Synopsis – Trial GT-11

Title of Trial

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

Investigators

Three investigators in Germany:

[redacted]

Coordinating and Signatory Investigator: Prof. Dr. med. [redacted]

Trial Centres

See above

Publication

None

Trial Period

First subject first visit – 20 February 2006

Last subject last visit – 25 April 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 (outside the grass pollen season). The subjects were randomised (3:1) to receive either Grazax® 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 approximately 50 children. In total 30 subjects were randomised. The subject distribution and treatment groups are presented below:

	Active All (N=22)		Placebo All (N=8)	
Full Analysis Set (ITT)	22	(100%)	8	(100%)
Subject completed	22	(100%)	8	(100%)

Cross-reference: Table 1

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 clinical history of allergy to tree or weed pollen requiring medication during the planned treatment period, no clinical history of perennial allergy requiring medication to which the subject was regularly exposed, 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)

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

Duration of Treatment

The duration of treatment was 28 days.

Criteria for Evaluation – Safety

Adverse events (AEs), clinical safety laboratory tests, vital signs, physical examinations and oral examination.

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 adverse 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. Adverse events were summarised by treatment according to MedDRA System Organ Class and Preferred term.

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	Active		Placebo	
	N	(%)	N	(%)
Number of Subjects	22		8	
Gender				
Female	9	(41%)	3	(38%)
Male	13	(59%)	5	(63%)
Age (Years)				
Mean (SD)	8.5 (2.2)		7.5 (2.3)	
Median	9.0		6.5	
P25% - P75%	7.0-10.0		6.0-9.0	
Min - Max	5-12		5-12	
Race				
Caucasian	21	(95%)	8	(100%)
Other	1	(5%)		
Height				
Mean (SD)	134 (14.8)		129 (14.1)	
Median	134		125	
P25% - P75%	124-142		122-132	
Min - Max	111-163		115-161	
Weight				
Mean (SD)	32.4 (11.2)		27.7 (6.8)	
Median	31.9		26.6	
P25% - P75%	22.5-36.4		23.2-30.0	
Min - Max	16-56		20-42	
Grass Pollen Allergy (Severity):				
Mild	3	(14%)	2	(25%)
Moderate	17	(77%)	6	(75%)
Severe	2	(9%)		
Grass Pollen Allergy (Years):				
Mean (SD)	2.7 (1.7)		2.8 (1.8)	
Median	2.5		2.5	
P25% - P75%	1.0-4.0		1.0-4.5	
Min - Max	1-6		1-5	

N=number of subjects, %=percent of subjects

Safety Results

- Overall, Grazax is well-tolerated in children aged 5-12 years
- A total of 553 treatment emergent adverse events were reported by 20 of 22 subjects receiving active treatment. Of these, 511 adverse events were considered related to trial medication. In the placebo group, 5 of 8 subjects reported 14 treatment emergent adverse events. Two of the events were considered related to trial medication
- The majority of the reported adverse events were mild or moderate in severity
- The most frequently reported adverse events were related to the mouth and throat, primarily oral pruritus and throat irritation. Further, mouth oedema, salivary gland enlargement and pharyngolaryngeal pain were frequently reported
- In general, the frequently reported adverse events occurred almost immediately after taking the tablet, lasted in average up to 37 minutes and tended in average to subside spontaneously within 4 to 15 days
- No serious adverse events or withdrawals due to adverse events occurred
- No safety concerns were identified upon reviewing the clinical laboratory parameters, vital signs, physical examination or oral examination

Conclusions

- Grazax® is in general well-tolerated in a 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*.