Integrated Clinical Trial Report

A phase III trial evaluating the tolerability of Grazax treatment in combination with antihistamine in subjects with seasonal grass pollen induced rhinoconjunctivitis

Investigational Medicinal Products:
Grazax + Aerius (desloratadine) 2.5 mg
Grazax + Aerius (placebo)

Clinical trial ID:	GT-19
EudraCT No.	2008-003593-18
Indication:	Seasonal grass pollen induced rhinoconjunctivitis
Development Phase:	III
First subject first visit:	15 September 2008
Last subject last visit:	8 January 2009
Investigators:	Signatory Investigator: Dr. [redacted]. Co-Investigators: [redacted], [redacted], [redacted] and [redacted]
Trial centre:	[redacted] Germany
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Report No. and date:	Final, 24 November 2009

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

Synopsis – Trial GT-19

Title of Trial
A phase III trial evaluating the tolerability of Grazax treatment in combination with antihistamine in subjects with seasonal grass pollen induced rhinoconjunctivitis

Investigators
Signatory Investigator: Dr. [redacted]. Co-Investigators: [redacted], [redacted], [redacted] and [redacted]

Trial Centre
[redacted] Germany

Publication
None

Trial Period
First subject first visit – 15 September 2008
Last subject last visit – 8 January 2009

Objectives
To evaluate whether intake of antihistamine in connection with Grazax treatment results in a reduction in number of subjects reporting treatment related adverse events the first day of Grazax exposure

Methodology
A randomised, double-blinded, cross-over, single-centre trial. The trial was initiated and completed after the grass pollen season 2008. At screening, all subjects were administered Grazax. Only subjects that reported treatment related allergic adverse events (local reactions in mouth and throat) after intake of Grazax at screening visit were eligible for the trial. Eligible subjects were randomly allocated to one of two treatment procedures (1:1). Both groups received Grazax treatment in combination with antihistamine (AH) and placebo AH on 2 single days separated by approximately two weeks to ensure wash out of AH.

Number of Subjects Planned and Analysed
Approximately 50 subjects were planned for enrolment. 79 subjects were screened and 46 subjects were randomised for the trial.

The subject disposition is tabulated below.

	All	
	N	**(%)**
Subjects screened	79	
Screening failures	31	
Full analysis set (FAS)	46	(100%)
Per protocol analysis set (PP)	46	(100%)
Safety analysis set	79	
Subjects withdrawn*)	2	
Reason for withdrawal		
Withdrawal of consent	1	(2%)
Lost to follow-up	1	(2%)
Subject completed	46	(100%)

N = Number of subjects
% = Percent subject of FAS
*) The 2 subjects were screened but were withdrawn before randomisation (visit 2)

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 two years or more requiring treatment during the grass pollen season, reporting of treatment related allergic adverse events (local reactions in mouth and throat) after intake of Grazax at screening (visit 1) and positive skin prick test (SPT) response (wheal diameter ≥ 3 mm larger than the negative control with a flare) to *Phleum pratense.*
Test Product, Dose and Mode of Administration, Batch Numbers Grazax, *Phleum pratense*, 75,000 SQ-T (2,800 BAU); administered sublingually. Batch no: 625605 Aerius, desloratadine, 2.5 mg; disintegrating tablet. Batch no: 370428A05
Reference Therapy, Dose and Mode of Administration, Batch Numbers Placebo Aerius, placebo desloratadine; disintegrating tablet. Batch no: 370375C04
Duration of Treatment All subjects were exposed to Grazax at screening. In addition, all randomised subjects were exposed to either Grazax + AH at visit 2 and Grazax + placebo AH at visit 3 or Grazax + placebo AH at visit 2 and Grazax + AH at visit 3
Criteria for Evaluation – Efficacy The primary endpoint was a binary endpoint; experience of a local allergic reaction or not, during treatment with Grazax in combination with AH compared to treatment with Grazax in combination with placebo AH. Local allergic reactions were defined as adverse events judged by the investigator to be possibly/probably related to Grazax treatment and which occurred in the mouth and/or throat. Reactions in the mouth also included reactions around the mouth i.e. lips. Reactions in the throat included reactions in pharynx and larynx.
Criteria for Evaluation – Safety Adverse events (AEs), vital signs, oral examination, physical examination and FEV_1
Statistical Methods The following analysis sets were used: Full Analysis Set (FAS): all randomised subjects. Safety Analysis Set: all screened subjects. Per Protocol Analysis Set (PP): all randomised subjects that received both treatments (i.e. Grazax + AH and Grazax + placebo AH) and did not take any prohibited medication prior to screening and for the entire trial period. The primary endpoint was analysed using a logistic regression analysis. The rationale for this analysis was: The probability of a 50-50 split between local allergic reactions occurring with treatment Grazax + AH and Grazax + placebo AH under the null hypothesis is equivalent to the odds ratio for local allergic reactions occurring with treatment Grazax + AH to the treatment Grazax + placebo AH being 1.0. Because logistic regression analysis models the natural logarithm of the odds, testing whether there is a 50-50 split between local reactions occurring with treatment Grazax + AH and treatment Grazax + placebo AH is comparable to testing whether the intercept term is null in a logistic regression analysis. To account for the possible period effect in the 2x2 crossover trial, a term for period was included in the logistic regression analysis.

Demography of Trial Population
Baseline characteristics for all subjects in the FAS analysis set are shown below.

	All (N=46)
Full analysis set (FAS)	46
Sex	
Male, N (%)	23 (50%)
Female, N (%)	23 (50%)
Ethnic origin	
Caucasian, N (%)	44 (96%)
African, N (%)	1 (2%)
Hispanic, N (%)	1 (2%)
Smoking	
Non-smoker, N (%)	36 (78%)
Smoker, N (%)	10 (22%)
History of asthma/allergic asthma	
Yes, N (%)	3 (7%)
No, N (%)	43 (93%)
Age	
N	46
Mean (SD)	34 (10.6)
Median	30
P25% - P75%	26 - 43
Min – Max	21 - 65
Years with grass pollen induced rhinoconjunctivitis	
N	46
Mean (SD)	18.2 (11.4)
Median	15.5
P25% - P75%	10.0 - 25.0
Min - Max	0.0 - 44.0

N= Number of subjects
SD= Standard deviation
%= Percent subjects of FAS

Efficacy Results
In this trial, intake of antihistamine (Aerius 2.5 mg melting tablet) in connection with Grazax treatment had no statistically significant influence on the number of subjects reporting local allergic reactions.

Safety Results
Intake of antihistamine (Aerius 2.5 mg melting tablet) in connection with Grazax treatment had no influence on the frequency, type, severity, duration or onset of adverse events. The treatment was well-tolerated and all adverse events were non-serious and mild in severity. All subjects recovered from the events.

Conclusions
In this trial, intake of antihistamine (Aerius 2.5 mg melting tablet) in connection with Grazax treatment had no statistically significant influence on the number of subjects reporting local allergic reactions.
The frequency, type, severity, duration and onset of adverse events were not influenced by the intake of antihistamine in connection with Grazax treatment. The treatment was well-tolerated and all adverse events were non-serious and mild in severity. All subjects recovered from the events.

Date of the Report
Final, 24 November 2009

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