GT-08 Extension Integrated Clinical Trial Report

5th Year Final Report

Grass Pollen Season 2009

A randomised, parallel-group, double-blind, placebo-controlled Phase III trial assessing the efficacy and safety of ALK Grass tablet *Phleum pratense* in subjects with seasonal grass pollen induced rhinoconjunctivitis

Investigational Medicinal Product: ALK Grass tablet *Phleum pratense* (GRAZAX®)

Clinical trial ID:	GT-08 Extension
EudraCT No.	2004-000083-27
Indication:	Seasonal allergic rhinoconjunctivitis caused by grass pollen
Development phase:	III
First subject first visit:	30 September 2004 (5th year extension period started the day after the end of the grass pollen season 2008 for each subject)
Last subject last visit:	30 September 2009
Investigators:	Coordinating Investigators: [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD, [redacted] MD Signatory Investigators: [redacted] MD, [redacted] MD
Trial centre:	43 sites from 7 countries (Austria, Germany, Denmark, Italy, Netherlands, Sweden, United Kingdom)
Sponsor:	ALK-Abelló A/S Bøge Allé 6-8 DK-2970 Hørsholm, Denmark
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Report No. and date:	GT-08 Extension – Grass Pollen Season 2009. 5th Year Report Final version: 26 March 2010

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

Synopsis – Trial GT-08 Extension - Grass Pollen Season 2009

Title of Trial
A randomised, parallel-group, double-blind, placebo-controlled Phase III trial assessing the efficacy and safety of ALK Grass tablet *Phleum pratense* in subjects with seasonal grass pollen induced rhinoconjunctivitis

Investigators
43 investigators in 7 countries. [redacted] MD (Austria), [redacted] MD (Denmark), [redacted] MD (Germany), [redacted] MD (Italy), [redacted] MD (Netherlands), [redacted] MD (Sweden) and [redacted] MD (United Kingdom) were appointed coordinating investigators in their respective countries.
[redacted] MD (Austria) and [redacted] MD (Denmark) were appointed signatory investigators of the report.

Trial Centres
43 sites participated: 2 in Austria, 10 in Denmark, 10 in Germany, 3 in Italy, 5 in the Netherlands, 4 in Sweden and 9 in United Kingdom.

Publications
- Dahl, R.; Kapp, A; Colombo, G.; de Monchy, J.; Rak, S.; Emminger, W; Fernandez-Rivas, M.; Ribel, M.; and Durham, S. Efficacy and safety of sublingual immunotherapy with grass allergen tablet for seasonal allergic rhinoconjunctivitis. Journal of Allergy and Clinical Immunology 2006; 118(2): 434-440 (GT-08 1st year data)
- Durham, S.R. and Riis, B. Grass allergen tablet immunotherapy relieves individual seasonal eye and nasal symptoms, including nasal blockage. Allergy 2007; 62(8):954-7 (GT-08, 1st year data)
- Calderon, M.A.; Birk, A.O.; Andersen, J.S. and Durham, S.R. Prolonged pre-seasonal treatment phase with Grazax sublingual immunotherapy increases clinical efficacy. Allergy 2007; 62(8):958-961 (GT-02, GT-07 and GT-08 1st year data)
- Dahl, R.; Kapp, A.; Colombo, G.; de Monchy, J.G.; Rak, S.; Emminger, W.; Riis, B.; Grønager, P.M. and Durham, S.R. Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. Journal of Allergy and Clinical Immunology 2008; 121(2): 512-518 (GT-08 Extension 2nd year data)
- Frølund, L.; Durham, S.R.; Calderon, M.; Emminger, W.; Andersen, J.S.; Rask, P. and Dahl, R. Sustained effect of SQ-standardized grass allergy immunotherapy tablet on rhinoconjunctivitis quality of life. Allergy 2009 [Epub ahead of print] (GT-08 Extension 4th year quality of life data)
- Durham S.R.; Emminger, W.; Kapp, A.; Colombo, G.; de Monchy, J.G.; Rak, S.; Scadding, G.K.; Andersen, J.S.; Riis, B. and Dahl, R. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. Journal of Allergy and Clinical Immunology 2010; 125(1): 131-138 (GT-08 Extension 3rd and 4th year data)

Trial Period
First subject first visit – 30 September 2004 (5th year extension period started the day after the end-of-season visit 2008 for each subject)
Last subject last visit – 30 September 2009

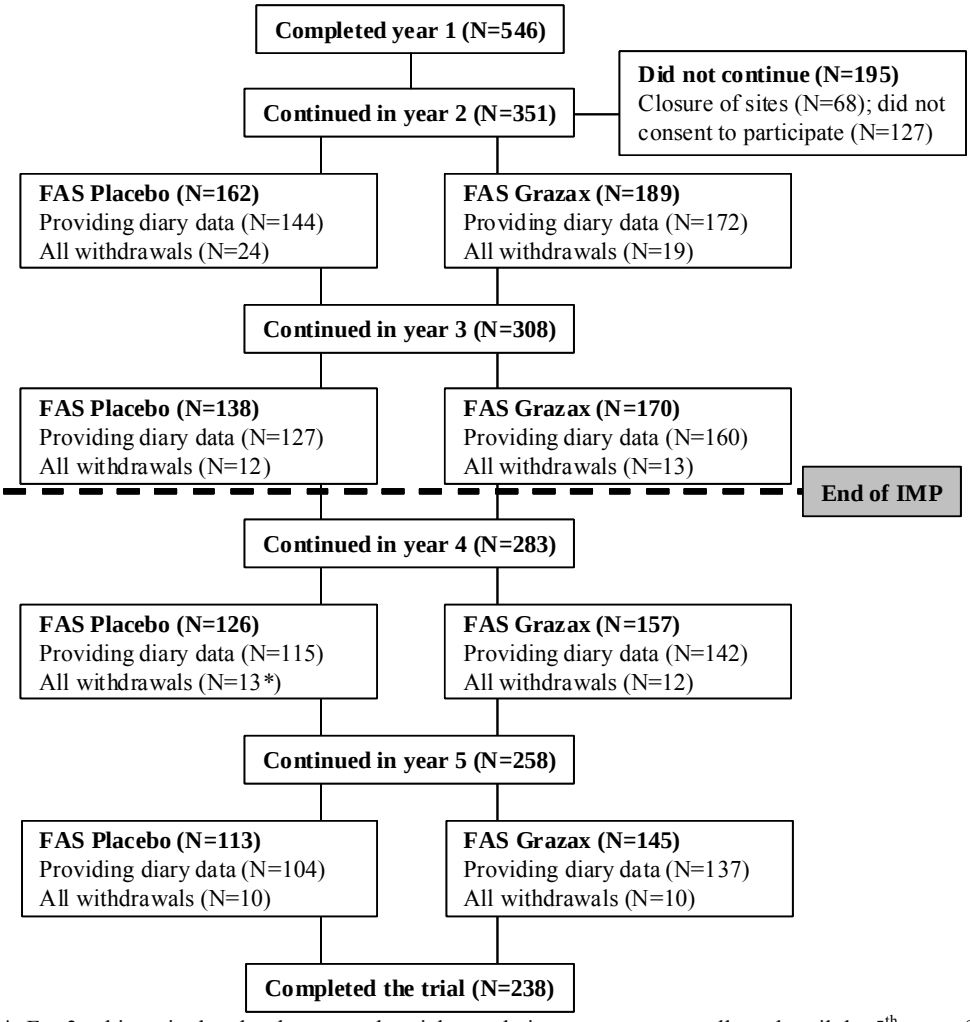
Objectives
To evaluate the sustained efficacy and tolerability of specific immunotherapy with ALK Grass tablet, 75,000 SQ-T (GRAZAX®), compared to placebo in adult subjects with grass pollen induced rhinoconjunctivitis.

Methodology

This was a randomised, parallel-group, double-blind, placebo-controlled, multi-centre trial.
The trial was an extension of GT-08 (subjects treated from autumn 2004 until the end of the grass pollen season 2005). Subjects participating in the extension of the trial continued treatment with Grazax or placebo until the end of the grass pollen season 2007. Subjects have been followed for a total of 2 years after the end of 3 years of blinded treatment; i.e. until the end of the grass pollen season 2009. The investigational treatment remained blinded during the 5 years of the trial. All subjects had access to open-label symptomatic medications for residual rhinoconjunctivitis and asthma symptoms during the entire trial.
The grass pollen season 2009 covered by this report was the last follow-up season, i.e. subjects did not receive any investigational medicinal product (IMP; Grazax or placebo).

Number of Subjects Planned and Analysed

It was planned to enrol approximately 350 subjects in the extension period; 175 in each group. 546 subjects completed year 1 of the trial; of them 351 accepted to participate in the trial extension. The subject distribution and treatment groups are presented below:



*: For 3 subjects in the placebo group the trial completion page was not collected until the 5th year of the trial, thus in the 4th year integrated clinical trial report these subjects were counted as continuing in the trial.

Main Inclusion Criteria

The main inclusion criteria were according to the original protocol:

- Males or females 18-65 years of age
- A clinical history of grass pollen induced allergic rhinoconjunctivitis of 2 years or more requiring treatment during the grass pollen season.
- A clinical history of severe rhinoconjunctivitis symptoms (interfering with usual daily activities or sleep), which remain troublesome despite treatment with anti-allergic drugs during the grass pollen season.
- Positive skin prick test response (wheal diameter ≥ 3 mm) to *Phleum pratense* and positive specific IgE against *Phleum pratense* (≥ IgE Class 2).
- FEV1 ≥ 70% of predicted value.
- No clinical history of symptomatic seasonal allergic rhinitis and/or asthma due to tree pollen or weed pollen adjacent to the start of and potentially overlapping the grass pollen season.
- No clinical history of significant active perennial allergic rhinitis and/or asthma caused by an allergen to which the subject is regularly exposed.

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

Not applicable; during this year of the trial subjects received open-label symptomatic medications only (i.e. standard symptomatic medications for rhinoconjunctivitis and asthma symptoms as needed).

Reference Therapy, Dose and Mode of Administration, Batch Numbers

Not applicable; during this year of the trial subjects received open-label symptomatic medications only (i.e. standard symptomatic medications for rhinoconjunctivitis and asthma symptoms as needed).

Duration of Treatment

The IMP treatment was administered 4-8 months prior to the anticipated start of the grass pollen season 2005 and double-blind treatment continued until the end of the grass pollen season 2007.

During the grass pollen season 2009 covered by this report, subjects received symptomatic medications only (i.e. standard therapy for rhinoconjunctivitis and asthma symptoms as needed).

Criteria for Evaluation – Efficacy

Primary Efficacy Endpoints

1: Average daily rhinoconjunctivitis symptom score for the entire grass pollen season 2009

2: Average daily rhinoconjunctivitis medication score for the entire grass pollen season 2009

Key Secondary Efficacy Endpoints

1: Average weekly overall rhinoconjunctivitis quality of life score for the entire grass pollen season 2009

2: Percentages of rhinoconjunctivitis symptom and medication free days for the entire grass pollen season 2009

Additional Secondary Efficacy Endpoints

- Combined rhinoconjunctivitis symptom and medication score for the entire grass pollen season 2009 (5 different measures constructed)
- Rhinoconjunctivitis symptom and medication scores for the peak grass pollen season 2009
- Rhinoconjunctivitis quality of life overall score for the peak grass pollen season 2009
- Rhinoconjunctivitis quality of life domain scores for the entire and peak grass pollen season 2009
- Rhinoconjunctivitis well days in the entire and peak grass pollen season 2009
- Symptom and medication free days in the peak grass pollen season 2009
- Days with severe symptoms in the entire and peak grass pollen season 2009
- Changes in immunological parameters (IgE, IgE-blocking factor, and IgG4)
- Assessment of rhinoconjunctivitis symptoms by visual analogue scale in the entire and peak grass pollen season 2009
- Global evaluations
  1: Global evaluation of most severe rhinoconjunctivitis symptoms during the grass pollen season 2009
  2: Global evaluation in the overall comparison of the grass pollen season 2009 versus the previous season
- Individual rhinoconjunctivitis nose and eye symptom scores for the entire and peak grass pollen season 2009
- Excellent rhinoconjunctivitis control based on well days and based on symptom and medication free days during the entire grass pollen season 2009
- Number of sensitivities defined by skin prick tests
- Pre-defined comparison of endpoints from the entire grass pollen seasons 2005, 2006, 2007, 2008 and 2009
- Average daily asthma symptom score for the subset of subjects with asthma at inclusion for the entire and peak grass pollen season 2009
- Average daily asthma medication score for the subset of subjects with asthma at inclusion for the entire and peak grass pollen season 2009
- Difference in number of subjects that may have developed asthma (based on asthma medication use)
- Difference in percentages of days with asthma symptoms during the entire grass pollen season 2009
- Analysis of influence of grass pollen season on symptom, medication, combined, and RQLQ scores
- Time to first use of any symptomatic medications, time to first use of nasal steroids, and time to first day with severe symptoms (from the start of the defined grass pollen season 2009)
- Difference in numbers of lost working hours, visits to general practitioner, unscheduled visits to an allergy specialist, visits to acute ward and hospitalisations during the entire and peak grass pollen season 2009
- Difference in quality of life (measured by SF-36, EQ-5D)

Criteria for Evaluation – Safety

The safety evaluation included data from the entire trial, as the safety endpoints other than adverse events were not evaluated in the previous yearly reports of the trial due to blinding issues. Safety endpoints included:

- Adverse events (FAS 2009 as well as safety analysis set)
- Physical examinations (safety analysis set)
- Vital signs (safety analysis set)
- FEV_1 (safety analysis set)
- Clinical laboratory tests (safety analysis set)

Statistical Methods

The following analysis sets were used:

- Full analysis set 2009 (FAS 2009) – comprising all randomised subjects entering the 5th year of the trial (the 5th year was defined as the period from the day after the end-of-season visit 2008 to the end-of-trial visit 2009). The efficacy analyses comprised those delivering diary data during the grass pollen season 2009.
- Safety analysis set – comprising all randomised subjects in the entire trial

The 2 treatment groups compared were placebo and Grazax. The primary efficacy analysis of the year 2005 data is considered to be the final primary efficacy analysis of the trial.
For all previous years (2005, 2006, 2007 and 2008), the primary endpoints were tested hierarchically and found statistically significant. The primary and key secondary endpoints for this year (i.e. 2009) were also tested hierarchically at unadjusted alpha=0.05. No adjustment for multiplicity in the additional secondary endpoint analyses was done.
The primary investigation of the comparison of the 2 treatment groups was done via a generalised linear mixed model (GLMM) with the average rhinoconjunctivitis symptom score or the average rhinoconjunctivitis medication score as response variable and treatment group as a fixed effect and pollen region (aggregated to country) as random effect as well as adjusting for different error variation for each treatment group. A 2-sided 95%-confidence interval for the difference in adjusted means between the two groups has been presented as well as the p-value. Also the difference in adjusted means between the two treatment groups relative to the adjusted mean of the placebo group has been presented as a percentage. Furthermore, confidence interval for the percentage difference relative to placebo is presented (found by bootstrapping). A p-value describing the statistical significance of the pollen region (aggregated to country) was included in the tables.
For the efficacy analyses no imputation of data was carried out, but all available data was used to its full extent. The only exception was for the excellent rhinoconjunctivitis control endpoint where withdrawals due to adverse events by default were counted as not having excellent control.

Demography of Trial Population

Generally, the demographics and baseline characteristics were well balanced between the 2 treatment groups.

Treatment Group	Placebo		Grazax		Overall	
Subjects, N (%)	**113**	**(100)**	**145**	**(100)**	**258**	**(100)**
Sex						
Men, N (%)	73	(65%)	95	(66%)	168	(65%)
Women, N (%)	40	(35%)	50	(34%)	90	(35%)
Age (Years)						
Mean (SD)	37.2	(10.1)	36.6	(9.81)	36.9	(9.91)
Median	37		36		36	
Q25% - Q75%	30.0 - 42.0		29.0 - 43.0		29.0 - 43.0	
Min-max	18.0 - 63.0		19.0 - 63.0		18.0 - 63.0	
Ethnic Origin						
Caucasian, N (%)	109	(96%)	142	(98%)	251	(97%)
Other, N (%)	4	(4%)	3	(2%)	7	(3%)
Country						
Austria, N (%)	5	(4%)	6	(4%)	11	(4%)
Denmark, N (%)	28	(25%)	36	(25%)	64	(25%)
Germany, N (%)	30	(27%)	46	(32%)	76	(29%)
Italy, N (%)	7	(6%)	8	(6%)	15	(6%)
Netherlands, N (%)	11	(10%)	6	(4%)	17	(7%)
Sweden, N (%)	14	(12%)	21	(14%)	35	(14%)
United Kingdom, N (%)	18	(16%)	22	(15%)	40	(16%)
Smoking						
Never smoked, N (%)	66	(58%)	95	(66%)	161	(62%)
Currently smoking, N (%)	27	(24%)	20	(14%)	47	(18%)
Stopped smoking, N (%)	20	(18%)	30	(21%)	50	(19%)
Severity of Grass Pollen Allergy						
Moderate, N (%)	52	(46%)	61	(42%)	113	(44%)
Severe, N (%)	61	(54%)	84	(58%)	145	(56%)
Grass Pollen Allergy (Years):						
N	112		145		257	
Mean (SD)	17.1	(10.5)	19.5	(10.5)	18.4	(10.6)
Median	16.5		19		18	
Q25% - Q75%	10.0 - 24.0		12.0 - 26.0		10.0 - 24.0	
Min-max	1.00 - 48.0		2.00 - 54.0		1.00 - 54.0	

N=number of subjects, %=percent of subjects of full analysis set.

Efficacy Results

The follow-up analysis 2 years after the end of 3 years of continuous all year round treatment, showed sustained significant and clinically relevant efficacy of Grazax compared to placebo in terms of the rhinoconjunctivitis symptom score. Thus, Grazax provides sustained long-term efficacy with disease modifying effect 2 years after end of treatment.

For the rhinoconjunctivitis medication score, a difference between Grazax and placebo was also found in favour of Grazax: however, not statistically significant. The 2009 grass pollen season was significantly milder than the previous seasons. Due to the confirmed influence of grass pollen exposure on the symptom and medication scores, this is inevitably influencing the size of the efficacy measurements.

Overall, the comparison of efficacy between Grazax and placebo showed improvements in favour of Grazax for the key secondary efficacy endpoints and most of the additional secondary efficacy endpoints 2 years after end of treatment.

The pre-defined comparison of efficacy endpoints in year 2009 to the previous seasons showed no statistically significant differences to the 1st follow-up season (2008) or the last treatment season (2007). However, for a few endpoints there were significant differences between year 2009 and year 2005 or year 2006. This may very well be due to natural variation between grass pollen seasons rather than true difference in treatment efficacy.

No efficacy in terms of prevention of new sensitisations and prevention of asthma could be verified. It should be noted that the trial was performed in an adult population, and very few new sensitisations and new asthma onsets were noted in any group.

Primary Efficacy Endpoints
The primary efficacy analysis showed that 2 years after completion of treatment, the Grazax group had a reduction of 25% in rhinoconjunctivitis symptom score when compared to placebo (p=0.0037) over the entire grass pollen season and a reduction of 20% in rhinoconjunctivitis medication score (p=0.1136).
Key Secondary Efficacy Endpoints
Subjects treated with Grazax reported better rhinoconjunctivitis quality of life during the entire grass pollen season 2 years after completion of the 3 years of treatment. A reduction in overall average weekly rhinoconjunctivitis quality of life score of 19% was found (p=0.0587) when comparing the Grazax group with placebo during the entire grass pollen season.
The difference in percentages symptom and medication free days during the entire grass pollen was 20% (p=0.17374) in favour of Grazax treatment.
Other Secondary Efficacy Endpoints
The differences in adjusted means relative to placebo for the combined scores (calculated in 5 different ways) were between 23%-27% in favour of treatment with Grazax (all statistically significant).
In the peak grass pollen season, a reduction of the rhinoconjunctivitis symptom score of 27% was found when compared to placebo (p=0.0004) and the use of rhinoconjunctivitis medication was reduced by 19% (p=0.1294).
The treatment effect on rhinoconjunctivitis quality of life during the peak grass pollen season was 25% (p=0.0081) in favour of Grazax.
The difference between treatment groups in individual RQLQ domain scores were all in favour of Grazax, both during the entire and the peak grass pollen season, however, only the sleep problems and the eye symptoms domains were consistently statistically significant. During the peak season also the activity limitation, non-nose/eye symptoms and nasal symptoms domains reached statistically significance.
The increase in percentage of well days for Grazax relative to placebo was 24% in the entire grass pollen season (p=0.0203), and 37% (p=0.0356) in the peak grass pollen season. The odds ratio of having a well day in the Grazax group versus the placebo group was 1.66 (p=0.0877) during the entire grass pollen season and 2.33 (p=0.0377) during the peak grass pollen season.
The difference in percentage of symptom and medication free days for Grazax relative to placebo was 33% in the peak grass pollen season (p=0.1671).
Analyses of the percentage of severe days during the entire grass pollen resulted in a statistically significant difference of 55% (p=0.0068) in favour of treatment with Grazax and correspondingly 64% (p=0.0002) during the peak grass pollen season. The odds ratio of having a severe day during the entire grass pollen season in the Grazax group versus the placebo group was 0.41 (p=0.0012) and 0.24 (p<0.0001) during the peak season.
Statistically significant differences in changes from baseline in specific IgG_4 and IgE-blocking factor between Grazax and placebo were maintained 2 years after end of treatment (p<0.0001). Also the levels of specific IgE were significantly different between the groups (p=0.0389).
The analysis rhinoconjunctivitis symptoms by VAS scores showed a statistically significant lower score for the Grazax group of 27% (p=0.0132) during the entire grass pollen season and 32% (p=0.0014) during the peak grass pollen season.
A statistically significant difference in global evaluation of the symptom score of 14% (p=0.0304) between Grazax and placebo was found.
The analysis of the global improvement in 2009 showed that the odds ratio of having improvement in year 2009 was 0.67 (p=0.0256), thus it was slightly more likely for the placebo group to improve relative to the 1st follow-up year than for the Grazax group.
There were statistically significant treatment effects of Grazax at a size of 23%-36% for the nose symptoms in total, the eye symptoms in total, and for all individual nose and eye symptom during the entire and the peak grass pollen season, except for the blocked nose symptom score during the entire grass pollen season (difference 16%, p=0.2336).
The statistical analysis showed that the odds for having excellent rhinoconjunctivitis control in the Grazax group were almost twice as high as in the placebo group (odds ratio: 1.82, p=0.0280).
Statistical analyses of the numbers of new skin sensitivities did not show any differences between the treatment groups.
For the asthma endpoints there were no statistically significant differences between the Grazax and the placebo group (for subjects with asthma at inclusion) during the entire or peak grass pollen season 2009. Further, the data set was too limited to draw any conclusions regarding the prevention of asthma (based on asthma symptom and medication free days in the subjects without asthma at inclusion) in the two groups.
The analysis of influence of grass pollen counts on symptom, medication, and combined score 3, showed that

the more grass pollen, the larger the difference between placebo and Grazax.
The analyses of time to first use of nasal steroids, time to first use of rhinoconjunctivitis symptomatic medications, and time to first day with severe symptoms during the entire grass pollen season 2009, showed distinctions between the treatment groups for each parameter, in favour of Grazax.
Analyses of lost working hours, general practitioner visits and unscheduled specialist visits during the entire grass pollen season 2009 could not be carried out as planned due to too few subjects reporting these.
The generic quality of life questionnaire SF-36 revealed no statistically significant differences between groups during the entire or peak grass pollen season 2009.
The EQ-5D health outcome instrument showed that 98% of the EQ-5D records in the Grazax group versus 96% in the placebo group was recorded as full health during the entire grass pollen season 2009 (p=0.2421). A post hoc analysis showed that 18% more subjects in the Grazax group had full health during the entire grass pollen season 2009 versus the placebo group (p=0.08).

Safety Results
During the 5 years of the trial, a total of 2607 AEs were reported by the 634 subjects. 1773 of the AEs were reported by the FAS 2009; 80% were assessed as unlikely related to the IMP. The most common IMP-related AEs were local application site related AEs, such as oral itching and mouth oedemas. The vast majority of the IMP-related AEs had onset during treatment initiation and had duration of less than one month.
No long-term safety issues in relation to the IMP (i.e. IMP-related AEs with onset during the follow-up years) were reported.
42 SAEs were reported during the 5 years of the trial; 24 in the placebo group and 18 in the Grazax group. All were assessed as unlikely related to the IMP. No events of anaphylactic reactions were reported during the 5 years of the trial.
Over the 5 years of the trial, 41 AEs led to withdrawals of a total of 29 subjects (including 1 death). 18 of the AE withdrawals belonged to the Grazax group and 11 to the placebo group. 24 of the AE withdrawals occurred during the 1st year of the trial, while the remaining 5 occurred in the extension (during the 2nd or 3rd year of the trial).
13 pregnancies were reported during the trial, 5 in the placebo group and 8 in the Grazax group. For one in the placebo group, a caesarean section was reported; the mother and baby fully recovered. For the remaining no complications were reported.
No issues were detected in lung function assessments, physical examinations, vital signs or safety laboratory analyses.

Conclusions
The trial met the primary objective with sustained long-term effect on the rhinoconjunctivitis symptom score, thus demonstrating disease modifying effect of tablet immunotherapy with Grazax, however, the second ranked endpoint, the rhinoconjunctivitis medication score did not reach statistically significance. Grazax provided a reduction of 25% in rhinoconjunctivitis symptom score (p=0.0037) and a reduction of 20% in rhinoconjunctivitis medication score (p=0.1136) when compared with placebo, during the entire grass pollen season 2009.
For the key secondary efficacy endpoints and most of the other secondary efficacy endpoints differences between Grazax and placebo were pronounced and in favour of specific immunotherapy with Grazax, although statistically significance were not reached for all endpoints. For the 5 different constructions of a combined symptom and medication score, including the one recommended by the World Allergy Organization, statistically significant differences were found in favour of Grazax.
The results for the 2nd follow-up year should be interpreted in the light of a significantly milder grass pollen season in 2009, than in previous years of the trial.
The clinical findings were supported by sustained immunological changes, comparable to what has previously been shown following completion of subcutaneous immunotherapy.
No long-term safety issues were identified during the trial.
In conclusion, the present analysis supports the benefit of 3 years of continuous all year round immunotherapy with Grazax, in a large-scale, randomised, double-blind, placebo-controlled trial, by showing sustained long-term efficacy and disease modifying effect in the post-treatment years.

Date of the Report
Final version: 26 March 2010

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