Integrated Clinical Trial Report

A phase III trial assessing the pharmacodynamic effect and the tolerability of Grazax treatment initiated in the grass pollen season in subjects with seasonal grass pollen induced rhinoconjunctivitis

Investigational Medicinal Product: Grazax® *Phleum pratense*

Clinical trial ID:	GT-18
EudraCT No.	2007-006009-26
Indication:	Seasonal allergic rhinoconjunctivitis caused by grass pollen
Development Phase:	III
First subject first visit:	7 May 2008
Last subject last visit:	8 September 2008
Investigators:	Signatory Investigators: Prof. Dr. Med. [redacted] (Germany) and Primera Dr. [redacted] (Austria)
Trial centres:	28 centres distributed in Germany and Austria
Sponsor:	Group Clinical Development ALK-Abelló A/S DK-2970 Hørsholm, Denmark
Medical Writer:	[redacted], PhD, ALK-Abelló A/S Telephone number: [redacted] Fax number: [redacted]
Report No. and date:	GT-18, 4 May 2009

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

Synopsis – Trial GT-18

Title of Trial
A phase III trial assessing the pharmacodynamic effect and the tolerability of Grazax treatment initiated in the grass pollen season in subjects with seasonal grass pollen induced rhinoconjunctivitis.

Investigators
28 investigators in Germany and Austria. Signatory investigators: Prof. Dr. Med. [redacted] (Germany) and Primera Dr. [redacted] (Austria).

Trial Centres
28 trial centres in Germany and Austria

Publications
None

Trial Period
First subject first visit – 7 May 2008
Last subject last visit – 8 September 2008

Objectives
Primary objective:
To investigate the pharmacodynamic effect of Grazax compared to placebo when treatment is initiated during the grass pollen season (GPS), based on IgE-blocking antibodies.

- To demonstrate a difference in the level of IgE-blocking antibodies at visit 4 (approximately 8 weeks after treatment initiation) in subjects treated with Grazax compared to subjects treated with placebo

Secondary objectives:
To investigate the pharmacodynamic effect of Grazax compared to placebo when treatment is initiated during the GPS, with respect to IgE and IgG_4.

- To describe the level of IgE and IgG_4 at visit 4 (approximately 8 weeks after treatment initiation) in subjects treated with Grazax compared to subjects treated with placebo

To evaluate the tolerability of Grazax treatment compared to placebo when initiated during the GPS, with regard to:

- The total number of Adverse Events (AE), type, and severity during the trial period
- The total number of discontinuations
- The rhinoconjunctivitis symptoms
- Use of allergy and/or asthma medication
- FEV_1, vital signs and physical examination at visit 4

Methodology
This was a randomised, parallel-group, double-blind, placebo-controlled, multi-centre trial conducted in 2008. 276 subjects were randomised 4:1 to receive either Grazax (75,000 SQ-T) or placebo once daily starting during the GPS. The subjects were treated for at least 8 weeks (+ 1-2 weeks).

Number of Subjects Planned and Analysed
A total of 359 subjects were screened. Of these, 276 subjects were randomised (83 (23%) were screening failures). The disposition of subjects is shown in the Table below.

Treatment Group	Placebo		Grazax		Overall	
	N	(%)	N	(%)	N	(%)
Screened					359	
Full Analysis Set (FAS)	57	(100%)	219	(100%)	276	(100%)
Per Protocol Set (PP)	53	(93%)	203	(93%)	256	(93%)
Subject withdrawals	5	(9%)	9	(4%)	14	(5%)
Reason for withdrawals						
Lost to follow-up	3	(5%)	1	(<1%)	4	(1%)
Non-compliance			2	(<1%)	2	(<1%)
Adverse Events	1	(2%)	6	(3%)	7	(3%)
Other	1	(2%)			1	(<1%)
Subjects completed	52	(91%)	210	(96%)	262	(95%)

N = Number of subjects, % = Percent subjects in treatment group of FAS

Diagnosis and Main Inclusion Criteria
Main inclusion criteria:

- A clinical history of moderate to severe persistent rhinoconjunctivitis symptoms, which remain troublesome despite treatment with anti-allergic drugs during the GPS of two years or more
- A clinical history of moderate to severe persistent rhinoconjunctivitis symptoms during the GPS causing symptoms more than 4 days per week (for > 4 weeks)
- Positive skin prick test (SPT) response (wheal diameter ≥ 3 mm) to *Phleum pratense*. The SPT must not be older than 12 months
- Positive specific IgE against *Phleum pratense* (≥ IgE Class 2)
- No uncontrolled asthma in the past 12 months
- $FEV_1 \geq 70\%$ of predicted value
- No history of an IgE mediated systemic reaction due to food, insect venom, any kind of medication or induced by exercise, where there are symptoms both from the skin and the respiratory system with or without hypotension
- No history of facial angioedema in the GPS or presence of facial angioedema at time of randomisation
- No history of swallowing difficulties in the GPS or presence of swallowing difficulties at time of randomisation
- No history of allergy symptoms in the GPS leading to hospital admission
- No history of allergy symptoms in the GPS leading to treatment with corticosteroids other than topical corticosteroids
- No previous treatment with immunotherapy with grass pollen allergens within the previous five years

Investigational Medicinal Product (IMP), Dose and Mode of Administration, Batch Number
Grazax® 75,000 SQ-T (*Phleum pratense* grass pollen allergen extract), blister cards of 10 tablets.
Oral lyophilisate for sublingual administration of one tablet once daily.
Batch number: 456444

Reference Therapy, Dose and Mode of Administration, Batch Number
Grazax placebo, blister cards of 10 tablets.
Oral lyophilisate for sublingual administration of one tablet once daily.
Batch number: 526958

Duration of Treatment
Treatment was initiated during the GPS and subjects were treated approximately 9 weeks on average.

Criteria for Evaluation – Pharmacodynamic effect
Evaluation of the pharmacodynamic effect included assessment of the immunological response to treatment.
Primary endpoint:
- The change from baseline of IgE-blocking factor at visit 4[1]

Secondary endpoints:
- The change from baseline of $\log_{10}$(IgE) at visit 4
- The change from baseline of $\log_{10}(IgG_4)$ at visit 4

Criteria for Evaluation – Tolerability
The tolerability endpoints included:
- Number, relationship, severity and outcome of AEs
- Number of AEs of special interest, which include asthma and systemic allergic reactions
- Number of Serious Adverse Events (SAEs)
- Number of discontinuations due to AEs
- Average daily rhinoconjunctivitis symptom scores during the treatment period
- Number of days with intake of rhinoconjunctivitis and/or asthma medication
- Global evaluation
- $FEV_{1,}$ Vital signs, and physical examinations

Statistical Methods
The following analysis sets were used:
Full-Analysis Set (FAS) – all randomised subjects following the Intent-To-Treat (ITT) ICH principle. The FAS was the primary set for analysis.
Per-Protocol set (PP) – all the subjects in the FAS who:
- Did not violate the inclusion/exclusion criteria significantly
- Did not take selected prohibited medication to close to or during the treatment period that may influence the primary pharmacodynamic endpoint. The prohibited mediation consisted of anti IgE antibodies and MAO-inhibitors
- Had sufficient trial drug compliance defined as having taken IMP corresponding to 6 weeks of treatment. This means that both the number of tablets used and the number of treatment days must have been at least 42
- Had blood samples for assessment of IgE-blocking factor and other immunological parameters at baseline taken at visit 2
- Did not have any other significant protocol deviations influencing the primary pharmacodynamic endpoint

The final PP analysis set was defined before un-blinding.
Safety Set (SS) – all randomised subjects (i.e. the SS is identical to the FAS).
Subgroup analysis - was performed on two subgroups of the SS defined as:
- Pre-medication: all subjects who have taken allergy/asthma medication in the last 3 days prior to the first IMP intake (visit 2)
- No pre-medication: all subjects who did not take any allergy/asthma medication during the last 3 days prior to the first IMP intake (visit 2)

[1] Instead of reporting IgE blocking antibodies as stated in the objectives of the trial, it was decided in the Statistical Analysis Plan to report IgE-blocking factor. This will have no effect on the pharmacodynamic endpoint since the change from baseline of IgE blocking antibodies and IgE-blocking factor (1- IgE blocking antibodies) numerically is the same.

Pharmacodynamic analyses:
The primary pharmacodynamic endpoint (the change from baseline of IgE-blocking factor at visit 4) was calculated as the level of IgE-blocking factor at visit 4 (approximately 8 weeks after treatment initiation) minus the level of IgE-blocking factor at visit 2 (treatment start). The null hypothesis was that the change from baseline of IgE-blocking factor was equal for Grazax and placebo. The alternative hypothesis was that the change from baseline of IgE-blocking factor was different for Grazax and placebo. The null hypothesis was tested using an ANCOVA, with the change from baseline of IgE-blocking factor as response variable, treatment as a fixed categorical variable, pollen region as a random categorical variable and the level of IgE-blocking factor at baseline (visit 2) as a regression variable. Different residual error for each treatment group was specified in the ANCOVA model. The primary outcome from the ANCOVA was the difference in adjusted means (Grazax-placebo) with the associated p-value and 95% confidence intervals.
The secondary pharmacodynamic endpoints (the change from baseline of $\log_{10}$(IgE) at visit 4 and the change from baseline of $\log_{10}(IgG_4)$ at visit 4) were calculated and analysed as described for the primary pharmacodynamic endpoint using the same ANCOVA model.

Tolerability analyses:
All AEs were summarised by treatment group, MedDRA System Organ Class, and Preferred Term displaying number of subjects in treatment group, number and percentages of subjects having the event as well as number and frequency of events. All AEs were broken down by severity (mild, moderate, and severe). All SAEs were summarised by treatment. Finally, AEs were summarised by subgroups defined by use of allergy or asthma medication before first tablet intake. 95% confidence intervals for percentage of subjects having the event were presented in the frequency tables. During the trial, AEs were reported individually and in this regard, to assure that important medical conditions were not overlooked a standardised approach of verifying individual reactions reported within a time frame of 24 hours was used. The "Standardised MedDRA Queries (SMQs)" were used for the analysis. SMQs are groupings of terms from one or more MedDRA SOCs that relate to a defined medical condition or area of interest. It should be emphasized that this it not reactions reported by the reporting investigator or sponsor. In the present trial, three different selected SMQs were performed: anaphylactic reaction, angiodema, and asthma/bronchiospasm. These three events were summarised by treatments group displaying number of subjects in treatment group, number and frequency of subjects having the event as well as number of events. Number of discontinuations due to AEs was summarised by treatment. Time until discontinuation was graphically presented by a Kaplan-Meier plot. Rhinoconjunctivitis symptom score was calculated for each subject as the sum of the daily score during the GPS and during the treatment period, divided by the number of days with recordings in the GPS/treatment period. Rhinoconjunctivitis symptom scores were summarised by treatment group displaying number of subjects, mean, standard deviation, median, 25 and 75-percentiles, 5 and 95-percentiles minimum and maximum. In addition, rhinoconjunctivitis symptom scores were summarised as nose symptoms, eye symptoms, individual symptoms and total symptoms. Number and percent of subjects with intake of rhinoconjunctivitis or asthma medication during the treatment period and during the GPS were displayed by allergy/asthma medication category and treatment. Also the number of days with intake of rhinoconjunctivitis/asthma medication for each subject during the treatment period and during the GPS were summarised by allergy/asthma medication category and treatment displaying number of subjects, mean, standard deviation, median, 25 and 75-percentiles, minimum and maximum. Global evaluation was summarised by treatment as number and percent in the 5 categories "Much Worse", "Worse", "The Same", "Better", "Much Better". Furthermore, Global evaluation was categorized binary as:

- Improvement = Better or Much better
- Non-improvement = The same or Worse or Much worse

FEV_1 and vital signs were summarised by treatment group and visit displaying number of subjects, mean, standard deviation, median, 25 and 75-percentiles, minimum and maximum. All physical examinations were summarised by examination and treatment group via shift tables displaying change in normal/abnormal from pre-treatment visit to post-treatment visit.

Demography of Trial Population

The subject demographic values at baseline are summarised in the Table below. No major differences between the treatment groups were observed.

Treatment Group	Placebo (N=57)	Grazax (N=219)	Overall (N=276)
Sex			
Female	28 (49%)	95 (43%)	123 (45%)
Male	29 (51%)	124 (57%)	153 (55%)
Ethnic Origin			
African	1 (2%)	-	1 (<1%)
Asian	-	1 (<1%)	1 (<1%)
Caucasian	56 (98%)	218 (>99%)	274 (>99%)
Smoking			
Non-smoker	32 (56%)	146 (67%)	178 (64%)
Previous smoker	9 (16%)	36 (16%)	45 (16%)
Smoker	16 (28%)	37 (17%)	53 (19%)
Daily	7 (12%)	27 (12%)	34 (12%)
Occasionally	9 (16%)	10 (5%)	19 (7%)
Age (years)			
Mean (SD)	35 (12)	34 (12)	35 (12)
Median	34	33	33
Q25% - Q75%	25-40	25-42	25-42
Min - max	18-65	18-66	18-66
History of grass allergy			
Yes	57 (100%)	219 (100%)	276 (100%)
No	-	-	-
History of Asthma			
Yes	25 (44%)	88 (40%)	113 (41%)
No	32 (56%)	131 (60%)	163 (59%)
Years with grass allergy			
Mean (SD)	15.7 (9.8)	15 (10.6)	15.1 (10.5)
Median	11.4	12.7	12.6
Q25% - Q75%	8.4-21.4	6.4-20.4	6.4-20.7
Min - max	0.6-38.4	0.0-47.5	0.0-47.5
Years with asthma			
Mean (SD)	11.6 (11.4)	10.4 (10.0)	10.7(10.3)
Median	8.4	6.4	7.2
Q25% - Q75%	1.4-18.3	2.4-16.4	2.2-16.4
Min - max	0.0-38.4	0.2-37.5	0.0-38.4

N = Number of subjects, % = Percent subjects in treatment group of FAS

Pharmacodynamic Results

Primary Pharmacodynamic Endpoint

- The level of IgE-blocking factor increased from baseline to visit 4 in both the placebo group and the Grazax group. The change from baseline was statistically significantly greater in the Grazax group compared to placebo (difference (Grazax – placebo): 0.09, $p<0.0001$).

Secondary Pharmacodynamic Endpoints

- The level of $\log_{10}(IgE)$ increased from baseline to visit 4 in both the placebo group and the Grazax group. The change from baseline was statistically significantly greater in the Grazax group compared to placebo (difference (Grazax – placebo): 0.38, $p<0.0001$).
- The level of $\log_{10}(IgG_4)$ increased from baseline to visit 4 in both the placebo group and the Grazax group. The change from baseline was statistically significantly greater in the Grazax group compared to placebo (difference (Grazax – placebo): 0.14, $p<0.0001$).

Taken together, in-season initiation of Grazax induced an immunological response with significantly higher inductions of IgE-blocking factor, IgE, and IgG_4 observed for the Grazax group as compared with the placebo group in subjects with grass pollen induced rhinoconjunctivitis with or without asthma.

Tolerability Results

- In-season initiation of Grazax treatment was generally well tolerated.
- The majority of the AEs (including AEs related to Grazax) were mild or moderate in severity.
- The most frequently reported AEs related to Grazax treatment were local reactions in ear, mouth and throat with oral pruritus being the most frequent. Oral pruritus was primarily reported from initiation of treatment.
- Overall, 4 subjects experienced symptoms consistent with anaphylactic reaction when the relevant SMQ was applied. It should be emphasised that no anaphylactic reactions were reported by the reporting investigator or by the sponsor. The reactions defined within the SMQ were all mild or moderate in severity and all subjects fully recovered. No changes were made regarding the IMP. The symptoms were considered as non-serious and all subjects stayed in the trial.
- A total of 4 SAEs occurred during the trial – all in the Grazax group. None of the SAEs were considered related to Grazax treatment.
- A total of 7 subjects withdrew from the trial due to 9 AEs; 6 subjects (3%) in the Grazax group and 1 subject (2%) in the placebo group. In the Grazax group, 6 of the 8 events leading to withdrawal were judged as related to the treatment.
- For a total of 7 subjects, treatment was temporarily interrupted due to 13 AEs; 6 subjects (3%) in the Grazax group and 1 subject (2%) in the placebo group.
- No obvious difference was observed between the Grazax and placebo group with regard to the rhinoconjunctivitis symptom score although the score was slightly lower in the Grazax group both during the whole treatment period and during the GPS.
- No obvious difference was observed between the Grazax and placebo group with regard to the use of allergy/asthma medication although the number of subjects using medication and the mean number of days with medication (in subjects taking medication) were slightly lower in the Grazax group compared to placebo.
- No obvious difference was observed between the Grazax and the placebo group with regard to global evaluation of rhinoconjunctivitis symptoms.
- No safety concerns were found for FEV_1, vital signs, and physical examination.

Conclusions
In the analyses of the phamacodynamic effect parameters IgE-blocking factor, specific IgE, and IgG_4, a significant immunological response in subjects treated with Grazax was revealed with significantly higher inductions of IgE-blocking factor, IgE, and IgG_4 observed for the Grazax group as compared with the placebo group after approximately 9 weeks of treatment. These results are in accordance with immunological results obtained in other clinical trials performed with Grazax.
The most frequently reported IMP related AEs were mild to moderate local reactions in the mouth, throat, or ear – primarily oral pruritus. No SAEs related to Grazax were reported during the trial. No obvious difference between Grazax and placebo was observed with regard to rhinoconjunctivitis symptoms or the use of rhinoconjunctivitis and/or asthma medication further supporting the acceptable tolerability of in-season initiation of Grazax treatment. Finally, no safety concerns were observed for FEV_1, vital signs or physical examinations.
Taken together, in-season initiation of Grazax was found to be well tolerated and the tolerability was comparable to what has been observed in other clinical trials performed with Grazax in which treatment was initiated prior to the GPS. However, a suitable powered trial would be required to confirm the safety profile of this dosing regimen.

Date of the Report
4 May 2009

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