Abbreviated Clinical Trial Report

GT-16

"A randomised, double-blind, placebo-controlled Phase IIIb study investigating changes in immunological parameters and cutaneous reactivity induced by a short course immunotherapy with ALK grass tablets"

Investigational Medicinal Product: ALK Grass Tablets (GRAZAX®)

Clinical trial ID:	GT-16
EudraCT No.	2006-005263-26
Indication:	Allergic rhinoconjunctivitis caused by grass pollen with or without asthma
Development Phase:	IIIb
First subject first visit:	11 January 2007
Last subject last visit:	31 August 2007
Investigator:	[redacted] MD, PhD, [redacted] (Madrid)
Trial centre:	[redacted] Spain
Sponsor:	ALK-Abelló S. A. Medical Department Miguel Fleta 19, 28037 Madrid, Spain
Clinical Trial Manager:	[redacted] MSc ALK-Abelló, S.A
Authors:	[redacted] ALK-Abelló, S.A
Report No. and date:	GT-16 Abbreviated Clinical Trial Report 2008 Final:24 July 2008

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

2. SYNOPSIS

Name of Sponsor/Company: ALK-Abelló, S.A.		
Name of Finished Product: ALK Grass Tablets (GRAZAX®)		
Name of Active Ingredient: *Phleum pratense* pollen allergen extract		

Title of Trial
A randomised, double-blind, placebo-controlled Phase IIIb study investigating changes in immunological parameters and cutaneous reactivity induced by a short course immunotherapy with ALK grass tablets.

Investigators:
Dr. [redacted]
Dr. [redacted]
Dr. [redacted]
Dr. [redacted]
Dr. [redacted]

Trial Centres:
[redacted]

Publications:
None.

Trial Period:
First subject first visit: 11 January 2007
Last subject last visit: 31 August 2007

Objectives:
To study the cutaneous and immunological changes induced by sublingual immunotherapy with grass tablets in patients with grass allergy. Change in IgG_4 levels until the beginning of the pollen season will be the main outcome of the study.

Methodology:
A multi-centre, randomised, double-blind, placebo-controlled study.
The subjects were treated with GRAZAX® treatment or placebo in a 2:1 ratio.
Depending on the date of enrolment, patients received treatment from 2 to 4 months before the pollen season, and continued until the season finishes.
Patients came to the clinic for Randomisation, Pre-season visit and Final control visits. Extra blood extractions were concerted in between these visits to guarantee a monthly serum sample. A maximum of six blood extractions were performed on a given subject during the period of the study.

VISIT	**1**	**2a / 2b**	**3**	**4**	**5**
	Selection (January-February)	Additional Extraction	Pre-Seasonal (16 - 30 April)	Intra-seasonal (21 May - 1 June)	Final (2 – 13 July)
IgG_4 *Phleum pratense*	•	•	•	•	•
IgE *Phleum pratense*	•	•	•	•	•
IgX *Phleum pratense*	•	•	•	•	•
IgG_4 Phl p 1, Phl p 5, Phl p 12	•		•		•
SPT	•		•		•
Intradermal test	•		•		•

Number of Subjects Planned and Analysed:
Planned: 75 patients.
Included: 78 patients, 78 randomised (52 in the GRAZAX® group, 26 in Placebo group).
Completed: 75 patients (50 in the GRAZAX® group, 25 in Placebo group).
Withdrawals: 2 in the GRAZAX® group (1 due to AE: SOC: Vascular disorders, LLT, blood pressure high, unrelated, moderate; 1 due to other reason), 1 in the placebo group due to AE (four simultaneous mild, resolved, adverse events: SOC: Cardiac disorders (unrelated), Nervous system disorders (related), Eye disorders (related) and General disorders and administration site conditions (related)).

Diagnosis and Main Inclusion Criteria:
Males or females 18-68 years of age fulfilling the following criteria:

- A clinical history of rhinitis (with or without concurrent asthma) to grass pollen of at least 1 year of evolution prior to trial entry.
- Positive SPT (ALK-Abelló, S.A.) response to *Phleum pratense* 20 µg/ml, wheal diameter ≥ 3 mm
- Documented positive IgE against grass pollen (CAP class ≥ 2)
- Negative pregnancy test for childbearing potential femalespatient's safety, were excluded.

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number:
ALK Grass tablets (GRAZAX®) 75,000 SQ-T (*Phleum pratense*, 15 µg Phl p 5).
Oral lyophilisate, for daily sublingual administration.
Bach number: J3679

Reference Therapy Dose and Mode of Administration, Batch Number:
ALK tablets placebo
Oral lyophilisate, for daily sublingual administration.
Bach number: J3679

Duration of Treatment:
Every subject started the treatments 2-4 months before the pollen season and continued until the end of the pollen season.

Criteria for evaluation of efficacy:
Primary efficacy endpoint:

- Differences between GRAZAX® and placebo groups in IgG_4 serum levels from the beginning of the trial to the start of grass season.

Secondary efficacy endpoints:

- Evolution along the treatment and differences between groups in specific IgG_4 *P. pratense* serum levels.
- Evolution along the treatment and differences between groups in specific IgE *P. pratense* serum levels.
- Evolution along the treatment and differences between groups in specific IgX *P. pratense* serum levels.
- Differences between GRAZAX® and placebo groups in immediate skin reactivity with *P. pratense*.
- Differences between GRAZAX® and placebo groups in intradermal skin tests with *P. pratense*

Criteria for evaluation of safety:

- Adverse events

Statistical Methods:
The estimation of sample size was based on the preliminary results of IgG4 from an immunotherapy ALK grass tablets study with a similar population.
After immunotherapy, the mean value of specific IgG4 of *Phleum pratense* in active group was 0.003 Arbitrary Units with 0.0004 Standard Deviation. The placebo group has a mean of 0 AU, 0.00023 SD. Assuming a 35% drop-out rate, 75 patients will have to be randomized 2:1 active vs. placebo to obtain a 5% significance level with a 90% power.

Serum specific IgG_4, IgE and IgX values and SPT areas have been transformed logarithmically for normalization.

Efficacy Evaluation (PP analysis)

Primary Efficacy Analysis:
Specific serum values IgG_4 to *P. pratense* at selection and pre-seasonal visits (V1 & V3), measured as Arbitrary Units per milliliter (AU/ml) conform the primary efficacy endpoint. Student T-tests has been used to estimate differences between groups. Data has been presented in a logarithmic scale.

Secondary Efficacy Analysis:

Skin Prick tests (immediate skin response) have been analysed by means of parallel line assay (AIASA CRS PLA). The cutaneous tolerance index has been calculated with its confidence interval for each visit as well as for the difference between groups at each visit.

Intradermal tests (delayed skin response) have been analysed by repeated measures ANOVA

Specific immunoglobulins (IgE, IgX, and IgG_4 to *Phleum* allergens) have been analysed by repeated measures ANOVA after log transformation. Tables show the significance of the treatment factor (intergroup) and the visit factor for each group. The overall p-value shows the significance of the intergroup and intragroups factors along the treatment and the same is given for every change between visits.

Data obtained from visit 2b have not been included in the analysis due to the low number of subjects who performed this visit.

Safety evaluation

All TEAE (Treatment Emergent Adverse Event) have been summarised by treatment group, System Organ Class severity and in their relation to the treatment.

Summary of evaluations

EFFICACY ENDPOINTS	**Visit 1 to Visit 3**	**Visit 1, 3 and 5**	**All visits**
Primary:			
Specific IgG_4 levels (*P. pratense*)	X		
Secondary:			
Specific IgG_4 levels (*P. pratense*)			X
Specific IgE levels (*P. pratense*)			X
Specific IgX levels (*P. pratense*)			X
Specific IgG_4 levels (Phl p 1)		X	
Specific IgG_4 levels (Phl p 5)		X	
Specific IgG_4 levels (Phl p 12)		X	
Skin Prick test (*P. pratense*)		X	
Delayed skin tests (*P. pratense*)		X	
SAFETY ENDPOINTS			
Frequency of adverse events			X

Demography of Trial Population:

Demographic baseline characteristics and baseline measurements were well balanced between the two treatments groups.

		Placebo		GRAZAX®		Total		p value
		N	%	N	%	N	%	
Number of Subjects		26	33.3%	52	66.7%	78	100%	
Sex	Male	13	50.0%	19	36.5%	32	41.0%	0.330
	Female	13	50.0%	33	63.5%	46	59.0%	
Ethnic origin	Caucasian	21	80.8%	49	94.2%	70	89.7%	0.126
	Hispanic	4	15.4%	3	5.8%	7	9.0%	
	Other	1	3.8%	0	0.0%	1	1.3%	
Smoker habit	Non-smoker	13	50.0%	37	71.2%	50	64.1%	0.185
	Smoker	6	23.1%	7	13.5%	13	16.7%	
	Previous smoker	7	26.9%	8	15.4%	15	19.2%	
Age (years, mean ± sd)		32.0 ± 7.3		30.8 ± 8.8		31.2 ± 8.3		0.560
Height (cm, mean ± sd)		169.5 ± 8.9		167.0 ± 11.1		167.8 ± 10.4		0.324
Weight (Kg, mean ± sd)		73.6 ± 15.5		68.7 ± 13.7		70.4 ± 14.4		0.158
IgE Phl (KU/L, geom. mean [95%CI])		16.9 [8.8 - 32.7]		23.0 [15.0 - 35.5]		20.8 [14.6 - 29.7]		0.472
IgG_4 Phl (mgA/L, geom. mean [95%CI])		0.14 [0.09 - 0.22]		0.20 [0.15 - 0.28]		0.18 [0.14 - 0.23]		0.173
SPT* (mm^2, geom. mean [95%CI])		54.7 [44.4 - 67.4]		49.3 [42.1 - 57.8]		51.0 [45.1 - 57.8]		ns (PLA)

*20 mcg/ml Phl p 5

Efficacy Results:

Primary efficacy endpoint: *Phleum pratense* IgG_4 (baseline V1 to pre-seasonal visit V3):

Subjects treated with GRAZAX® experienced a significant increase in their IgG_4 levels to the *P. pratense* extract ($p<0.001$). On the contrary, the placebo group did not show significant changes. The comparison of changes in the GRAZAX® and placebo group was highly significant ($p<0.001$) (please refer to Tables 14.1 to 14.2 and Figure 14.1).

Secondary efficacy endpoints

***Phleum pratense* IgG_4 (along the treatment):**

The analysis of the IgG_4 levels along the treatment showed that the GRAZAX® treated group behaved differently than the placebo group through the study period. While GRAZAX® treated patients experienced a constant and significant increase, The placebo group had similar IgG_4 levels until the pollen season. Then, the levels of IgG_4 rose significantly from pre-season visit (V3) to in-season visit (V4) and to the post-season visit (V5). The change observed in these latest visits was similar to the change in the GRAZAX® group. The IgG_4 levels in GRAZAX® group showed significant changes as soon as one month after the start of GRAZAX® administration (please refer to Tables 14.3 to 14.4 and Figure 14.2).

***Phleum pratense* IgE**

P. pratense IgE levels showed a significant ($p<0.001$) differential response in the GRAZAX® and placebo groups. In the GRAZAX® group, an increase in IgE has been observed until the intraseasonal visit (V4). In the placebo group the IgE levels remain unchanged until the preseasonal visit (V3)

increasing after the start of the pollen season. IgE levels rose significantly in the GRAZAX® group already after the first month of treatment (please refer to Tables 14.5 to 14.6 and Figure 14.3).

***Phleum pratense* IgX**

IgX levels showed a sustained decrease in the GRAZAX® group from the first to the last visit. In the placebo group, IgX levels were kept constant before the starting of the pollen season and afterwards fell down significantly. Consistently with IgG_4 and IgE levels, IgX levels decreased significantly in the GRAZAX® group already after the first month of treatment (please refer to Tables 14.7 to 14.8 and Figure 14.4).

Specific IgG_4 against major allergens

IgG_4 specific for *P. pratense* major allergens (Phl p 1, Phl p 5 and Phl p 12) were also analysed.
GRAZAX® treated group showed a statistically significant increase in IgG_4 for the three allergens while in the placebo group the levels were kept without significant changes. Overall, a significant difference between groups was found. The first post-treatment analysis of allergen specific IgG4 was performed in the pre-seasonal visit, 70 days in average after the initiation of the treatment. Statistically significant changes were observed at this point (please refer to Tables 14.9 to 14.14 and Figure 14.5 to 14.7).

Immediate skin reactivity (SPT)

Subjects treated with GRAZAX® showed a significant reduction in their immediate cutaneous response as shown by an increase in the Cutaneous Tolerance Index (CTI). On the other hand, placebo treated patients showed a decrease in their CTI only once started the pollen season (please refer to Table 14.15 and Figure 14.8).

Delayed skin reactivity (ID)

The evolution of the delayed response to indradermal test was not significantly different in the two treatment groups. However, the GRAZAX® group experienced a significant reduction along the treatment due to the change during the pollen season (V3 to V5) not shown in the placebo group.
Only subjects who showed a delayed response larger than the immediate were analysed (please refer to Tables 14.16 to 14.17 and Figure 14.9).

Safety Results:

A total of 305 adverse events were reported, 235 in the GRAZAX® group and 70 in the placebo. More than 90% were of mild severity and there were not neither severe nor serious adverse events.

In the GRAZAX® group, 135 AEs (57.4%) were related with the treatment while only 16 (22.9%) in the placebo.

AEs by SOC

	GRAZAX®						**Placebo**					
	Mild		Moderate		Total		Mild		Moderate		Total	
	R	NR	R	NR	R	NR	R	NR	R	NR	R	NR
Cardiac disorders	0	0	0	1	0	1	0	1	0	0	0	1
Congenital, familial and genetic disorders	0	0	0	0	0	0	0	1	0	0	0	1
Ear and labyrinth disorders	19	0	0	0	19	0	0	1	0	0	0	1
Endocrine disorders	0	1	0	0	0	1	0	0	0	0	0	0
Eye disorders	9	1	0	0	9	1	2	2	0	0	2	2
Gastrointestinal disorders	61	13	1	0	62	13	1	2	0	0	1	2
General disorders and administration site conditions	0	6	4	0	4	6	1	3	0	0	1	3
Infections and infestations	0	21	0	1	0	22	0	12	0	0	0	12
Injury, poisoning and procedural complications	0	1	0	0	0	1	0	0	0	0	0	0
Investigations	1	0	0	0	1	0	0	0	0	2	0	2
Metabolism and nutrition disorders	0	1	0	0	0	1	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	0	9	0	1	0	10	0	2	0	2	0	4
Nervous system disorders	2	12	0	1	2	13	3	9	0	0	3	9
Psychiatric disorders	0	4	0	1	0	5	0	0	0	0	0	0
Renal and urinary disorders	0	0	0	1	0	1	0	0	0	0	0	0
Reproductive system and breast disorders	0	4	0	0	0	4	0	6	0	0	0	6
Respiratory, thoracic and mediastinal disorders	37	12	1	1	38	13	9	6	0	2	9	8
Skin and subcutaneous tissue disorders	0	5	0	0	0	5	0	1	0	1	0	2
Surgical and medical procedures	0	1	0	1	0	2	0	0	0	0	0	0
Vascular disorders	0	0	0	1	0	1	0	1	0	0	0	1
Total	129	91	6	9	135	100	16	47	0	7	16	54

Subjects with AEs

	GRAZAX®						**Placebo**					
	Mild (45)		Moderate (6)		Total (45)		Mild (17)		Moderate (5)		Total (19)	
	R	NR	R	NR	R	NR	R	NR	R	NR	R	NR
N of subjects	34	35	2	5	34	37	8	16	0	5	8	18

Conclusions:

Short treatment with GRAZAX® induces an increase in IgG_4 to *Phleum pratense* allergen extract in a pre-seasonal 2-3 month course of immunotherapy. This increase is evident already after 1 month of administration and is significantly different than in the placebo group which did not change during this pre-seasonal phase. These data are confirmed by an early increase in IgE and decrease in IgX and by changes in IgG_4 to *Phleum pratense* main allergens. The immediate and delayed cutaneous reactivity showed also a decrease in the subjects treated with GRAZAX®, not observed in the placebo group.

Date of the Report:
24 July 2008

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