GT-08 Integrated Clinical Trial Report

Pollen Season 2005

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

Investigational Medicinal Product: ALK Grass tablet *Phleum pratense*

Clinical trial ID:	GT-08
EudraCT No.	2004-000083-27
Indication:	Seasonal allergic rhinoconjunctivitis caused by grass pollen
Development Phase:	III
First subject first visit:	30 September 2004
Last subject last visit:	9 September 2005
Investigators:	*Coordinating Investigators*: [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD
Trial centres:	51 sites from 8 countries (AU, DE, DK, ES, IT, NL, SE, UK)
Sponsor:	Group Clinical Development ALK-Abelló A/S DK-2970 Hørsholm, Denmark
Trial Manager:	[redacted], MSc, ALK-Abelló A/S
Report No. and date:	GT-08 Integrated Trial Report Pollen Season 2005. 24 October 2005

This trial was conducted in compliance with the principles of *Good Clinical Practice*.

Synopsis GT-08 Pollen Season 2005

Title of Trial

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

Investigators

51 investigators in 8 countries. [redacted] MD (AU), [redacted] MD (DE), [redacted] MD (DK), [redacted] MD (ES), [redacted] MD (IT), [redacted] MD (NL), [redacted] MD (SE) and [redacted] MD (UK) were appointed coordinating investigators in their respective countries.

Trial Centres

51 sites participated: 3 in Austria, 10 in Germany, 10 in Denmark, 3 in Spain, 6 in Italy, 5 in the Netherlands, 4 in Sweden and 10 in United Kingdom.

Publications

None

Trial Period

First subject first visit – 30 September 2004

Last subject last visit – 9 September 2005

Objectives

Primary Objective:
To evaluate the efficacy of specific immunotherapy with the 75,000 SQ-T ALK Grass tablet compared to placebo in subjects with grass pollen induced rhinoconjunctivitis, based on the rhinoconjunctivitis symptom score as well as the rhinoconjunctivitis medication score during the grass pollen season 2005.

Main Secondary Objectives:
To evaluate the efficacy of specific immunotherapy with the 75,000 SQ-T ALK Grass tablet compared to placebo in subjects with grass pollen induced rhinoconjunctivitis during the grass pollen season 2005 based on:

- Rhinoconjunctivitis symptom and medication score during the peak grass pollen season 2005
- Quality of Life (QoL) in the entire grass pollen season 2005
- Number of well days in the entire grass pollen season 2005 and in the peak grass pollen season 2005 (well day= no rescue medication and symptom score ≤2)
- Rhinoconjunctivitis symptoms on visual analogue scale (VAS)
- Global Evaluation of rhinoconjunctivitis symptoms in the grass pollen season 2005
- Global Evaluation of rhinoconjunctivitis symptoms in the grass pollen season 2005 compared to symptoms in the grass pollen season 2004
- Excellence of rhinoconjunctivitis control during the entire grass pollen season 2005 (excellent rhinoconjunctivitis control = more than 50% well days in the grass pollen season)

Further, to evaluate the safety and tolerability of the 75,000 SQ-T ALK Grass tablet compared to placebo in 2005.

Methodology

This was a randomised, parallel group, double-blind, placebo-controlled, multi-centre trial. The trial was initiated in the autumn 2004 and the subjects received the ALK Grass tablet for 4-6 months prior to the grass pollen season and during the grass pollen season 2005. The subjects were randomised (1:1) to receive either ALK Grass tablet 75,000 SQ-T or placebo once daily. Double-blind treatment continues for additionally 2 years followed by 2 years of follow-up.

Number of Subjects Planned and Analysed

It was planned to enrol 600 subjects, 300 in each group. In total 888 subjects were screened, 254 of which were screening failures. The subject distribution and treatment groups are presented below:

Treatment Group	75,000 SQ-T		Placebo		Overall	
	N	(%)	N	(%)	N	(%)
Screened					888	
Full Analysis Set	316	(100)	318	(100)	634	(100)
Completed Year 1	274	(87)	272	(86)	546	(86)
Withdrawn from Year 1	42	(13)	46	(14)	88	(14)
Reasons for withdrawal:						
Adverse event	16	(5)	8	(3)	24	(4)
Death					1*	(0)
Lack of efficacy					1	(0)
Lost to follow-up	5	(2)	7	(2)	12	(2)
Other	6	(2)	14	(4)	20	(3)
Pregnancy					3	(0)
Subject non-compliance	4	(1)	10	(3)	14	(2)
Withdrawal of consent	9	(3)	4	(1)	13	(2)
Withdrawal initiated by:						
Investigator	8	(3)	9	(3)	17	(3)
Sponsor	3	(1)	8	(3)	11	(2)
Subject	31	(10)	29	(9)	60	(9)
Continued in extension	188	(59)	163	(51)	351	(55)

N=number of subjects, %=percent of subjects, *Not related to the ALK Grass tablet

Main Inclusion Criteria

Males or females 18-65 years of age fulfilling the following criteria:

- A clinical history of grass pollen induced allergic rhinoconjunctivitis of 2 years or more requiring treatment during the grass pollen season.
- A clinical history of severe rhinoconjunctivitis symptoms (interfering with usual daily activities or sleep), which remain troublesome despite treatment with anti-allergic drugs during the grass pollen season.
- Positive Skin Prick Test (SPT) response (wheal diameter ≥ 3 mm) to *Phleum pratense* and positive specific IgE against *Phleum pratense* (≥ IgE Class 2).
- $FEV_1 \geq 70\%$ of predicted value.
- No clinical history of symptomatic seasonal allergic rhinitis and/or asthma due to tree pollen or weed pollen adjacent to the start of – and potentially overlapping - the grass pollen season.
- No clinical history of significant active perennial allergic rhinitis and/or asthma caused by an allergen to which the subject is regularly exposed.

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number

ALK Grass tablets 75,000 SQ-T (*Phleum pratense*, 15 µg phl p5)

Oral lyophilisate, for sublingual administration once daily.

Batch Numbers
141292/141302
141293/141308
141295/141326
141296/141327

Reference Therapy, Dose and Mode of Administration, Batch Number

ALK Grass tablets Placebo

Oral lyophilisate, for sublingual administration once daily.

Batch Numbers
141329/141333
141331/141335
141330/141334

Duration of Treatment

For every subject the treatment started at least 4-6 months prior to the anticipated start of the grass pollen season. All subjects received treatment throughout the pollen season, and 351 subjects are continuing double-blind treatment for additionally 2 years.

Criteria for Evaluation Year 2005– Efficacy

The primary efficacy endpoints were the average daily rhinoconjunctivitis symptom score as well as the average daily rhinoconjunctivitis medication score. These 2 average scores were calculated for each subject as the average of the observed total daily scores throughout the entire grass pollen season 2005.

Secondary efficacy endpoints were:
The average daily rhinoconjunctivitis symptom and medication score in the peak pollen season 2005.
The percentage of “well days” in the entire pollen season 2005.
The percentage of “well days” in the peak pollen season 2005.
The average daily VAS score over the entire pollen season 2005.
The average daily VAS score over the peak pollen season 2005.
The total weekly overall RQLQ score for the entire pollen season 2005.
Global evaluation of most severe rhinoconjunctivitis symptoms during the grass pollen season 2005 assessed at end of the season visit.
Global evaluation of rhinoconjunctivitis symptoms in the grass pollen season 2005 compared to previous seasons.

Additional endpoint: "excellent rhinoconjunctivitis control" defined as more than 50% well days in the grass pollen season.

Criteria for Evaluation – Safety

Adverse events (AEs) were the only safety parameter evaluated in this report.

Statistical Methods

The following analysis sets were used:

- *Full-Analysis Set* (FAS) – comprising all subjects randomised following the Intention to Treat (ITT) ICH principle. The FAS was the primary set for analysis.
- *Per-Protocol Set* (PP) – comprising subjects without major protocol deviations.

Defined major protocol deviations were incorrect administration of the trial medication or non-attendance at trial assessments and non-compliance with the diary that significantly affects the outcome of the data. Consequently the PP analysis set comprise subjects who:

1. Did not take prohibited medication
2. Had sufficient pre-seasonal treatment defined as at least 20 weeks treatment prior to the start of the pollen season
3. Had sufficient drug compliance defined as a drug compliance of at least 80%, i.e. number of tablets used compared to number of treatment days
4. Provided sufficient diary data defined as at least 50% of diary data in the pollen season

All statistical analyses were carried out by an independent CRO [redacted] to ensure that ALK-Abelló trial personnel and other external personnel associated with the trial remained blinded through the entire trial period. To ensure the blinding, it was decided that if less than 2 observations per treatment group were available, only the overall result was presented in the tables and only the 5 and the 95 percentile displayed. Minimum and maximum values were left out.

The 2 treatment groups compared were placebo and ALK Grass tablets 75,000 SQ-T. The approach to the multiple comparisons with 2 primary endpoints was a hierarchical ordering of the null hypotheses. Hence, no statistical conclusions were based on test of a null hypothesis that had a rank lower than or equal to the null hypothesis that was the first not to be rejected.

The ranking of the null hypotheses was as follows:

1. 75,000 SQ-T versus placebo on rhinoconjunctivitis symptom score
2. 75,000 SQ-T versus placebo on rhinoconjunctivitis medication score

Hence, the outcome of rhinoconjunctivitis symptom score alone defines whether the trial has failed or succeeded in confirming treatment efficacy. As the ranking of null hypotheses has been pre-specified no formal adjustment of the statistical significance is necessary.

The primary investigation of the comparison of the 2 treatment groups was done via an analysis of variance (ANOVA) with the average rhinoconjunctivitis symptom score or the average rhinoconjunctivitis medication score as response variable and treatment group as a fixed effect and pollen region as random effect, as well as adjusting for different error variation for each treatment group. A 2-sided 95%-confidence interval for the difference in adjusted means between the 2 groups is presented as well as the coherent p-value. Also the difference in adjusted means between the 2 treatment groups relative to the adjusted mean of the placebo group is presented as a percentage. A p-value describing the statistical significance of the pollen region is also presented.

Demography of Trial Population

Generally, the demographics, baseline characteristics, baseline measurements and vital signs were all well balanced between the 2 treatment groups; including grass pollen allergy severity and years since grass pollen allergy was diagnosed.

Treatment Group	75,000 SQ-T		Placebo		Overall	
	N	(%)	N	(%)	N	(%)
Number of Subjects	316		318		634	
Sex						
N	316		318		634	
Men	179	(57)	193	(61)	372	(59)
Women	137	(43)	125	(39)	262	(41)
Age (Years)						
N	316		318		634	
Mean (SD)	33.8	(9.6)	34.5	(10.0)	34.2	(9.8)
Median	33.0		33.0		33.0	
Q5% - Q95%	21	- 53	20	- 54	20	- 53
Ethnic Origin						
N	316		318		634	
African	2	(1)	4	(1)	6	(1)
Asian	8	(3)	3	(1)	11	(2)
Caucasian	299	(95)	308	(97)	607	(96)
Other	7	(2)	3	(1)	10	(2)
Country						
N	316		318		634	
Austria	13	(4)	12	(4)	25	(4)
Denmark	60	(19)	62	(19)	122	(19)
Germany	77	(24)	75	(24)	152	(24)
Italy	34	(11)	36	(11)	70	(11)
Netherlands	19	(6)	21	(7)	40	(6)
Spain	24	(8)	22	(7)	46	(7)
Sweden	32	(10)	31	(10)	63	(10)
United Kingdom	57	(18)	59	(19)	116	(18)
Grass Pollen Allergy (Severity):						
N	316		318		634	
Moderate	137	(43)	144	(45)	281	(44)
Severe	179	(57)	174	(55)	353	(56)
Grass Pollen Allergy (Years):						
N	313		316		629	
Mean (SD)	15.9	(9.8)	15.7	(10.4)	15.8	(10.1)
Median	14.0		14.5		14.0	
Q5% - Q95%	3	- 34	2	- 36	2	- 35

N=number of subjects, %=percent of subjects

Efficacy Results

Overall, the comparison of efficacy between the ALK Grass tablet 75,000 SQ-T and placebo showed highly statistically significant improvements in favour of the ALK Grass tablet for all efficacy endpoint. These improvements were confirmed by the PP analyses.

Primary Efficacy Analysis

The primary efficacy analysis showed that the ALK Grass tablet 75,000 SQ-T provided a reduction of 30% in rhinoconjunctivitis symptom score and a reduction of 38% in rhinoconjunctivitis medication score when compared with placebo. Both reductions were highly statistically significant (p<0.0001).

Secondary efficacy Analyses

All analyses of the secondary endpoints were in favour of the ALK Grass tablet.

- Rhinoconjunctivitis symptom and medication score in the peak pollen season were statistically significantly reduced by 26% and 36% respectively (p<0.0001) when compared with placebo.
- The percentage of well days in the entire as well as the peak pollen season statistically significantly increased by 21% and 20% when compared with placebo (p<0.0001 and p=0.0043).
- The rhinoconjunctivitis symptom VAS score in the entire as well as the peak pollen season was statistically significantly reduced by 31% and 30% when compared to placebo (p<0.0001).
- Rhinoconjunctivitis quality of life was improved (reduced RQLQ score) by 23% with the ALK Grass tablet when compared to placebo (p<0.0001)
- The global evaluation of rhinoconjunctivitis symptoms at the end of the pollen season 2005 were 21% better with the ALK Grass tablet compared to placebo (p<0.0001)
- The comparison of rhinoconjunctivitis symptoms in previous grass pollen seasons with the grass pollen season 2005 showed a significantly higher improvement of 49% with the ALK Grass tablet when compared to placebo.

Treatment Group	75,000 SQ-T		Placebo	
	N	(%)	N	(%)
Number of Subjects	316		318	
Overall symptom assessment of 2005 compared to previous seasons:				
Number of subjects	283		284	
MUCH BETTER	96	(35)	45	(16)
BETTER	132	(47)	106	(39)
THE SAME	41	(15)	89	(32)
WORSE	7	(3)	25	(9)
MUCH WORSE	2	(1)	10	(4)
Improved	228	(82)	151	(55)
Not improved	50	(18)	124	(45)

N=number of subjects, %=percent of subjects

Additional Endpoint

The additional endpoint of excellent rhinoconjunctivitis control showed that 54% of subjects treated with the ALK Grass tablet and 36% of subjects treated with placebo obtained excellent rhinoconjunctivitis control. The 49% difference between the ALK Grass tablet and placebo were highly significant (p<0.0001).

All efficacy results are summarised below.

Endpoint (FAS)	75,000 SQ-T mean	Placebo mean	p-value	Reduction *
Rhinoconjunctivitis symptom score	**2.36**	**3.37**	**<0.0001**	**30 %**
Rhinoconjunctivitis symptom score peak pollen season	3.19	4.31	<0.0001	26%
Rhinoconjunctivitis medication score	**1.38**	**2.23**	**<0.0001**	**38 %**
Rhinoconjunctivitis medication score peak pollen season	1.85	2.89	<0.0001	36%
Percentage well days	54%	45%	<0.0001	21%
Percentage well days peak pollen season	42%	35%	0.0043	20%
Rhinoconjunctivitis symptom VAS score	12	17	<0.0001	31%
Rhinoconjunctivitis symptom VAS score peak pollen season	16	23	<0.0001	30%
RQLQ score	0.84	1.08	<0.0001	23%
Global evaluation of rhinoconjunctivitis symptoms	7.09	8.95	<0.0001	21%
Global improvement of rhinoconjunctivitis symptoms	0.82	0.55	<0.0001	49%
Excellent rhinoconjunctivitis control	0.543	0.364	<0.0001	49%

FAS=full analysis set, VAS=visual analogue scale, RQLQ=rhinoconjunctivitis quality of life questionnaire,

**Reduction* = $\left|\frac{Active - Placebo}{Placebo}\right| \times 100$

Safety Results

- Treatment with the ALK Grass tablet was well tolerated.
- The most frequently reported related adverse events were events in the mouth and throat.
- The majority of the related adverse events were reported by subjects treated with the ALK Grass tablet 75,000 SQ-T and they were mild or moderate in severity.
- No drug related serious adverse event was reported.
- No severe systemic adverse events were reported.
- Withdrawals due to adverse events were infrequent; the majority of the withdrawals were due to events in the mouth or throat.

The AE incidence is summarised below:

Treatment Group	75,000 SQ-T			Placebo			Overall		
	N	(%)	E	N	(%)	E	N	(%)	E
Number of Subjects	316			318			634		
All Adverse Events	265	(84)	824	205	(64)	507	470	(74)	1331
Causality:									
Probable Related	212	(67)	419	27	(8)	39	239	(38)	458
Possible Related	74	(23)	104	47	(15)	67	121	(19)	171
Unlikely Related	165	(52)	301	183	(58)	401	348	(55)	702
Severity:									
Mild	243	(77)	593	177	(56)	321	420	(66)	914
Moderate	118	(37)	208	75	(24)	159	193	(30)	367
Severe	16	(5)	23	21	(7)	26	37	(6)	49
NA							1	(0)	1
Seriousness:									
Not Serious	264	(84)	817	205	(64)	503	469	(74)	1320
Serious*	6	(2)	7	4	(1)	4	10	(2)	11

*N=number of subjects, %= percent of subjects, E=number of events, NA=not available, *treatment emergent adverse event*

Conclusions

The trial met the primary objective identified in the protocol with confirmatory effect on the 2 primary endpoints. The ALK Grass tablet 75,000 SQ-T provided a reduction of 30% in rhinoconjunctivitis symptom score ($p<0.0001$) and on top of this a reduction of 38% in rhinoconjunctivitis medication score ($p<0.0001$) when compared with placebo.

The ALK Grass tablet 75,000 SQ-T investigated in this trial was well tolerated and clinically effective as treatment of seasonal allergic rhinoconjunctivitis. For all efficacy endpoints differences between the ALK Grass tablet 75,000 SQ-T and placebo were pronounced, highly statistically significant and in favour of the ALK Grass tablet.

A favourable benefit-risk profile of the 75,000 SQ-T dose has been documented.

Date of the Report

24 October 2005

This trial was conducted in compliance with the principles of *Good Clinical Practice*.