Synopsis – trial GT-22

Title of trial
An interventional trial assessing the tolerability and safety of GRAZAX® in adults with grass pollen allergy

Coordinating investigators
Prof. Dr. Med [redacted] and Prim. Dr. [redacted] were appointed signatory investigators of the trial. The following investigators were appointed national coordinating investigators: Prim. Dr. [redacted] (Austria), Prof. Dr. [redacted] (Germany), and Prof. Dr. Med [redacted] (Denmark)

Trial sites
A total of 17 trial sites in 3 countries (Austria, Denmark and Germany) enrolled subjects for the trial

Publications
None

Trial period
First subject first visit – 16 February 2010
Last subject last visit – 02 July 2013

Objectives
Primary objective

- To investigate the safety and tolerability of GRAZAX.

The objective 'safety and tolerability' is explored by collecting information about adverse events (AEs) and asking questions regarding patients' overall experience with the experienced AEs.

Secondary objective

- To evaluate the patients' satisfaction with GRAZAX.

The objective 'satisfaction' is explored by assessing compliance and asking questions regarding patient convenience and treatment satisfaction when taking GRAZAX.

Methodology
This trial was a non-controlled open-label, multi-national, multi-centre trial. All 55 subjects included received treatment with GRAZAX once daily for 3 years in accordance with normal clinical practice. Assessments of safety issues as well as compliance, convenience and satisfaction with treatment was recorded at each of 7 trial visits with approximately 6 months in between and at 1 follow-up telephone contact. The overall trial design is shown below.

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit7	Follow up
Screening and first GRAZAX administration							telephone contact
Initiation of trial	App. 6 mo after visit 1	App. 6 mo after visit 2	App. 6 mo after visit 3	App. 6 mo after visit 4	App. 6 mo after visit 5	App. 6 mo after visit 6	App. 1 wk after visit 7

Number of subjects planned and analysed

56 subjects were screened, and 55 subjects were included for treatment

	n	(%n)
Subjects screened	56	
Subjects included*	55	(100%)
Countries		
Austria	4	(7%)
Denmark	27	(49%)
Germany	24	(44%)
Discontiunations		
Subjects withdrawn	18	(33%)
Reasons for withdrawal		
• Withdrawal of consent	3	(5%)
• Lost to follow-up	5	(9%)
• Adverse event	8	(15%)
• Other	2	(4%)
Subjects completed	37	(67%)

* The GT-22 trial was conducted as an aftermath to the GT-08 extension trial. Subjects randomised and treated with placebo in the GT-08 extension trial were invited to be included in the GT-22 trial

Main selection criteria

Subjects were eligible for the trial if they had participated and received placebo treatment in the GT-08 extension trial (7). Subject selection was based on the inclusion and exclusion listed below.The addition of additional country-specific inclusion and exclusion criteria is provided below.

Inclusion criteria

1. Written informed consent obtained before entering the trial
2. Willing and able to comply with the trial protocol regimen
3. Participated in the GT-08 extension trial and received placebo treatment
4. Will be prescribed GRAZAX in line with approved SmPC (5)
5. Female subjects, who are fertile must be willing to practice appropriate contraceptive methods for the duration of the trial (Austria only)

Exclusion criteria

1. History of allergy, hypersensitivity or intolerance to any of the excipients (except *Phleum pratense*)
2. Malignancy or systemic diseases affecting the immune system e.g. autoimmune diseases, immune complex diseases or immune deficiency diseases
3. Alcohol and drug abuse (Germany only)
4. Immunosuppressive treatment (Germany only)
5. Inflammatory conditions in the oral cavity with severe symptoms such as oral lichen planus with ulcerations or severe oral mycosis
6. Uncontrolled or severe asthma (FEV_1 < 70% of predicted value after adequate pharmacologic treatment)
7. Pregnancy
8. Conditions or diseases which are contra indicated or otherwise not in line with the approved GRAZAX SmPC (Germany only)
9. Simultaneously participating in a different trial including a treatment intervention and/or an investigational medicinal product (IMP)

Investigational medicinal product, dose and mode of administration, batch numbers

Administration and dose regimen was 1 oral lyophilisate (one GRAZAX tablet) daily with the strength of 75,000 SQ-T, batch numbers: 125212, 125213, 125214, 135092, 135093, 135094.

Reference therapy, dose and mode of administration, batch numbers
None

Duration of treatment
36 months.

Criteria for evaluation – safety and tolerability
Safety assessments included AEs, AE discontinuations, serious adverse events (SAEs) and tolerability of AEs. In addition, compliance and a number of patient satisfaction endpoints were assessed.

Statistical methods
The trial operates with one analysis set only, the full analysis set, which includes all subjects enrolled in the trial. In the tables, the population is referred to as 'all subjects' with the heading 'overall'.

All data was summarised by descriptive statistics. No formal statistical tests or sample size calculation were performed for this trial.
Continuous data was summarised with number of observations (n), mean, standard deviations (SD), 25% percentiles, 75% percentiles, minimum observation (min), and maximum observation (max).
Categorical variables (e.g. AEs) were summarised in frequency tables.
For some of the endpoints (overall evaluation, tolerability, treatment satisfaction, compliance, and convenience) data were displayed by visit. In addition to the by visit summary, an overall count of all of the assessments for all subjects at all visits were included in the end of the tables.

Demography of trial population
Among the 55 included (treated) subjects, the trial population consisted of 34 males (62%) and 21 females (38%) with 54 (98%) being of Caucasian origin. 27 of the subjects (48%) were enrolled in Denmark, 24 of the subjects (45%) were enrolled in Germany, and 4 subjects (7%) were enrolled in Austria. All subjects suffered from allergic rhinitis. In addition, 48/55 (87%) subjects suffered from conjunctivitis, and 17/55 (31%) suffered from asthma bronchiale at baseline. The majority of subjects (64%) reported 2 clinical manifestations with 31% having all 3 manifestations.

Treatment satisfaction results

- The majority of the subjects (80%-91%) attending the visits had a treatment compliance ≥80%, whereas only 2-3% of subjects had a treatment compliance <50%. For subjects with treatment compliance <80%, the main reason for not adhering to the dosing regimen was oversight, AEs or other reasons, occurring in 4-5% of all subjects.
- The majority of subjects found it simple to take GRAZAX, ranging from 87-93% of all subjects attending the visits.
- The convenience of taking GRAZAX was reported as comfortable in 42%-72%, and acceptable in 28%-54% of the subjects attending the visits. Only a minority of subjects found it uncomfortable taking GRAZAX (ranging from 0-10% of subjects attending the visits).
- The majority of subjects and investigators (ranging from 80%-94%) were very satisfied or satisfied with the treatment.

Safety results

- A total of 46 (84%) of the subjects reported 191 AEs during the trial. The majority of all reported AEs were mild (69%) or moderate (27%) in intensity. Eight (4%) of the AEs were reported in 6 (11%) subjects as severe in intensity.
- 124 (65%) of the 191 AEs were considered as possibly related to IMP. The majority of IMP-related AEs were mild (78%) or moderate (19%) in intensity. 2 (3%) of the IMP-related AEs were reported in 2 (4%) subjects as severe in intensity.
- The most commonly reported IMP-related AEs were local reactions in mouth and throat such as oral pruritus in 21 (38%) of the subjects, followed by throat irritation in 13 (24%), tongue pruritus in 10 (18%), and paraesthesia oral in 6 (11%) of the subjects.
- One SAE occurred during the trial. This event of cholelithiasis was regarded as severe in intensity, but not related to IMP.
- In total, 17 AEs (9%) in 8 subjects (15%) led to discontinuation of the IMP. Six of the subjects discontinued due to 13 IMP-related AEs.
- The majority of AEs (96%) were recovered.
- For the majority of subjects, AEs did not seem to influence the their physical state of health and mental ability to any considerable extent. Neither did AEs seem to influence the majority of subjects's common satisfaction to any considerable extent.

Conclusions

Overall, this trial demonstrated that once-daily dosing of GRAZAX for 3 years was well tolerated and safe in line with the known safety profile for GRAZAX.

The majority of subjects attending the assessment visits had a compliance ≥80%, were satisfied or very satisfied with the treatment, and found it simple and comfortable taking GRAZAX. Among the subjects experiencing an adverse event, the event did not influence, or did influence only at a small part of the time, their physical state of health, mental ability or common satisfaction with GRAZAX.

Date of the report

26 June 2014

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