Synopsis – Trial GT-10

Title of Trial

A randomised, parallel-group, open, controlled Phase III trial assessing the treatment compliance with Grazax® in subjects with seasonal grass pollen induced rhinoconjunctivitis

Investigators

40 investigators in Austria, Denmark, Germany, The Netherlands, and Sweden

Trial Centres

39 centres in Austria, Denmark, Germany, The Netherlands, and Sweden

Publication

None

Trial Period

First subject first visit – 20 February 2006

Last subject last visit – 25 November 2006

Objectives

Primary: To evaluate if subject compliance of once daily dosing with Grazax in adult subjects with grass pollen induced allergic rhinoconjunctivitis can be increased by providing subjects with a compliance device.

Secondary: To evaluate the safety of Grazax

Methodology

A randomised, parallel group, open, controlled, multi-centre trial. The trial was initiated in February 2006 and subjects received Grazax for approximately 6-12 weeks prior to the grass pollen season and during the grass pollen season 2006. Approximately 500 subjects were planned for inclusion in the trial. The subjects were randomised (1:1) and 250 subjects would receive the compliance device and 250 would not. All subjects received Grazax.

Number of Subjects Planned and Analysed

500 subjects were planned for inclusion in the trial. A total of 460 subjects enrolled in the trial and 240 of them were randomised to receive the Memozax device.

Treatment Group	GRAZAX + Memozax		GRAZAX - Memozax		Overall GRAZAX	
	N	(%)	N	(%)	N	(%)
Screened					472	
Full Analysis Set #	240	(100 %)	220	(100 %)	460	(100 %)
Subjects withdrawn	36	(15 %)	44	(20 %)	80	(17 %)
Subjects completed	204	(85 %)	176	(80 %)	380	(83 %)
Reason for Withdrawal						
Withdrawal of consent	3	(1 %)	3	(1 %)	6	(1 %)
Pregnancy			2	(<1 %)	2	(<1 %)
Lost to follow-up	4	(2 %)	1	(<1 %)	5	(1 %)
Non-Compliance with Protocol	5	(2 %)	6	(3 %)	11	(2 %)
Adverse event	19	(8 %)	25	(11 %)	44	(10 %)
Other	5	(2 %)	7	(3 %)	12	(3 %)

N = Number of subjects; % = Percent subjects

Full Analysis Set comprises all randomised subjects

36 subjects (15%) withdrew from the Memozax group while 44 subjects (20%) withdrew from the non-Memozax group. The main reason for withdrawals in both groups was adverse events, and most withdrawals were initiated by the subjects themselves.

Diagnosis and Main Inclusion Criteria

Subjects suffering from grass pollen induced rhinoconjunctivitis, with or without asthma.

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

Grazax – 75,000 SQ-T; sublingual administration, batch No. 382250

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

None

Duration of Treatment

One grass pollen season, including 6-12 weeks pre-treatment.

Criteria for Evaluation – Compliance and Efficacy

- Subject compliance
- Global evaluation
- Memozax questionnaire

Criteria for Evaluation – Safety

Adverse events (AEs)

Statistical Methods

The following analysis set was used:

full-analysis set (FAS) – all randomised *subjects*

Primary Endpoint

The primary endpoint is "excellent" versus "less excellent" compliance. "Excellent" compliance is defined as subjects with a compliance of 90% or more while "less excellent" compliance is less than 90% from Visit 1 to Visit 3. The proportion of subjects with "excellent" compliance in the two groups was analysed using a two-sided Fisher's exact test with a significance level of 5%. The primary analysis was based on subjects who had records of investigational medicinal product (IMP) use from Visit 1 to Visit 3. This period is approximately the same as standard GRAZAX treatment for one grass pollen season.

Secondary Endpoints

In a supplementary analysis, missing values were replaced by past compliance. This corresponds to a variation of the Last Observation Carried Forward (LOCF) methodology.

A secondary statistical analysis of the compliance was done by testing the compliance percentage:

Compliance (%) = 100 x (tablets used) / (number of treatment days)

for the two groups (device and no device). All subjects were included with the data available, i.e. subjects who withdrew prior to Visit 3 were included with the data until withdrawal. The statistical analysis was done by an ANOVA test with the compliance (%) as response variable and treatment group and country as fixed effects.

Global evaluation was an overall comparison of this grass pollen season compared to previous seasons. At the last treatment visit (Visit 3), each subject was asked: "*Compared to your rhinoconjunctivitis symptoms in previous grass pollen seasons, how have you felt overall in this grass pollen season (2006)?"* Response possibilities were: much better, better, the same, worse, much worse. The Global Evaluation is tabulated with all 5 response categories. Prior to statistical analysis the responses were categorised as:

Improvement = Much better or Better

No improvement or worsening = The same or Worse or Much Worse

From a previous trial (GT-08 first year data) the placebo response showed a Global Evaluation of 151 subjects (55%) who felt improved while 124 subjects (45%) did not feel an improvement. A non-confirmatory, explorative, statistical test of the overall Global Evaluation from the current GT-10 trial (with or without Memozax device) compared to the placebo response from the GT-08 trial (historic data) was done by a test of proportions. The Global Evaluation was analysed using a Fisher's exact test.

Additional Endpoints

In Germany and Netherlands a country specific amendment (No. 1) regarding the compliance device was implemented. The subjects who consented to the Amendment were asked questions regarding the compliance device Memozax in a separate Patient Questionnaire (see Appendix I.1). The questionnaire included six different questions. The response to the Memozax Patient Questionnaire is tabulated and listed. No statistical testing was done in relation to those data.

Demography of Trial Population

There were no major differences in the baseline characteristics of the two groups. The mean age of subjects included was 34 years in the Memozax group and 35 years in the non-Memozax group (overall range 17 to 66 years of age). The average number of years with grass pollen allergy was 15 years in the Memozax group and 17 in the non-Memozax group.

Compliance and Efficacy Results

The compliance with Grazax treatment was generally high. There was no significant difference in treatment compliance between the group issued with a Memozax compliance device and the group not issued with a Memozax device. 46% felt that Memozax had made it "much easier" or "easier" for them to remember taking their daily IMP, while 24% would use it in the future in its present form, 15% would use it after improvements, and 21% would maybe use it. A one-season treatment with Grazax resulted in 82% of subjects rating their rhinoconjuctivitis symptoms as Improved compared to previous seasons.

Safety Results

- Overall 277 (60%) of the 460 subjects randomised reported a total of 485 TEAEs during the trial. The percentage of subjects who reported a TEAE in each of the two groups was very similar, 58% in the Memozax group and 62% in the non-Memozax group.
- 3 subjects (0.7%) had SAEs that were judged as related to IMP treatment. A further 5 subjects had SAEs that were judged unlikely related to IMP treatment.
- 44 subjects (10%) withdrew from the trial due to an AE, the most common being throat irritation, oral pruritus and oedema mouth.
- 141 subjects had a total of 178 related TEAEs with onset on the same day as first IMP intake. This corresponds to 67% of all subjects reporting a related TEAE during the entire trial period, and to 55% of all related TEAEs reported during the entire trial period.
- The median duration of ear pruritus was 1 day (mean 3 days; maximum 18 days), while oral pruritus, throat irritation, and oedema mouth had median durations of 8.0, 8.5, and 9.0 days (mean 35, 29, and 38 days; maximum 230, 178, and 164 days)
- 41% of the subjects, who in addition to grass pollen, were sensitised to tree pollen according to their SPT reported a related TEAE during the trial, while 51% of the non-tree-sensitised subjects did so. The main differences between the two groups were seen for oral pruritus (20% of subjects in the tree-sensitised group, 28% of subjects in the non-tree-sensitised group) and throat irritation (4% of subjects in the tree-sensitised group, 7% of subjects in the non-tree-sensitised group).
- 63% of the asthma subjects reported a related TEAE during the trial, while 40% of the non-asthma subjects did so. The main differences between the two groups were seen for oral pruritus (31% of subjects in the asthma group, 20% of subjects in the non-asthma group), throat irritation (9% of subjects in the asthma group, 4% of subjects in the non-asthma group), asthma (4% of subjects in the asthma group, <1% of subjects in the non-asthma group), and oedema mouth (4% of subjects in the asthma group, 7% of subjects in the non-asthma group).
- 50% of the men and 40% of the women reported at least one related TEAE during the trial. There was no major difference in the types or numbers of events between the genders.

Conclusions

The compliance rate of subjects taking Grazax immunotherapy in this clinical trial was generally high, and it was not significantly improved by providing subjects with the Memozax compliance device.

Date of the Report

29 June 2007

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