 2 puffs (per nostril) twice daily)	1 (per puff)
3	Prednisone 5 mg tablets; up to 50 mg once daily	1.6 (per tablet)
	Asthma	
A	Salbutamol inhaler (200 µg inhalation 1-2 times twice daily)	2 (per inhalation)
B	Fluticasone inhaler (250 µg inhalation 1-2 times twice daily)	2 (per inhalation)
C	Prednisone 5 mg tablets; up to 50 mg once daily	1.6 (per tablet)

NUMBER OF SUBJECTS PLANNED AND ANALYSED

It was planned to enrol a total of 105 subjects. In total 114 subjects were randomised. The subject disposition is shown below:

Group	Placebo (N=40)		75.000 SQ-T (N=74)		Overall (N=114)	
Screened					130	
Full analysis set	40	(100%)	74	(100%)	114	(100%)
Per-protocol set	32	(80.0%)	61	(82.4%)	93	(81.6%)
Completed trial	36	(90.0%)	66	(89.2%)	102	(89.5%)
Withdrawals	4	(10.0%)	8	(10.8%)	12	(10.5%)
Reason for Withdrawal						
Adverse event	0	0	3	(4.1%)	3	(2.6%)
Non-compliance with protocol	0	0	1	(1.4%)	1	(<1.0%)
Lost to follow-up	1	(2.5%)	2	(2.7%)	3	(2.6%)
Other	3	(7.5%)	2	(2.7%)	5	(4.4%)

N = Number of subjects; % = Percent subjects of Full Analysis set (all randomised subjects)
Cross-reference: EOT Table 1.1

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Male or female subjects 18-65 years of age with clinical history of significant grass pollen induced allergic rhinoconjunctivitis and mild to moderate grass pollen induced asthma of 2 years or more, a positive skin prick test and specific IgE to *Phleum pratense* (≥ CAP allergy Class 2).

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

ALK Grass tablets *Phleum pratense* 75,000 SQ-T (120 µg grass allergen extract). Batch no. 68301/68304
The ALK Grass tablet was administered once daily sublingually, as self medication.

DURATION OF TREATMENT

The treatment was initiated 12±2 weeks before the start of the grass pollen season and the maximum duration of treatment was 24 weeks.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Placebo ALK Grass tablet. Batch no. 68293/68296.
The placebo tablet was administered once daily sublingually, as self medication.

CRITERIA FOR EVALUATION – SAFETY

Asthma medication score, asthma symptom score, peak flow, spirometry to measure forced expiratory volume in one second (FEV_1), adverse events (AE), physical examination, vital signs, and safety laboratory assessments (haematology, urinalysis and chemistry).

CRITERIA FOR EVALUATION – EFFICACY

Rhinoconjunctivitis symptom score and rhinoconjunctivitis medication score.

STATISTICAL METHODS

As all analyses of safety endpoints as well as efficacy endpoints were planned to be descriptive no formal statistical sample size and power considerations were made. The following analysis sets were defined: The full analysis set (FA set) was all randomised subjects (previously called ITT population). The per-protocol analysis set (PP set) was all subjects randomised and exposed to at least one dose of trial medication as well as having completed the trial and fulfilled the following criteria: Correct administration of the trial medication, attendance at trial, compliance with the diary, at least 10 weeks of pre-seasonal treatment with trial medication. The PP set was defined prior to unblinding.

Pollen counts were collected by the European Pollen Information Ltd. The start of the grass pollen season was defined as first day of 3 consecutive days with pollen count larger than or equal to 10 grains per m^3. The end of the season was defined as the last day before 3 consecutive days with pollen count less than 10 grains per m^3 where the last day of the 3 days was after 28 July.

Demographics, concomitant medication, disease history and allergy history were summarised by treatment group using descriptive statistics. No formal statistical comparison of treatments groups at baseline was performed.

Safety analyses:

Summary tables describing the average asthma medication score[a] for the pollen season were presented by treatment group displaying number of subjects, mean, SD, median, 5%-quantile, 95%-quantile, minimum and maximum.

Summary tables describing the average asthma symptom score[a] for the pre-pollen and pollen seasons as well as the average asthma medication score for the pre-pollen season was made by treatment group displaying number of subjects, mean, SD, median, 5%-quantile, 95%-quantile, minimum and maximum.

Efficacy analyses:

Summary tables describing the average rhinoconjunctivitis symptom score[a] as well as the average rhinoconjunctivitis medication score[a] for the pollen season were made by treatment group displaying number of subjects, mean, SD, median, 5%-quantile, 95%-quantile, minimum and maximum.

Post hoc statistics:

The pre-defined efficacy endpoints (average rhinoconjunctivitis symptom score and rhinoconjunctivitis medication score) were after unblinding subject to a post hoc statistical analysis testing for treatment differences between the actively treated subjects and those who received placebo.

Rhinoconjunctivitis symptom score:

The difference between the treatment groups were tested in three ANOVA models: 0) Assuming unequal variance between treatment groups and with pollen region as random effect, treatment groups as fixed effect and rhinoconjunctivitis symptom score as response variable; 1) Assuming unequal variance between treatment groups and with treatment groups as fixed effects and rhinoconjunctivitis symptom score as response variable; 2) Assuming equal variance between treatment groups and rhinoconjunctivitis symptom score as response variable.

Rhinoconjunctivitis medication score:

The same models were tested; however, the underlying model assumptions (normal distribution of residuals) were not fulfilled. This was improved, but not entirely fulfilled, by a square root transformation of the response variable. In addition to model 2, a Wilcoxon Rank-sum test was therefore also performed.

[a] The average score was defined for each subject as the average of daily scores over the pollen season.

DEMOGRAPHY OF TRIAL POPULATION

There were no major differences between the groups at baseline, though a few more females were randomised to the placebo group. The pollen season for the 5 pollen regions on average lasted 52 days (range 52-60 days).

Group	Placebo (N=40)	75.000 SQ-T (N=74)	Overall (N=114)
Sex			
Male	24 (60.0%)	53 (71.6%)	77 (67.5%)
Female	16 (40.0%)	21 (28.4%)	37 (32.5%)
Country			
Denmark	33 (82.5%)	63 (85.1%)	96 (84.2%)
Sweden	7 (17.5%)	11 (14.9%)	18 (15.8%)
Age (years)			
Mean (SD)	34.1 (9.9)	36.5 (10.6)	35.7 (10.4)
Min - Max	20 - 60	18 - 64	18 - 64
Height (cm)			
Mean (SD)	177 (9.2)	176 (8.8)	176 (8.9)
Min - Max	161 - 198	156 - 196	156 - 198
Weight (kg)			
Mean (SD)	78.5 (17.3)	79.2 (14.8)	79.0 (15.7)
Min - Max	45 - 140	49 - 138	45 - 140
Smoking			
Never Smoked	18 (45.0%)	46 (62.2%)	64 (56.1%)
Currently Smoking	13 (32.5%)	15 (20.3%)	28 (24.6%)
Stopped Smoking	8 (20.0%)	13 (17.6%)	21 (18.4%)
Grass Pollen Induced Rhinoconjunctivitis - Severity			
Mild	3 (7.5%)	2 (2.7%)	5 (4.4%)
Moderate	23 (57.5%)	48 (64.9%)	71 (62.3%)
Severe	14 (35.0%)	24 (32.4%)	38 (33.3%)
Grass Pollen Induced Asthma - Severity			
Mild	24 (60.0%)	46 (62.2%)	70 (61.4%)
Moderate	15 (37.5%)	28 (37.8%)	43 (37.7%)
Severe	1 (2.5%)	0	1 (<1%)
Grass Pollen Induced Rhinoconjunctivitis: Years			
Mean (SD)	19.4 (12.5)	19.6 (9.8)	19.5 (10.8)
Min - Max	4 - 51	2 - 45	2 - 51
Grass Pollen Induced Asthma: Years			
Mean (SD)	12.5 (8.5)	14.0 (10.8)	13.5 (10.0)
Min - Max	2 - 36	2 - 45	2 - 45

N=number of subjects
% = percent subjects of Full Analysis set (all randomised subjects)
Cross-reference: EOT Table 2.1.1a and 2.1.2a

Safety Summary

Overview of adverse events.

	Placebo (N=40)			75,000 SQ-T (N=74)			Overall (N=114)		
	N	(%)	E	N	(%)	E	N	(%)	E
All AEs	36	(90%)	113	70	(95%)	360	106	(93%)	473
Mild AEs	29	(73%)	77	66	(89%)	250	95	(83%)	327
Moderate AEs	16	(40%)	31	38	(51%)	97	54	(47%)	128
Severe AEs	4	(10%)	5	9	(12%)	13	13	(11%)	18
AEs with possible or probable relation to trial medication	14	(35%)	31	63	(85%)	220	77	(68%)	251

AE=adverse event; N=number of subjects; %=percent of subjects having the event; E=number of events;
Cross-reference: EOT Table 5.1a, 5.3a, 5.4a, 5.6a

Safety Results

- The treatment caused no increase in asthma symptoms or use of asthma medication.
- No serious AEs were reported.
- Most AEs were reported in the active treatment group.
- The most frequently reported AEs were related to the mouth and throat, primarily oral pruritus. AEs in mouth and throat typically started in relation to first medication intake.
- There was no difference between treatment groups regarding AEs related to asthma.
- Three subjects withdrew from the trial due to AEs; all were related to trial medication and all subjects received active treatment. They all recovered.
- No safety concerns were identified for any of the clinical laboratory parameters, vital signs, physical examinations or lung function assessments.

The AE profile in this trial was similar to the AE profile in non-asthmatic grass allergy patients.

EFFICACY RESULTS

- The efficacy analysis showed that the ALK Grass tablet 75,000 SQ-T provided a reduction of 25% in the rhinoconjunctivitis symptom score when compared to placebo (p=0.05). This finding was supported by efficacy analysis in the PP set, where a 37% reduction were seen (p<0.01).
    - The reduction in total symptom score was mainly obtained through reduced nose symptoms.
- A reduction of 32% in rhinoconjunctivitis medication score was found with the ALK Grass tablet 75,000 SQ-T when compared to placebo (p=0.17). Again efficacy analysis in the PP set supported the finding showing a 41% reduction (p=0.04).
    - The difference in medication score was mainly obtained through reduced use of Loratadine.

CONCLUSIONS

No safety concerns appeared, and treatment with the ALK Grass tablet in a dose of 75,000 SQ-T was generally well tolerated by subjects with grass pollen induced rhinoconjunctivitis and asthma. The treatment caused no increase in asthma symptoms or use of asthma medication.

The ALK Grass tablet 75,000 SQ-T provided a reduction of 25% in rhinoconjunctivitis symptom score and a reduction of 32% in rhinoconjunctivitis medication score when compared to placebo.

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