Synopsis – Trial GT-09

Title of Trial
A randomised, double-blind, placebo-controlled, multi-centre Phase I Trial investigating the safety of ALK Grass tablet in children aged 5-12 years with grass pollen induced rhinoconjunctivitis (with/without asthma).

Investigators
Dr. [redacted] (MD)
Dr. [redacted] (MD)

Trial Centres
[redacted] Spain
[redacted] Spain

Publication
None

Trial Period
First subject first visit – 15 March 2006
Last subject last visit – 4 May 2006

Objectives
To confirm the safety of Grazax in children aged 5-12 years

Methodology
This was a randomised, parallel group, double-blind, placebo-controlled, multi-centre trial. The trial was initiated in the spring 2006. The subjects were randomised (3:1) to receive either Grazax 75,000 SQ-T or placebo once daily. Subjects received treatment for 28 days and attended a trial completion visit at day 29.

Number of Subjects Planned and Analysed
It was planned to enrol up to 32 subjects. In total 31 subjects were screened, 1 of which was a screening failure. Therefore, 30 subjects were enrolled in the trial, 23 in the active group and 7 in the placebo group. The subject distribution and treatment groups are presented below:

Treatment Group	Active		Placebo		Overall	
	N	(%)	N	(%)	N	(%)
Screened					31	
Full Analysis Set	23	(100)	7	(100)	30	(100)
Completed	21	(91)	7	(100)	28	(93)
Subjects Withdrawn	2	(9)	0	(0)	2	(7)
Reasons for withdrawal:						
Adverse event	2	(9)	0	(0)	2	(7)

N=number of subjects, %=percent of subjects, Cross-reference: Table 1

2 withdrawn – 2 actively treated subjects withdrew. 1 subject due to 4 AEs (moderate eye pruritus, moderate pharyngolaryngeal pain, moderate non-cardiac chest pain and moderate dysphagia) and the other subject due to a SAE (asthma) with the following symptoms: dyspnoea, shortness of breath, chest tightness, wheezing and dry cough.

Diagnosis and Main Inclusion Criteria

Children aged 5-12 years with clinical history of grass pollen induced rhinoconjunctivitis (with/without asthma) requiring treatment during at least one grass pollen season. A positive Skin Prick Test (SPT) response (wheal diameter ≥3 mm) and positive specific IgE against *Phleum pratense* (≥ 0.7 kU/L), no clinical history of severe asthma, no current food allergies with oral allergy syndrome, no current severe atopic dermatitis and no previous treatment by immunotherapy with grass pollen allergen or any other allergen within the previous 5 years.

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

Grazax 75,000 SQ-T (*Phleum pratense*); batch No. 276862

Mode of administration:

Oral lyophilisate, for sublingual administration once daily. The tablet was placed under the tongue and kept there for one minute before swallowing.

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

Placebo; Batch No. 271013
Oral lyophilisate, for sublingual administration once daily.

Duration of Treatment

The duration of treatment was 28 days for the 75,000 SQ-T and the placebo groups.

Criteria for Evaluation – Safety

Adverse events (AEs), clinical safety laboratory tests, vital signs, physical examinations and oral examination were the safety data evaluated in this report.

Statistical Methods

The sample size for this Phase I trial followed empirical considerations. No formal sample size estimation was performed. Only one analysis set, the full-analysis set (FAS), was considered for the trial. The FAS consisted of all randomised subjects. All randomised subjects received trial medication. No formal statistical comparison of treatment groups at baseline was performed. For numeric data the following summary statistics were used:

N = number of observations (subjects)
E = number of events
Mean = mean (average) of the observations
SD = standard deviation
Median = median (50 percentile)
P25% = lower 25 percentile
P75% = upper 75 percentile
Min = minimum value
Max = maximum value

All assessments were summarised by pooling data on treatment and placebo respectively. For categorical data frequencies and percentages were used in the presentation of data. AEs were summarised by treatment according to MedDRA System Organ Class and Preferred term.

Demography of Trial Population

The trial population comprised more males (73%) than females (27%) and all subjects were Caucasian. Subjects were aged between 5-12 years. Age, height and weight were higher in the placebo group compared to the active group. Generally, 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	Active		Placebo	
	N	(%)	N	(%)
Number of Subjects	23		7	
Gender				
Female	8	(35%)		
Male	15	(65%)	7	(100%)
Age (Years)				
Mean (SD)	8.3 (2.2)		11.1 (1.2)	
Median	8.0		12.0	
P25% - P75%	7.0-10.0		10.0-12.0	
Race				
Caucasian	23		7	
Height				
Mean (SD)	137 (17.4)		155 (6.4)	
Median	131		152	
P25% - P75%	125-148		150-158	
Weight				
Mean (SD)	36.8 (15.8)		54.7 (11.6)	
Median	30		51.5	
P25% - P75%	25.9-42.5		48.0-62.0	
Grass Pollen Allergy (Severity):				
N	23		7	
Mild	5	(22%)	1	(14%)
Moderate	17	(74%)	6	(86%)
Severe	1	(4%)		
Grass Pollen Allergy (Years):				
N	23		7	
Mean (SD)	3.0 (1.0)		4.0 (1.4)	
Median	3.0		3.0	
P25% - P75%	2.0 - 4.0		3.0 - 6.0	

N=number of subjects, %=percent of subjects. Cross-reference: Tables 2.1, 2.2 and 4.1.

Safety Results

- 2 actively treated subjects withdrew from the trials. One subject withdrew due to 4 AEs (moderate eye pruritus, moderate pharyngolaryngeal pain, moderate non-cardiac chest pain and moderate dysphagia). The other subject withdrew due to a SAE (asthma) with the following symptoms: dyspnoea, shortness of breath, chest tightness, wheezing and dry cough.
- 301 mild, 90 moderate and 4 severe (2 treatment related) treatment emergent AEs were reported by 17 actively treated subjects compared to 14 mild and 14 moderate AEs reported by 5 placebo treated subjects.
- The most frequently reported AEs were related to the mouth and throat, primarily oral pruritus and throat irritation. Further, mouth oedema, ear pruritus, stomatitis and abdominal pain were frequently reported.
- In general, most of the AEs occurred almost immediately after taking the tablet, lasted in average from few minutes up to 85 minutes and tended in average to subside spontaneously within 1 to 16 days.
- Only 2 subjects in the active group reported in total 5 treatment related AEs that could indicate change in asthma symptoms (2 events of cough and 3 events of dyspnoea).
- No safety concerns were identified upon reviewing the clinical laboratory parameters, vital signs, physical examination or oral examination.

Conclusions

Grazax 75,000 SQ-T was in general well tolerated in the paediatric population and considered suitable for further clinical investigations in children.

Date of the Report

29 September 2006

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