Synopsis – Trial GT-14

Title of Trial A phase III trial assessing the efficacy and safety of Grazax in subjects with seasonal grass pollen induced rhinoconjunctivitis with or without asthma
Investigators 28 principal investigators participated in the trial. Dr [redacted], MD, The Clinical Research Center, LLC, 1040 North Mason, Suite 112, St. Louis, MO 63141, USA was appointed signatory investigator.
Trial Sites The trial was conducted at 28 sites in the USA
Publications None
Trial Period *First subject first visit* – 13 December 2006 *Last subject last visit* – 20 August 2007
Objectives The primary objective of the trial was: • To evaluate the efficacy of specific immunotherapy with Grazax compared to placebo during the entire grass pollen season based on the rhinoconjunctivitis symptom score. The secondary objectives of the trial were: • To evaluate the efficacy and safety of specific immunotherapy with Grazax compared to placebo based on: o Rhinoconjunctivitis medication score in the entire grass pollen season o Rhinoconjunctivitis symptom and medication scores in the peak grass pollen season o Rhinoconjunctivitis symptoms assessed by VAS o Asthma symptom and medication score o QoL in the grass pollen season o Number of well days in the grass pollen season o Global Evaluation of treatment efficacy o Adverse Events o Physical Examination o Vital signs o FEV_1 o Safety Laboratory Assessments o Pharmacoeconomic Assessments o Immunological Assessments
Methodology A randomised, parallel-group, double-blind, placebo-controlled, multi-centre trial.

Number of Subjects Planned and Analysed

It was planned to enrol approximately 300 subjects. A total of 405 subjects were screened. Of these 329 subjects were randomised (76 subjects were screening failures).

The disposition of subjects is shown below.

Treatment Group	Placebo N	(%)	Grazax N	(%)	Overall N	(%)
Screened					405	
Full Analysis Set (FAS)	166		163		329	
Per protocol (PP)	119	(72%)	121	(74%)	240	(73%)
Subjects with diary data (entire grass pollen season)	150	(90%)	139	(85%)	289	(88%)
Subjects with diary data (peak grass pollen season)	143	(86%)	137	(84%)	280	(85%)
Withdrawn from Trial	26	(16%)	27	(17%)	53	(16%)
Reason for Withdrawal						
Withdrawal of consent	7	(4%)	8	(5%)	15	(5%)
Lost to follow-up	5	(3%)	2	(1%)	7	(2%)
Non-compliance with protocol	3	(2%)	1	(<1%)	4	(1%)
Pregnancy	2	(1%)	-	(-)	2	(<1%)
Adverse event	5	(3%)	10	(6%)	15	(5%)
Other	4	(2%)	6	(4%)	10	(3%)
Withdrawal Initiated by						
Investigator	6	(4%)	7	(4%)	13	(4%)
Sponsor	1	(<1%)	-	(-)	1	(<1%)
Subject	19	(11%)	20	(12%)	39	(12%)
Completed	140	(84%)	136	(83%)	276	(84%)

N= Number of subjects
%= Percent of the full analysis set (all randomised subjects)

Diagnosis and Main Inclusion Criteria

Male and female subjects, 18-65 years of age, with a clinical history of grass pollen induced allergic rhinoconjunctivitis of at least two years requiring treatment during the grass pollen season; with a clinical history of significant rhinoconjunctivitis symptoms (interfering with usual daily activities or sleep), which remain troublesome despite treatment with anti-allergic drugs during the grass pollen season; with positive skin prick test (SPT) response (wheal diameter ≥ 5 mm larger than the negative control with a flare) to *Phleum pratense* and with positive specific IgE against *Phleum pratense* (≥ IgE class 2).

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

Grazax 75,000 SQ-T/2,800 BAU (*Phleum pratense*); batch no. 498955

Administered once daily preferably in the morning. The tablet was to be placed under the tongue and swallowing was to be avoided for one minute.

Reference Therapy, Dose and Mode of Administration, Batch Numbers

Placebo Grazax tablets; batch no. 526958

Administered once daily preferably in the morning. The tablet was to be placed under the tongue and swallowing was to be avoided for one minute.

Duration of Treatment

Subjects received treatment for at least 8-16 weeks prior to and during the grass pollen season 2007.

Criteria for Evaluation – Efficacy

Primary Efficacy Endpoint

- The primary efficacy endpoint was the average rhinoconjunctivitis symptom score during the entire grass pollen season, calculated for each subject as the sum of the individual daily rhinoconjunctivitis symptom scores during the entire grass pollen season, divided by the number of rhinoconjunctivitis symptoms dairy recordings during the entire grass pollen season.

Key Secondary Efficacy Endpoints

- The average weekly overall RQLQ score for the entire pollen season, calculated for each subject as the average of the observed average RQLQ scores each week for the entire pollen season.
- The average rhinoconjunctivitis medication score in the entire grass pollen season calculated for each subject as the sum of the individual daily rhinoconjunctivitis medication scores during the entire grass pollen season, divided by the number of rhinoconjunctivitis medication diary recordings during the entire grass pollen season.
- The percentage of rhinoconjunctivitis well days in the entire pollen season, calculated for each subject as the average of the observed percentage well days throughout the entire grass pollen season.

Other Secondary Efficacy Endpoints

- The average rhinoconjunctivitis symptom score in the peak grass pollen season.
- The average nose symptom score in the entire/peak grass pollen season.
- The average eye symptom score in the entire/peak grass pollen season.
- The average rhinoconjunctivitis medication score in the peak grass pollen season.
- The average rhinoconjunctivitis combined score (sum of the symptom and the medication score) in the entire/peak grass pollen season.
- The average rhinoconjunctivitis symptom/medication score during the first 7 days of the grass pollen season.
- The average daily VAS[1] score over the entire grass pollen season, calculated for each subject as the average of the observed daily VAS scores throughout the entire/peak grass pollen season.
- Global evaluation of most severe rhinoconjunctivitis symptoms during the grass pollen season assessed after the end of the grass pollen season (at visit 6).
- Global overall evaluation.
- Excellent rhinoconjunctivitis control[2].
- The percentage of rhinoconjunctivitis well days in the peak grass pollen season, calculated for each subject as the average of the observed percentage well days throughout the peak grass pollen season.
- The percentage of rhinoconjunctivitis days without use of rescue medication and without symptoms in the entire grass pollen season, calculated for each subject as the average of the observed percentage days without use of rescue medication and without symptoms throughout the entire/peak grass pollen season.
- The average daily asthma symptom score over the entire grass pollen season as well as over the peak grass pollen season, calculated for each subject as the average of the observed total daily score throughout the entire/peak grass pollen
- The average daily asthma medication score over the entire grass pollen season as well as over the peak grass pollen season, calculated for each subject as the average of the observed total daily score throughout the entire/peak grass pollen
- The percentage of asthma well days[3] in the entire as well as in the peak grass pollen season, calculated for each subject as the average of the observed asthma well days throughout the entire/peak grass pollen season.

[1] The daily VAS score is a variable with values between 0 and 100 recorded on a 100 mm line in the electronic diary
[2] The endpoint is binary dividing the subjects into execellent rhinoconjunctivitis control or not. Excellent rhinoconjunctivitis control is defined as more than 50% well days in the entire grass pollen season.

Criteria for Evaluation – Immunology • IgE • IgE-blocking antibodies (IgX) • IgG_4
Criteria for Evaluation – Safety • Adverse Events • Physical Examination • Vital signs • FEV_1 • Safety Laboratory Assessments

[3] An asthma well day is defined as a day without use of asthma medication and an asthma symptom score less than or equal to 1.

Statistical Methods

The following analysis sets were used:

- Full analysis set (FAS): All randomised subjects following the ITT ICH principle
- Safety analysis set: All randomised subjects, i.e. the safety analysis set corresponded to the full analysis set
- Per protocol analysis set (PP): Subjects who did not have major protocol deviations

Suggested protocol deviations were:

- Incorrect administration of the trial medication, non-attendance at trial assessments
- Non-compliance with the diary

Consequently it was decided that the PP analysis set comprised subjects who:

- Did not take prohibited medication
- Had sufficient trial drug compliance defined as at least 80% of drug compliance, i.e. number of tablets used compared to number of treatment days
- Provided sufficient diary data defined as at least 50% of diary data in the pollen season
- Did not have any other significant protocol deviations with influence on the primary endpoint

Primary Efficacy Analysis

The primary efficacy endpoint was the average rhinoconjunctivitis symptom score during the entire grass pollen season. For subjects where the recorded period did correspond to the entire grass pollen season, the average score was calculated using the data available in the grass pollen season.

The two treatment groups compared in this analysis were:

- Placebo
- Grazax

The primary investigation of the comparison of the two treatment groups was done via an ANOVA with the average rhinoconjunctivitis symptom score as response variable and treatment group as a fixed effect and pollen region as a random effect as well as adjusting for different error variation for each treatment group. The primary outcome was the difference in adjusted means between the two groups with 2-sided 95% confidence interval as well as the p-value. In addition, the difference in adjusted means between the two treatment groups relative to the adjusted mean of the placebo group was presented as a percentage with 2-sided 95% confidence interval. Furthermore, adjusted means for the two treatment groups with standard errors and 2-sided 95% confidence intervals were presented. Finally, a p-value describing the statistical significance of the pollen region was also presented.

Secondary Efficacy Analysis

All secondary efficacy analyses, except for the RQLQ analysis, the last part of global evaluation and the excellent rhinoconjunctivitis control were carried out the same way as the primary efficacy analysis. In addition to the parametric tests, non-parametric tests were performed.

The weekly overall RQLQ analysis was analysed using a repeated measurement ANOVA including treatment group as a fixed effect and pollen region as a random effect as well as adjusting for week and subject variation.

The first part of the global evaluation, i.e. the assessment of the question “how do you assess the severity of your rhinoconjunctivitis symptoms, when they were the most severe during the previous/this grass pollen season” with the 6 rhinoconjunctivitis symptoms scored 0 to 3 was analysed in the same manner as the primary efficacy analysis, however including assessment of grass pollen season 2006 as a covariate. The second part of the global evaluation, i.e. the assessment of the question “compared to your rhinoconjunctivitis symptoms in the previous grass pollen season, how have you felt overall in this grass pollen season (2007)” was tabulated with all five categories (much better, better, the same, worse, much worse). The data were analysed as an ordered categorical variable in a proportional odds regression.

Furthermore, the global evaluation score was categorized binary as:

Improvement= Much better or better
No improvement or worsening= The same or worse or much worse

The binary values of global evaluation score and the excellent rhinoconjunctivitis control were both binary outcomes and were analysed accordingly using a generalized linear mixed model with a logit link function, treatment group as fixed effect and pollen region as a random effect. Furthermore, a contingency table was analysed using a Fishers exact test.

Statistical Methods - continued

For the excellent rhinoconjunctivitis control endpoint, subjects who withdrew due to adverse events were counted as having "not excellent rhinoconjunctivitis control" even if the diary records showed more than 50% well days. This was a conservative approach ensuring the adverse event withdrawals were not treated favourable. Also adverse event withdrawals on placebo were regarded as "not excellent rhinoconjunctivitis control". Other withdrawals were not replaced by any value. In the PP analysis of that endpoint adverse event withdrawals were not included.

Other Efficacy Presentations

The daily average rhinoconjunctivitis symptoms score as well as the daily average rhinoconjunctivitis medication score for all subjects were displayed graphically by treatment group to the extend of data available from the daily diary. Furthermore, data were in general displayed graphically to support interpretability of the primary and secondary efficacy analysis results.

From the daily rhinoconjunctivitis symptom and medication scores in the grass pollen season 2007, a combined score was constructed. The combined score was calculated as the sum of the daily symptom score and the daily medication score.

Furthermore, the following were calculated:

Difference in symptom score and medication score in the first week (7 days) of the grass pollen season.

Difference in nose symptoms and in eye symptoms during the entire grass pollen season and during the peak grass pollen season. Furthermore, each of the four nose symptoms (runny nose, blocked nose, sneezing and itchy nose) and the two eye symptoms (gritty feeling/red/itchy eye and watery eyes) were summarised.

Difference in the percentage of well days per week during the grass pollen season.

Asthma symptom score, asthma medication score and asthma well days.

In addition to the efficacy endpoints mentioned in the trial protocol a more clinically intuitive endpoint was introduced in the Statistical Analysis Plan. The endpoint was binary dividing the subjects into excellent rhinoconjunctivitis control or not.

Demography of Trial Population

Baseline characteristics for all subjects in the FAS are shown below.

	Placebo	**Grazax**	**Overall**
Number of Subjects	166	163	329
Sex			
Male, N(%)	78 (47%)	75 (46%)	153 (47%)
Female, N(%)	88 (53%)	88 (54%)	176 (53%)
Ethnic Origin			
American Indian/Alaska Native, N(%)	1 (<1%)	-	1 (<1%)
Asian, N(%)	1 (<1%)	3 (2%)	4 (1%)
Black/African American, N(%)	21 (13%)	21 (13%)	42 (13%)
Hispanic/Latino	6 (4%)	4 (2%)	10 (3%)
Native Hawaiian/Other Pacific, N(%)	1 (<1%)	-	1 (<1%)
White, N(%)	134 (81%)	134 (82%)	268 (81%)
Other, N(%)	2 (1%)	1 (<1%)	3 (<1%)
Smoking			
Non-smoker, N(%)	121 (73%)	128 (79%)	249 (76%)
Previous smoker, N(%)	24 (14%)	26 (16%)	50 (15%)
Smoker, N(%)	21 (13%)	9 (6%)	30 (9%)
Age (years)			
Mean (SD)	35.9 (11.7)	35.9 (11.7)	35.9 (11.7)
Median	35.5	35.0	35.0
Min-max	18-62	18-65	18-65
Q25%-Q75%	26-45	24-45	25-45
Years with Grass Pollen Allergy			
Mean (SD)	20.5 (12.0)	21.4 (12.9)	21.0 (12.4)
Median	18.0	19.0	18.2
Min-max	1.3-59	2.0-58	1.3-59
Q25%-Q75%	11-28	11-32	11-29
History of Grass Pollen Allergy			
Yes, N(%)	166 (100%)	163 (100%)	329 (100%)
No, N(%)	-	-	-
History of Asthma			
Yes, N(%)	43 (26%)	46 (28%)	89 (27%)
No, N(%)	123 (74%)	117 (72%)	240 (73%)

N= Number of subjects

%= Percent subjects of FAS (all randomised subjects)

Efficacy Results

Primary Efficacy Endpoint

- No statistically significant difference was found between Grazax and placebo in the average rhinoconjunctivitis symptom score during the entire grass pollen season.

Key Secondary Efficacy Endpoints

- A reduced use of rescue medication was shown for subjects treated with Grazax as compared to placebo subjects (p=0.0827).
- No difference between Grazax and placebo was found in the analysis of the overall average weekly RQLQ (all domains) (p=0.5293).
- No differences between Grazax and placebo was found in the analysis of percentage well days during the entire grass pollen season (p=0.6965).

Other Secondary Efficacy Endpoints

- The overall global evaluation of the rhinoconjunctivitis symptoms performed at the end of the grass pollen season (at visit 6) showed that more subjects in the Grazax group (69%) versus the placebo group (49%) felt that their rhinoconjunctivitis symptoms were improved compared to previous grass pollen seasons (Odds ratio 2.24, p=0.0010).
- No differences were found between the Grazax and the placebo treated subjects for the other secondary efficacy endpoints, however all efficacy endpoints were in favour of Grazax.

Immunological Parameters

- In the analyses of the immunological parameters IgE, IgG_4 and IgE-blocking antibodies, a significant immunological response in subjects treated with Grazax was revealed with significantly higher inductions of IgE, IgG_4 and IgE-blocking antibodies observed for the Grazax group as compared with the placebo group.

Safety Results

- Treatment with Grazax was generally well-tolerated
- The most frequently reported adverse events related to the IMP were local reactions within the eye, mouth or throat – primarily oral pruritus
- None of the two serious adverse events reported were related to the IMP
- Five non-serious significant adverse reactions occurred (all in the Grazax group); three of these were treated with epinephrine. The reactions were all mild or moderate in severity, predominated by local symptoms; and all five subjects recovered without sequelae.
- 15 subjects withdrew due to adverse events during the trial (10 in the Grazax group and 5 in the placebo group). Six of the adverse event withdrawals in the Grazax group were considered to be related to the IMP.
- No safety concerns were observed for vital signs, physical examination and FEV_1

Conclusions

Overall, the trial did not reveal any statistically significant differences between Grazax and placebo in the clinical efficacy parameters, although all were in favour of Grazax.

In the analyses of the immunological parameters IgE, IgG_4 and IgE-blocking antibodies, a significant immunological response in subjects treated with Grazax was revealed with significantly higher inductions of IgE, IgG_4 and IgE-blocking antibodies observed for the Grazax group as compared with the placebo group.

Treatment with Grazax was generally well-tolerated with the most frequently reported IMP related adverse events being mild to moderate local reactions within the eye, mouth or throat – primarily oral pruritus.

Date of the Report

Final version, 29 August 2008

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