Synopsis

TITLE OF TRIAL

A double-blind, randomised, placebo-controlled, parallel group, dose-ranging study assessing the efficacy and safety of grass-pollen allergen tablets once a day in adult subjects with seasonal grass pollen allergic rhinoconjunctivitis

INVESTIGATORS

55 principal investigators in eight countries. [redacted] and [redacted] were appointed signatory investigators

TRIAL SITES

A total of 55 sites participated: 9 in Germany, 2 in Belgium, 8 in Denmark, 8 in Sweden, 5 in Austria, 4 in Norway, 4 in United Kingdom and 15 in Canada

PUBLICATIONS

None

TRIAL PERIOD	**DEVELOPMENT PHASE**
Baseline phase: 20 February 2002 - 23 October 2002 Treatment phase: 7 February 2003 - 8 September 2003	Phase II/III

OBJECTIVES

Primary objective:

- To evaluate the efficacy of specific immunotherapy with three doses of ALK Grass Tablets, 2,500, 25,000 and 75,000 SQ-U (Step 0 trial medication), compared to placebo (Step 0 trial medication), in adult subjects with grass pollen induced allergic rhinoconjunctivitis receiving other active trial medications as needed (Steps 1 to 3 for rhinoconjunctivitis symptoms), based on combined[a] rhinoconjunctivitis symptom and medication score over the season

Key secondary objectives:

- To assess the efficacy of specific immunotherapy with ALK Grass Tablets at 75,000 SQ-U (Step 0 trial medication) compared to placebo (Step 0 trial medication), in subjects receiving placebo Step 1 trial medication, based on rhinoconjunctivitis symptom score[b] over the season
- To assess the efficacy of specific immunotherapy with 75,000 SQ-U ALK Grass Tablets (Step 0) plus placebo (Step 1) compared to placebo (Step 0) with active antihistamine (Step 1), based on the rhinoconjunctivitis symptom score[b] over the season

Additional secondary objectives:

- To assess the dose-effect relationship between the three doses of ALK Grass Tablets (Step 0) and placebo (Step 0), in subjects receiving active antihistamine Step 1 medication, based on the combined[a] rhinoconjunctivitis symptom and medication score over the season
- To evaluate the safety and tolerability of the three doses of ALK Grass Tablets (Step 0) compared to placebo (Step 0)
- To evaluate the efficacy of specific immunotherapy with the three doses of ALK Grass Tablets (Step 0) compared to placebo (Step 0), in subjects receiving active antihistamine (Step 1) medication, using secondary assessments such as overall rhinoconjunctivitis/asthma score, asthma score, rhinoconjunctivitis symptom score, additional trial medication use, grass-pollen induced asthma and quality of life total domain score and pharmacoeconomic assessments

For further details concerning the different treatment groups analysed, see "Number of Subjects Planned and Analysed" and "Statistical Methods".

[a] *The analysis of the combined rhinoconjunctivitis symptom score and medication scores was replaced by separate analyses of the two scores. The primary objective was, however, not changed.*

[b] *An analysis of the rhinoconjunctivitis medication score was also included*

METHODOLOGY

This was a multinational, multicentre, double-blind, randomised, parallel group, placebo-controlled trial. The trial was conducted in countries with a spring grass pollen season and was divided into two phases, a baseline phase during the grass pollen season in year 2002 and a treatment phase in year 2003. The subjects were enrolled into two cohorts (Cohort I and II). Only subjects from Cohort I were enrolled in the baseline phase of the trial (year 2002), and all completed and protocol compliant subjects from the baseline phase were allowed to continue in the treatment phase (year 2003). In year 2003, additional subjects from Cohort I and all subjects from Cohort II were enrolled. The baseline phase in year 2002 consisted of four visits (one screening visit, two on-season visits and one post-season visit). The subjects enrolled in the baseline phase did not receive any trial medication, although rescue medication for relief of rhinoconjunctivitis and asthma symptoms was allowed. The baseline phase was only introduced to allow inclusion of baseline season scores to be used descriptively in the statistical analyses. For further details regarding the baseline phase, see Appendix I (Appendix 8 of the protocol). The treatment phase in year 2003 consisted of six visits and a telephone follow-up. During the treatment phase subjects received double-blind Step 0 medication (2,500, 25,000 or 75,000 SQ-U ALK Grass Tablets or placebo) once daily. In case of continuing symptoms of allergic rhinitis, subjects received additional single-blind Step 1 medication (loratadine or placebo). If this was ineffective or if asthma symptoms were present, subjects were given further, active, open label medication (Steps 2 and 3 for rhinoconjunctivitis symptoms and Steps A and B for asthma symptoms). Step A and B medication were not used in Canada, as no Canadian subjects with asthma were allowed to enter the trial.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

It was planned to enrol a total of approximately 860 subjects (360 subjects in Cohort I and 500 subjects in Cohort II). In total, 1008 subjects were screened, 153 of which were screening failures. The subject disposition and treatment groups for the treatment phase in year 2003 are shown below:

Treatment Group: Step 0 (Grass Tablet)[a]: Step 1 (Loratadine)[b]:	Group 1 Placebo + Active N (%)	Group 2 2,500 SQ + Active N (%)	Group 3 25,000 SQ + Active N (%)	Group 4 75,000 SQ + Active N (%)	Group 5 Placebo + Placebo N (%)	Group 6 75,000 SQ + Placebo N (%)	Overall N (%)
Screened year 2003							1008
Subjects randomised	136(100.0%)	136(100.0%)	139(100.0%)	141(100.0%)	150(100.0%)	153(100.0%)	855(100.0%)
Safety analysis set	136(100.0%)	136(100.0%)	139(100.0%)	141(100.0%)	150(100.0%)	153(100.0%)	855(100.0%)
ITT analysis set	136(100.0%)	136(100.0%)	139(100.0%)	141(100.0%)	150(100.0%)	153(100.0%)	855(100.0%)
PP analysis set	122(89.7%)	122(89.7%)	125(89.9%)	124(87.9%)	128(85.3%)	127(83.0%)	748(87.5%)
Completed study	126(92.6%)	128(94.1%)	130(93.5%)	129(91.5%)	139(92.7%)	138(90.2%)	790(92.4%)
Withdrawn after randomis.	10(7.4%)	8(5.9%)	9(6.5%)	12(8.5%)	11(7.3%)	15(9.8%)	65(7.6%)
Reason for withdrawal							
Adverse event	1(0.7%)	4(2.9%)	4(2.9%)	7(5.0%)	2(1.3%)	7(4.6%)	25(2.9%)
Adverse event-not by inv.	0(0.0%)	0(0.0%)	0(0.0%)	1(0.7%)	0(0.0%)	0(0.0%)	1(0.1%)
Physician decision	0(0.0%)	0(0.0%)	1(0.7%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.1%)
Subject consent withdrawn	0(0.0%)	1(0.7%)	0(0.0%)	1(0.7%)	2(1.3%)	1(0.7%)	5(0.6%)
Non-compliance study drug	1(0.7%)	1(0.7%)	1(0.7%)	0(0.0%)	1(0.7%)	1(0.7%)	5(0.6%)
Sponsor request	0(0.0%)	1(0.7%)	0(0.0%)	0(0.0%)	1(0.7%)	1(0.7%)	3(0.4%)
Lack of efficacy	0(0.0%)	0(0.0%)	1(0.7%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.1%)
Protocol deviation	1(0.7%)	0(0.0%)	0(0.0%)	1(0.7%)	0(0.0%)	1(0.7%)	3(0.4%)
Adm. of excluded med.	1(0.7%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.7%)	0(0.0%)	2(0.2%)
Lost to follow-up	2(1.5%)	1(0.7%)	1(0.7%)	0(0.0%)	2(1.3%)	3(2.0%)	9(1.1%)
Insuff. therapeutic effect	2(1.5%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.7%)	0(0.0%)	3(0.4%)
Other	2(1.5%)	0(0.0%)	1(0.7%)	2(1.4%)	1(0.7%)	1(0.7%)	7(0.8%)

[a] Step 0 Medication = ALK Grass Tablet active or placebo.
[b] Step 1 Medication = Active (Loratadine 10 mg) or placebo.
inv.: investigator
N = Number of subjects. % = Percent subjects of randomised subjects

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Male or female subjects 18-65 years of age with significant grass pollen induced allergic rhinoconjunctivitis of two years or more, and with positive skin prick test and specific antigen IgE to *Phleum pratense.* Furthermore, an adequate level of symptomatology in the previous pollen season (year 2002) was required.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Step 0 medication:
ALK Grass Tablets *Phleum pratense* 2,500 SQ-U (4 µg grass allergen extract). Batch no. 21631AHC
ALK Grass Tablets *Phleum pratense* 25,000 SQ-U (40 µg grass allergen extract). Batch no. 21629AHD
ALK Grass Tablets *Phleum pratense* 75,000 SQ-U (120 µg grass allergen extract). Batch nos. 22334AHE, 22736AHE, 21750AHE and 21749AHE
The ALK Grass Tablet was administered once daily sublingually.

DURATION OF TREATMENT

The treatment was initiated approximately eight 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

Step 0 medication:
Placebo ALK Grass Tablet. Batch no. 21845AHL. The placebo tablet was administered once daily sublingually.
Step 1 medication:
Loratadine 10 mg. Batch no. 78012-081. Loratadine was administered orally once daily as needed.
Placebo loratadine. Batch no. 78012-079. The placebo tablet was administered orally once daily as needed.
Steps 2-3 and A-B medication:
Commercially available preparations were used: Budesonide nasal spray for Step 2, prednisolone/prednisone tablets for Step 3, salbutamol inhalation for Step A and fluticasone inhalation (and prednisolone/prednisone tablets) for Step B.

CRITERIA FOR EVALUATION – EFFICACY

Rhinoconjunctivitis symptom score, rhinoconjunctivitis medication score, asthma symptom score and asthma medication score, visual analogue scale (VAS) score, well days

CRITERIA FOR EVALUATION – SAFETY

Adverse events, physical examination, spirometry to measure forced expiratory volume in one second (FEV_1), vital signs, safety laboratory assessments (haematology, urinalysis and chemistry) and ECG

CRITERIA FOR EVALUATION – OTHER ASSESSMENTS

Quality of life, pharmacoeconomics and immunological assessments

STATISTICAL METHODS

Four analysis sets were defined:

- The intention-to-treat (ITT) analysis set (full analysis set) defined as all randomised subjects.
- The per-protocol (PP) analysis set defined as all subjects randomised, who had been exposed to at least one dose of trial medication and who completed the trial, took sufficient trial medication (defined as at least 80% on days with non-missing diary data) and who provided sufficient diary data (defined as at least 30% of diary data distributed over at least 50% of the weeks in the entire pollen season).
- The baseline phase analysis set defined as all subjects participating in the baseline phase (year 2002).
- The safety analysis set defined as all subjects exposed to at least one dose of trial medication (ALK Grass Tablet or matching placebo). As the safety analysis set and the ITT analysis set are identical only the ITT analysis set is used.

All statistical analyses and confidence intervals were two-sided and a significance level of 5% was used.
The primary efficacy endpoint (the average rhinoconjunctivitis symptom and medication scores for the entire pollen season) was analysed for Groups 2-4 versus Group 1 by an ANOVA with average rhinoconjunctivitis symptom score or rhinoconjunctivitis medication score as response variable and treatment group and pollen region as fixed effects. In addition, two ANOVAs on transformed response variables were performed, one for the logarithm and one for the square root.
The key secondary efficacy endpoint (average rhinoconjunctivitis symptom and medication scores for the entire as well as the peak pollen season) was compared between Groups 1, 5 and 6 (i.e. Group 6 versus Group 5 and Group 6 versus

STATISTICAL METHODS - Continued

Group 1) by an ANOVA with the average rhinoconjunctivitis symptom score as well as the average rhinoconjunctivitis medication score in the entire as well as in the peak pollen season as response variable and with treatment group and pollen region as fixed effects.

An analysis of the average rhinoconjunctivitis symptom score in a period censored by the first intake of Steps 2, 3 or B medication was made in a similar way comparing Groups 6 and 5 and Groups 6 and 1, respectively.

The dose-effect relationship (for the average rhinoconjunctivitis symptom and medication scores) was pair wise compared between Groups 1-4 by an ANOVA similar to the one used for the primary efficacy analysis. The asthma symptom and medication scores were analysed by an ANOVA with treatment group and pollen region as fixed effects in the same way and with the same pair wise comparisons as described for the primary and key secondary efficacy analysis.

Quality of life questionnaire scores were analysed for the two on-season visits and the post-season visit by a repeated measurement analysis with the same pair wise comparisons as for the dose-effect relationship and the key secondary efficacy analysis. The model included treatment, pollen region, visit and the interaction treatment x visit as fixed effects. Subjects were included as a random effect and screening visit values as a covariate. Pre-season visit, start of season visit, the two on-season visits and the post-season visits were included as response in the model. The modelling for the treatment group was done separately and therefore there were two models with different pair wise comparisons.

VAS scores (for both asthma and hayfever) were analysed in the same way and with the same pair wise comparisons as for the dose-effect relationship and the key secondary efficacy analysis. The modelling for the treatment group was done as for the quality of life analysis.

Time from start of season to first use of Steps 1, 2, 3, A and B medication (the relative risk) was analysed as a Cox proportional hazard model including treatment (Groups 5 and 6) and pollen region as fixed effects. Kaplan Meier plots were also made.

The percentage of well days (days with no intake of Steps 1-3 and A-B medication and with a rhinoconjunctivitis symptoms score no larger than 2) was analysed in the same way and with the same pair wise comparisons as for the analysis of the VAS scores.

In addition to the pre-defined efficacy analyses, further efficacy analyses were made after unblinding of the trial:

An analysis identical to the primary efficacy analysis as well as the uncensored part of the key secondary efficacy analysis was performed on the ITT analysis set excluding subjects not having received at least eight weeks of pre-seasonal treatment with the ALK Grass Tablet. A pooled analysis merging Groups 1 and 5 as well as Groups 4 and 6 were performed on the ITT analysis set in the same way as the primary efficacy analysis including the allowed use of Step 1 medication (active/placebo) as a fixed effect. A pooled analysis as the one described above was also performed on the ITT analysis set excluding subjects not having received at least eight weeks of pre-seasonal treatment with the ALK Grass Tablet.

Adverse events, FEV_1, vital signs and physical examination were evaluated by summary statistics. Safety laboratory parameters (haematology, urinalysis and chemistry) were evaluated by shift tables.

Pharmacoeconomic data and immunological parameters are analysed in separate reports.

DEMOGRAPHY OF TRIAL POPULATION

Baseline characteristics for all subjects exposed are shown below.

Treatment Group: Step 0 (Grass Tablet)[a]: Step 1 (Loratadine)[b]:	Group 1 Placebo + Active N (%)	Group 2 2,500 SQ + Active N (%)	Group 3 25,000 SQ + Active N (%)	Group 4 75,000 SQ + Active N (%)	Group 5 Placebo + Placebo N (%)	Group 6 75,000 SQ + Placebo N (%)	Overall N (%)
Sex							
Male	89(65.4%)	84(61.8%)	92(66.2%)	84(59.6%)	89(59.3%)	95(62.1%)	533(62.3%)
Female	47(34.6%)	52(38.2%)	47(33.8%)	57(40.4%)	61(40.7%)	58(37.9%)	322(37.7%)
Race							
White, not Hispanic	129(94.9%)	131(96.3%)	130(93.5%)	135(95.7%)	133(88.7%)	136(88.9%)	794(92.9%)
Black, not Hispanic	4(2.9%)	1(0.7%)	2(1.4%)	3(2.1%)	10(6.7%)	5(3.3%)	25(2.9%)
Asian or Pacific Islander	0(0.0%)	3(2.2%)	3(2.2%)	1(0.7%)	3(2.0%)	10(6.5%)	20(2.3%)
Hispanic	1(0.7%)	1(0.7%)	0(0.0%)	2(1.4%)	0(0.0%)	0(0.0%)	4(0.5%)
Other	2(1.5%)	0(0.0%)	4(2.9%)	0(0.0%)	4(2.7%)	2(1.3%)	12(1.4%)
Country							
Germany	30(22.1%)	28(20.6%)	26(18.7%)	30(21.3%)	0(0.0%)	0(0.0%)	114(13.3%)
Belgium	6(4.4%)	6(4.4%)	6(4.3%)	6(4.3%)	0(0.0%)	0(0.0%)	24(2.8%)
Denmark	19(14.0%)	21(15.4%)	25(18.0%)	24(17.0%)	0(0.0%)	0(0.0%)	89(10.4%)
Sweden	32(23.5%)	30(22.1%)	34(24.5%)	32(22.7%)	0(0.0%)	0(0.0%)	128(15.0%)
Austria	7(5.1%)	9(6.6%)	6(4.3%)	10(7.1%)	25(16.7%)	29(19.0%)	86(10.1%)
Norway	7(5.1%)	8(5.9%)	8(5.8%)	7(5.0%)	24(16.0%)	25(16.3%)	79(9.2%)
United Kingdom	11(8.1%)	11(8.1%)	10(7.2%)	9(6.4%)	30(20.0%)	29(19.0%)	100(11.7%)
Canada	24(17.6%)	23(16.9%)	24(17.3%)	23(16.3%)	71(47.3%)	70(45.8%)	235(27.5%)
Age (years)							
N	136	136	139	141	150	153	855
Mean (SD)	33.4(9.2)	34.2(9.2)	34.2(9.8)	36.5(9.3)	36.0(10.5)	36.1(10.9)	35.1(9.9)
Median	33.1	33.5	32.4	36.0	35.4	34.9	34.3
P5% - P95%	20.5-50.4	21.4-53.0	21.4-55.7	21.7-54.1	20.6-54.6	20.1-55.3	20.9-54.0
Min - Max	18 - 61	18 - 61	19 - 59	19 - 62	18 - 64	18 - 66	18 - 66
Weight (kg)							
N	136	136	139	141	150	153	855
Mean (SD)	74.6(15.3)	73.6(12.2)	74.8(13.9)	75.1(13.0)	79.7(16.0)	75.9(14.7)	75.7(14.4)
Median	72.6	74.1	75.0	72.8	78.7	75.0	75.0
P5% - P95%	53.0-106.0	55.0-95.0	54.0-97.0	56.0-98.0	54.0-109.0	54.0-98.0	54.4-100.0
Min - Max	43 - 116	45 - 109	45 - 119	45 - 126	49 - 130	48 - 118	43 - 130
BMI (kg/m²)							
N	136	136	139	141	150	153	855
Mean (SD)	24.2(3.8)	24.2(2.9)	24.4(3.6)	24.4(3.5)	26.0(4.5)	25.2(4.0)	24.8(3.8)
Median	23.5	24.5	24.1	23.9	25.8	24.6	24.3
P5% - P95%	19.3-32.1	19.1-29.9	19.4-31.6	19.9-29.8	19.5-33.5	19.3-31.7	19.4-31.9
Min - Max	18 - 37	17 - 32	18 - 35	17 - 37	18 - 42	17 - 39	17 - 42
History of Allergy to Grass (years)							
N	45	60	53	54	84	87	383
Mean (SD)	18.2(10.9)	17.2(11.2)	17.4(10.4)	19.2(12.1)	22.6(12.9)	20.5(12.9)	19.6(12.1)
Median	16.0	14.0	15.0	17.0	21.0	18.0	17.0
P5% - P95%	4.0-36.0	4.0-42.5	4.0-39.0	5.0-43.0	4.0-43.0	5.0-44.0	4.0-43.0
Min - Max	2.0-43.0	2.0-50.0	3.0-43.0	3.0-53.0	3.0-56.0	0.0-50.0	0.0-56.0
Other Allergic History (years)							
N	105	99	104	105	107	99	619
Mean (SD)	18.4(11.7)	17.8(11.9)	17.1(11.2)	20.4(13.5)	18.4(14.7)	20.4(14.4)	18.7(13.0)
Median	16.0	15.0	15.0	19.0	18.0	18.0	16.0
P5% - P95%	1.0-42.0	0.0-42.0	0.0-39.0	2.0-43.0	0.0-43.0	0.0-43.0	0.0-43.0
Min - Max	0.0-47.0	0.0-43.0	0.0-43.0	0.0-52.0	0.0-54.0	0.0-49.0	0.0-54.0

[a] Step 0 Medication = ALK Grass Tablet active or placebo. [b] Step 1 Medication = Active (Loratadine 10 mg) or placebo. N = Number of subjects. % = Percent of subjects.
If history of allergy to grass was not recorded the history was more than 2 years.

EFFICACY RESULTS

Overall Summary of Efficacy Results

- Overall, the comparison of efficacy between three doses of ALK Grass Tablets (2,500 SQ-U, 25,000 SQ-U and 75,000 SQ-U) and placebo showed a dose related response with highest reductions in the rhinoconjunctivitis symptoms and medication scores for the ALK Grass Tablet 75,000 SQ-U when compared to placebo.
- All efficacy analyses (both pre-defined and additional analyses) supported the clinical efficacy of the ALK Grass Tablet 75,000 SQ-U.

Primary Efficacy Analysis

- The primary efficacy analysis showed that the ALK Grass Tablet 75,000 SQ-U (Group 4) provided a reduction of approximately 16% in the rhinoconjunctivitis symptoms when compared with placebo (Group 1) (not statistically significant, p=0.071).
- A reduction of approximately 28% in the rhinoconjunctivitis medication score (p=0.047) was found with the ALK Grass Tablet 75,000 SQ-U (Group 4) when compared with placebo (Group 1). However, due to the hierarchical structure of the testing procedure used no claim of significance can be made despite the high reduction in use of medication and the low p-value.
- Analysis on square root transformed average rhinoconjunctivitis scores showed statistically significant reductions of both the symptom and medication score for the ALK Grass Tablet 75,000 SQ-U (Group 4) when compared to placebo (Group 1) (p=0.034 and p=0.009, respectively).

Key Secondary Efficacy Analysis

- The ALK Grass Tablet 75,000 SQ-U (Group 6) reduced both the average symptom and medication score compared to placebo (Group 5). The reductions were approximately 13% (p=0.088) and 30% (p=0.017), respectively.
- No differences in efficacy were found between the ALK Grass Tablet 75,000 SQ-U (Group 6) and active loratadine (Group 1).

Dose-Effect Relationship

- Dose-effect relationships for the symptom and medications scores were indicated for the ALK Grass Tablet with lower rhinoconjunctivitis symptom and medication scores for the ALK Grass Tablet 75,000 SQ-U (Group 4) when compared to placebo and to the lower doses of the ALK Grass Tablet (Groups 1-3).

Other Analyses

- Statistically significant better rhinoconjunctivitis quality of life was obtained after treatment with the ALK Grass Tablet 75,000 SQ-U when compared to treatment with placebo (Group 4 versus Group 1) and treatment with active loratadine (Group 6 versus Group 1). The quality of life for subjects treated with the ALK Grass Tablet 75,000 SQ-U was estimated to be 17-20% better than the quality of life for subjects treated with placebo and 26% better than the quality of life for subjects treated with active loratadine.
- A statistically significant higher percentage of well days in the pollen season (p=0.041) was obtained for subjects treated with ALK Grass Tablet 75,000 SQ-U (Group 4) when compared to placebo (Group 1).
- A statistically significant lower hay fever VAS score (p=0.004) was obtained for the ALK Grass Tablet 75,000 SQ-U when compared with placebo in subjects receiving placebo Step 1 medication (Group 6 versus Group 5).
- Reduced risks of taking Steps 1, 2, 3, A and B medication were found for the ALK Grass Tablet 75,000 SQ-U relative to placebo (Groups 6 versus Group 5) and relative to active loratadine (Group 6 versus Group 1), although these differences were not statistical significant.

Additional Analyses

- For subjects treated with the ALK Grass Tablet 75,000 SQ-U for at least eight weeks pre-season, reductions in the rhinoconjunctivitis symptom and medication scores were observed when compared to placebo. This was shown both for subjects treated with active Step 1 medication (Group 4 versus Group 1) (reduction in symptom score=21%, p=0.027; medication score=29%, p=0.064) and for subjects treated with placebo Step 1 medication (Group 6 versus Group 5) (reduction in symptom score=19%, p=0.05; medication score=28%, p=0.071).
- Pooled data, where Groups 4 and 6 and Groups 1 and 5 were merged (i.e. the number of subjects included in the analysed groups was increased) showed statistically significant reductions in the rhinoconjunctivitis symptom and medication score for the ALK Grass Tablet 75,000 SQ-U when compared to placebo (15%, p=0.014 and 29%, p=0.003, respectively).

EFFICACY RESULTS - Continued

- An analysis based on pooled data and only including subjects treated for more than eight weeks pre-season confirmed the results obtained in the two separate analyses with statistical significant reductions in the rhinoconjunctivitis symptom and medication scores of 21% (p=0.002) and 29% (p=0.012), respectively for the ALK Grass Tablet 75,000 SQ-U (Group 4/6) compared to placebo (Group 1/5).

SAFETY RESULTS

- Treatment with the ALK Grass Tablet in doses up to 75,000 SQ-U was generally well tolerated.
- The most frequently reported related adverse events were events in the mouth and throat, primarily oral pruritus and throat irritation.
- The majority of the events related to oral sensations had onset within the first day after start of treatment.
- The majority of the related adverse events was reported in subjects treated with the ALK Grass Tablet 25,000 SQ-U and 75,000 SQ-U and were mild or moderate in severity.
- One drug related serious adverse event was reported (uvula oedema in the 25,000 SQ-U group).
- Withdrawals due to adverse events were infrequent; the majority of the withdrawals were due to events in the mouth or throat.
- No safety concerns were observed for any of the clinical laboratory parameters, vital signs, physical examination or FEV_1.

CONCLUSIONS

- Overall, the comparison of efficacy between three doses of ALK Grass Tablets (2,500 SQ-U, 25,000 SQ-U and 75,000 SQ-U) and placebo showed a dose related response with highest reductions in the rhinoconjunctivitis symptom and medication scores for the ALK Grass Tablet 75,000 SQ-U when compared to placebo.
- All efficacy analyses showed consistent reductions in the rhinoconjunctivitis symptom and medication score for the ALK Grass Tablet 75,000 SQ-U when compared to placebo.
- For subjects with at least eight weeks pre-seasonal treatment with the ALK Grass Tablet 75,000 SQ-U, statistically significant and clinically relevant reductions in rhinoconjunctivitis symptom and medication scores were found.
- Statistically significant better rhinoconjunctivitis quality of life was obtained after treatment with the ALK Grass Tablet 75,000 SQ-U when compared to treatment with placebo and treatment with loratadine.
- A statistically significant higher percentage of well days in the pollen season was obtained for subjects treated with ALK Grass Tablet 75,000 SQ-U when compared to placebo.
- The most frequently reported related adverse events were events in the mouth and throat and were mild or moderate in severity.
- One drug related serious adverse event was reported (uvula oedema in the 25,000 SQ-U group).
- Treatment with the ALK Grass Tablet in doses up to 75,000 SQ-U was generally well tolerated.

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