SYNOPSIS

Name of Sponsor/Company: ALK-Abelló A/S **Name of Finished Product:** **Name of Active Ingredient:** *Phleum pratense* allergen grass-pollen extract	**Individual Study Table Referring to Part of the Dossier** Volume: Page:	**(For National Authority Use Only)**

Title of Study:

A randomised, multiple dose, dose-escalation, double-blind, placebo-controlled Phase I study to investigate the safety of ALK Grass Tablets *Phleum pratense* in subjects with seasonal rhinoconjunctivitis caused by grass pollen allergy

Investigator: Priv.-Doz. Dr. med. [redacted]

Study Centre:

PAREXEL GmbH, Institute of Clinical Pharmacology
Klinikum Westend, Haus 18
Spandauer Damm 130
D-14050 Berlin (Germany)

Publication (reference): None	
Study Period (Years): First subject screened: 11-Nov-2002 Last subject completed: 9-May-2003	**Clinical Phase:** I

Objective:

To identify a dose range of ALK Grass Tablets *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 Phase I study with seven dosage groups (25,000, 75,000, 150,000, 300,000, 500,000, 750,000, and 1,000,000 SQ-U ALK Grass Tablets *Phelum pratense*). The dosage groups commenced treatment in a staggered manner at intervals of approx. one week. Progression to the next higher dose was done only, if the safety profile after 3-days treatment with the preceding dose was considered safe and well tolerated by the Safety Committee. Each dosage group consisted of 12 subjects randomised either to active treatment or placebo (3:1). Subjects received daily treatment for 28 days and attended a follow-up visit 1–2 weeks after the last dosing. The study was conducted outside the grass pollen season.

Number of Subjects (planned and analysed):

Number of subjects screened:	156	(109 male, and 47 female)
Number of subjects included:	84	(64 male, and 20 female)
Number of subjects completed:	84	(64 male, and 20 female)
Number of subjects analysed:	84	(64 male, and 20 female)
Number of subjects withdrawn:	0	

Name of Sponsor/Company: ALK-Abelló A/S **Name of Finished Product:** **Name of Active Ingredient:** *Phleum pratense* allergen grass-pollen extract	**Individual Study Table Referring to Part of the Dossier** Volume: Page:	**(For National Authority Use Only)**

Diagnosis and Main Criteria for Inclusion:

Male and female volunteers aged 18–65 years (both inclusive) who gave informed consent, with the following principal selection criteria: Clinical history of at least two year's duration consistent with significant grass-pollen-induced seasonal allergic rhinoconjunctivitis; positive specific IgE (CAP class ≥2) against *Phleum pratense*; positive skin prick test (wheal ≥3 mm) for *Phelum pratense*; no clinical history of significant asthma outside the grass pollen season; FEV_1 ≥70% of predicted value.

Test Products, Doses and Mode of Administration, Batch Number:

Formulation:	Orodispersible tablet
Strength:	25,000 SQ-U and 125,000 SQ-U
Mode of administration:	Oral
Batch Nos.:	25,000 SQ-U: 26122H527 125,000 SQ-U: 26133A577; 26133A580; 26132H529; 26132H528

Reference (Placebo) Therapy, Dose and Mode of Administration, Batch Number:

Formulation:	Orodispersible tablet	
Strength:	Not applicable	
Mode of administration:	Oral	
Batch Nos.:	matching tablets with 25,000 SQ-U:	28062H534
	matching tablets with 125,000 SQ-U:	28063A579

Duration of Treatment:

Each subject received one daily dose of ALK Grass Tablets *Phleum pratense* or placebo for 28 days

Criteria for evaluation:

Adverse events monitoring, safety laboratory, physical examination, vital signs, 12-lead ECG and oral examination.

Statistical Methods:

Descriptive statistics were applied for all randomised subjects who received at least one dose or partial dose of study medication (ITT population). All statistical summaries were provided within each dose level. Subjects who received placebo were pooled from all dosage groups. Statistical summaries and analyses were done using SAS®.

Data from safety laboratory, vital signs and quantifiable data from 12-lead ECGs were summarized per treatment group (placebo and the seven dose levels of ALK Grass Tablets). Pre- to post-dose changes were calculated and summarized as well. Adverse events were listed and summarized per treatment.

Demographic and safety variables were listed and summarized by descriptive statistics as appropriate. All quantifiable safety data were summarised by treatment. Pre- to post-dose changes were calculated and summarised.

Name of Sponsor/Company: ALK-Abelló A/S	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product:	Volume:	
Name of Active Ingredient: *Phleum pratense* allergen grass-pollen extract	Page:	

SUMMARY OF SAFETY RESULTS

Generally, ALK Grass Tablets were well tolerated with no significant treatment-related systemic AEs. The overall incidence in particular of short-lasting, local treatment-related effects was quite high. Thus, 62 (74%) of the 84 enrolled subjects reported a total of 1013 AEs. The incidence of local, but not systemic AEs clearly increased with the dose administered. All 84 subjects completed the study as planned. There were no deaths and no other serious or significant (leading to withdrawal) AEs. All AEs resolved without sequelae by the end of the study and all subjects completed the study as planned.

The proportion of subjects with possibly or probably treatment-related AEs increased from 19% and 22% for the treatment with placebo and 25,000 SQ-U up to 67% for 75,000 SQ-U and 150,000 SQ-U, each. In contrast, nearly all subjects (89%–100%) at doses between 300,000 and 1,000,000 SQ-U had treatment-related AEs.

All AEs were of mild (870 AEs) or moderate (143 AEs) intensity and were mainly considered to be treatment related (972 AEs). Most treatment-related AEs started immediately after intake of the study medication and lasted for one minute to nearly three hours with a trend towards a shorter daily duration over time. In general AEs affecting the mouth, throat, eyes, and ears (i.e. 'itching sensations') were mainly found during active treatment with the highest incidences for 750,000 SQ-U and 1,000,000 SQ-U. For 300,000 to 1,000,000 SQ-U more than 66% of the subjects reported 'throat irritation' and almost all subjects (89%) had 'oral pruritus' at the two highest doses.

Objective oral findings occurred more frequently, lasted longer and recurred more often for 750,000 SQ-U and 1,000,000 SQ-U, when compared with placebo and the five lowest treatment groups.

Pain and anti-inflammatory medication for the treatment of AEs was required in 13 (15%) of 84 subjects. No other concomitant medications were used for treatment of AEs in any other subject

Clinical laboratory investigations did not reveal any clinically significant findings or changes. There were also no clinically significant findings or changes from baseline in vital sings and 12-lead ECG. Although some 'borderline' QTc intervals of 432–441 ms were recorded, no QTc interval exceeded 450 ms and no individual QTc change from screening was greater than 60 ms during active treatment. The most remarkable finding was a 'prolonged' QTc interval (459 ms) in a placebo subject at the follow-up examination.

The results of the immunological tests will be analysed later and will be presented as an amendment to this report.

Name of Sponsor/Company: ALK-Abelló A/S	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product:	Volume:	
Name of Active Ingredient: *Phleum pratense* allergen grass-pollen extract	Page:	

CONCLUSIONS:

Based on this multiple dose Phase I study, the results showed that:

- The most frequently AEs reported were related to itching sensations in and around the mouth and itching in the eyes and ears. These AEs were primarily mild in intensity, started shortly after medication intake and lasted for minutes to a few hours maximum. The duration of the single AEs tended to decrease over time in individuals having itching sensations on consecutive dosing days.
- The proportion of subjects with treatment-related AEs increased with increasing doses (19% for placebo; 22% for 25,000 SQ-U; 67% for 75,000 SQ-U and 150,000 SQ-U; 89–100% for doses between 300,000 SQ-U and 1,000,000 SQ-U).
- Findings from the oral examination were seen under active treatment only. The proportion of subjects with oral findings increased with increasing doses (0-11% for 25,000 to 500,000 SQ-U; 44% for 750,000 SQ-U and 56% for 1,000,000 SQ-U). In the highest doses these oral findings occurred more frequently, lasted longer and recurred more often up to Day 28 compared with the five lowest doses.
- No clinically significant observations were found in safety laboratory, vital signs and 12-lead ECG over the course of the study.
- There were no deaths and no other serious or significant (leading to withdrawal) AEs. All AEs were of mild to moderate intensity.
- Overall, it can be concluded that the ALK Grass Tablets *Phleum pratense,* given sublingual in dosages between 25,000 and 1,000,000 SQ-U daily can be regarded as safe and well tolerated and is considered to have a safety profile that allows investigation in further clinical trials.

Date of the Report: 28-Oct-2003