Integrated Clinical Trial Report

GT 17

Investigational Medicinal Product: Grazax®

Clinical trial ID:	GT17 Italy
EudraCT No.	2006-004820-35
Indication:	Grass-induced Allergy Rhinitis
Development Phase:	Phase IV Trial
First subject first visit:	16 March 2007
Last subject last visit:	22 April 2009
Investigator:	Principal Investigator: [redacted] (Italy)
Trial centres:	Multicenter trial: 23 Allergy Clinics in Italy. (See List)
Sponsor:	ALK-Abelló Medical Department Italy, Lainate (Milan)
Clinical Trial Manager:	[redacted] MD, ALK-Abelló Italy.
Report No. and date:	GT17 14 September 2009

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

Synopsis – Trial GT17

Title of Trial
A randomized, parallel-group, Phase IV, open trial evaluating compliance to the treatment with Grazax tablets in patients with seasonal grass pollen rhinoconjuntivitis.

Principal Investigator
Principal Investigator: Prof [redacted] (Italy).

Trial Centres
A total of 23 Centers in Italy participated in this trial (see list).

Publication: Poster presentation at EACCI 2009

Trial Period
First subject first visit – 16 March 2007
Last subject last visit – 22 April 2009

Objectives
Primary:

- To evaluate if compliance of once daily dosing with Grazax in adult subjects with grass pollen induced allergic rhinoconjunctivitis can be increased by providing patients with or without a compliance device (Memozax®) given from the beginning of immunotherapy .

Secondary:

- To evaluate after 48 weeks of treatment with Grazax tablets the impact on quality of life, symptom score, and patient's acceptance in comparison with previous pollen seasons.
- To evaluate safety and tolerability of Grazax treatment.

Methodology
A randomized, parallel group multicentre controlled trial.

Number of Subjects Planned and Analysed
It was planned to randomised 240 patients. Actually, a total of 261 patients were screened. A total of 261 were enrolled and randomised.

Treatment	Grazax +Memozax	%	Grazax - Memozax	%	Overall	%
Screened	139	**100**	122	**100**	261	**100**
FAS	139	**100**	122	**100**	261	**100**
Subject withdrawn	26	**19**	23	**19**	49	**19**
Subject completed	113	**81**	99	**81**	212	**81**
Reason for withdrawn						
Pregancy	1 (V5)	**0.7**	0	**0**	1	**0.3**
Lost to Follow up	20	**14**	17	**14**	37	**14**
Adverse event	6	**4.3**	6	**5**	12	**4.5**

261 treated (139 randomize3d to Memozax; 122 without Memozax)
212 completed
49 withdrawn: 12 due to AE, 37 not presented to study visit (lost to follow up)
1 pregnancy (at V5)
261 analysed (ITT); 212 (PP).

Diagnosis and Main Inclusion Criteria
Subjects, men and women, >18 years of age and <65 years
• A clinical history of grass pollen-induced allergic rhinoconjunctivitis (with or without asthma) having received treatment during the previous grass pollen season.
• Positive skin prick test (SPT) response (wheal diameter ≥3mm) to *Phleum pratense*
• Positive specific IgE against *Phleum pratense* (≥IgE class 2)
• No clinical history of chronic sinusitis during the last 2 years or of symptomatic perennial or seasonal allergic rhinitis and/or asthma having received regular medication, due to another allergen during – or potentially overlapping – the grass pollen season.
• No clinical history of severe asthma (GINA Step 4 and children with FEV_1 < 80% of expected value after treatment with inhaled corticosteroids *and* short-acting β_2 agonists)
• 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, one tablet 75.000 SQ-T per day sublingual, Batch N 0000095106
Blister of 10 tablets

Reference Therapy, Dose and Mode of Administration, Batch Number
Not applicable

Duration of Treatment
48 weeks (+ 1 week for screening). Total duration of trial 49 weeks.

Criteria for Evaluation – Efficacy
Primary Endpoint
- Global compliance to the treatment
- Evaluation of percentage of patient with a compliance ≥90% in relation to the use of the devices (primary endpoint) in comparison with the compliance in the group without the device.

Secondary Endpoints
- Impact of the therapy on symptoms of rhinoconjunctivitis (secondary end point) (evaluated by the patient: VAS; and by the Investigator)
- Incidence of Adverse Events

Criteria for Evaluation – Safety
Adverse events (AEs) rate, severity and causality and physical examinations

Statistical Methods
The following analysis sets were used:
Full Analysis Set (FAS) – all randomised *subjects*, following the Intention To Treat (ITT) ICH principle as defined in the ICH-E9 Guideline. The FAS was the primary set for analysis.= 261
Per-Protocol set (PP) – all *subjects* in the FAS who:
– did not violate the inclusion/exclusion criteria significantly.
– did not take prohibited medication in the period prior to onset of grass pollen season.
=212
Safety Set=261
For inferential statistic analysis the following tests were used:
- Fisher Exact Test
- ANOVA test

For statistical analysis the GraphPad and SPSS softwares were used.
All statistical tests were two-tailed.

Demography of Trial Population
A total of 261 patients were enrolled in the study. The mean age of FAS population was 32.8±10 years.
Men were 149 (57%) and women 112 (43%). All patients were polisensitized (seasonal). A total of 50 subjects (19% of FAS population) suffered from mild asthma (Step:I-III GINA Classification). A total of 191 patients suffered of moderate/severe form of rhinitis (73% of FAS population). Ethnic origin was: Caucasian for 246 patients (94%), Asian in 2 subjects 0.8%, Latin American in 3 patients (1.2%), African for 1 patient (0.4%). For 9 subjects data on ethnic origin were not available. All these characteristics were well balanced in the two groups.

Efficacy Results
The primary endpoint in this trial was a comparison of the degree of compliance in the two groups (Memozax and non-Memozax). For this purpose compliance was categorised as Excellent (≥90%) or Less Excellent <90%). The proportion of subjects with Excellent compliance in the Memozax group was similar to the non-Memozax group (79% vs. 78%). The difference was not statistically significant (p=0.5). At the end of the study mean value of compliance expressed in % in subjects who completed the trial was 91.7/% in the Memozax group and 90.3% in the no Memozax group (NS).

Safety Results
No SAE or SUSAR were reported in this study. No death was reported.
For 33 subjects (13% of the FAS population) a total of 79 AE were reported. Of the 33 patients with AE, 12 (38%) (6 patients in each study group) (4.5% of FAS) withdrew from the trial due to an AE, the most common being mouth and tongue oedema and dyspnea. Of these 12 subjects, 3 had also concomitant asthma (25%) whereas 9 subject only allergic rhinitis. Of the 79 AE recorded, 63 (79%) were considered probably related to IMP. Overall 96% of AE were mild/moderate in nature, Only 4% of AE were judged severe in intensity.

Conclusions
The compliance rate of subjects taking Grazax immunotherapy in this clinical trial was generally high (78% of patients with a compliance >90% after 48 weeks of Grazax treatment), and it was not significantly improved by providing subjects with the Memozax compliance device (79% of patients with excellent compliance in comparison with 78% of patients without Memozax). In the global evaluation, a total of 81% of patients reported an improvement of symptoms after treatment with Grazax, evaluated through a 10-cm VAS in comparison with the previous season. Investigators evaluated the efficacy of treatment good or very good in 85% of patients. This is a strong indication that treatment with Grazax is effective in relieving these symptoms, and it is in line with results from previous Grazax trials.

Date of the Report
10 September 2009

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