Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunological changes over 2 years

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Background: The trial is a randomized, double-blind, placebo-controlled Phase III trial with 3 years of daily treatment with grass tablet immunotherapy (GRAZAX®, ALK-Abelló A/S) or placebo followed by two years of follow-up to assess the persistent efficacy.

Objective: To evaluate the efficacy and safety of specific immunotherapy with grass allergen tablets compared to placebo after treatment covering two consecutive grass pollen seasons.

Methods: The interim analyses included 351 adult participants with moderate to severe allergic rhinoconjunctivitis due to grass pollen. Participants were treated with active (N=189) or placebo (N=162) tablets for on average 22 months. All participants were allowed to use symptomatic rescue medication.

Results: The primary efficacy analysis showed highly significant mean reductions of 36% in rhinoconjunctivitis symptom score (p<0.0001) (median reduction 44%) and 46% in rhinoconjunctivitis medication score (p<0.0001) (median reduction 73%) in the active group relative to placebo. Mean rhinoconjunctivitis quality of life was 33% better (p<0.0001) (median 40%). Clinical improvements were paralleled by significant changes in allergen specific immunoglobulins. The treatment was well-tolerated and adverse events led to withdrawal in less than 1% of participants. There were no serious adverse events related to treatment.

Conclusion: Grass allergen tablet immunotherapy showed progressive immunological changes and highly significant efficacy over two years of continued treatment.

Clinical Implication: Sublingual tablet immunotherapy with grass allergen tablets is effective in reducing rhinoconjunctivitis symptoms, use of medication and in improving quality of life during the grass pollen season, with a progressive immunological effect when administered during two consecutive years.
Capsule summary: We have shown that sublingual immunotherapy with the grass allergen tablet provides sustained clinical benefit over 2 years coupled with progressive immunological changes that support its long-term use.

Key words: Allergy, asthma, grass pollen, immunotherapy, sublingual, rhinoconjunctivitis, tablet-based, double-blind, placebo-controlled, Phleum pratense

Abbreviations: GPS: grass pollen season; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
Introduction

An estimated 45 million people in Europe suffer from grass pollen allergy (1), and many patients feel that the allergy impacts their quality of life (2). A survey of adult hay fever patients, prescribed a non-sedating antihistamine and nasal steroid spray, revealed that there was a significant burden of residual symptoms, even among those receiving current optimal therapy, which identifies a substantial unmet need and a requirement for novel therapies for allergic rhinoconjunctivitis (3).

Immunotherapy has an advantage compared to symptomatic treatment of allergy in view of its potential to target the immunological process underlying allergic diseases and induce long-term remission (4). Based on results from subcutaneous immunotherapy e.g. (5-8), international clinical guidelines recommend that immunotherapy maintenance treatment is continued for 3-5 years (4;9-11), and studies have further demonstrated a maintained clinical effect in the years following termination of treatment (12-15). There are increasing data to support that this may also be true for the sublingual route (16-18).

A fast-dissolving, once-daily grass immunotherapy tablet (GRAZAX®, Phleum pratense, ALK-Abelló A/S) for treatment of grass pollen allergy has been developed. The safety and efficacy of the grass allergen tablet during the first treatment season has been demonstrated and reported previously (19-24). In view of the need of long-term data on sublingual immunotherapy, this trial (24) was extended to cover long-term and persistent efficacy. This paper reports the interim results after the second grass pollen season when the participants had received daily treatment for approximately 22 months.
Methods

A randomized, parallel group, double blind, placebo-controlled, multi-centre trial. The trial is an extension of a previously published trial, in which participants received double blind treatment from the autumn 2004 and until the end of the grass pollen season 2005 (24). 351 participants from 43 sites in 7 countries continued treatment with grass allergen tablets or placebo in the extension of the trial and will continue treatment until the end of the grass pollen season 2007. The participants will provide data for additionally 2 grass pollen seasons; thus the participants will be followed for a total of 5 years. This paper covers the period from September 2005 through August 2006; i.e. the efficacy and safety of the grass allergen tablet during the grass pollen season 2006.

Written informed consent was obtained from all participants before entering the trial, and the trial was performed in accordance with the Declaration of Helsinki (25) and Good Clinical Practice. The ethics committees in each of the participating countries approved the trial. The main inclusion criteria were as described previously (24): males or females, 18-65 years of age, a clinical history of moderate to severe grass pollen induced allergic rhinoconjunctivitis of 2 years or more requiring treatment during the grass pollen season, which remain troublesome despite treatment with anti-allergic drugs, a positive skin prick test response (wheal diameter ≥ 3 mm) to *Phleum pratense*, a positive specific IgE against *Phleum pratense* (≥ IgE Class 2), a 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 and no clinical history of significant active perennial allergic rhinitis and/or asthma caused by an allergen to which the participant is regularly exposed.
The treatment started 4-8 months prior to the anticipated start of the grass pollen season 2005; and by the time of this interim analysis all participants had received treatment with the grass allergen tablet or placebo for approximately 22 months.

For each pollen region the grass pollen season was defined as the first day of 3 consecutive days with grass pollen counts $\geq 10$ grains/m$^3$ to the last day before 3 consecutive days with grass pollen count < 10 grains per m$^3$.

The primary efficacy endpoints were rhinoconjunctivitis symptom and medication scores. The rhinoconjunctivitis symptom score was based on 6 rhinoconjunctivitis symptoms (4 nose symptoms: runny nose, blocked nose, sneezing and itchy nose and 2 eye symptoms: gritty feeling/red/itchy eyes and watery eyes), that were scored on a daily basis on a scale with the following values: 0 (no symptoms); 1 (mild symptoms); 2 (moderate symptoms) or 3 (severe symptoms). The rhinoconjunctivitis medication score was based on the following rescue medication: Desloratadine (5 mg) up to 1 tablet daily, 6 points per tablet; Olopatadine eye drops (1.0 mg/ml) up to 1 drop in each eye twice daily, 1.5 points per drop; Budesonide nasal spray (32 µg/puff) up to 2 puffs per nostril twice daily, 1 point per puff; and Prednisone (5 mg/tablet), 1.6 points per tablet. The scores presented are averages of the daily rhinoconjunctivitis symptom or medication score for each participant for the entire grass pollen season. Other efficacy endpoints included quality of life assessed using Juniper’s Rhinocconjunctivitis Quality of Life Questionnaire (RQLQ) (26); symptom and medication free (healthy) days; and global evaluations of the most severe rhinoconjunctivitis symptom during the 2006 season.
Furthermore changes in immunological blood markers (specific IgE, IgE-blocking antibodies and IgG4) were investigated for the Danish sites only in 2005 but for all sites in 2006. *Phleum pratense* specific IgE was measured using an ADVIA Centaur Immunoassay System (Bayer Healthcare, NY, USA) as described by Petersen et al (27). The inhibitory capacity of IgE-blocking antibodies for the reaction between IgE and *Phleum pratense* allergens (termed IgX), was estimated as a ratio between IgE measured using a modification of the Petersen et al protocol (excluding the first washing step, thus allowing non-IgE antibodies to compete with IgE for the allergen) and IgE measured using the conventional protocol (19;22). The *Phleum pratense* specific IgG4 assay was performed similar to the IgE assay with few modifications. Anti human IgE were replaced with a murine monoclonal anti human IgG4 and to counteract for the amount of non specific IgG4 in the serum samples, sera were diluted. The amount of specific IgG4 in the serum samples were estimated to a dilution of a standard serum pool (arbitrary unit, AU) in order to obtain a standardized measure. Adverse events were assessed and comprised the safety evaluation.

Comparison of the two treatment groups was done by analysis of variance with the efficacy endpoint as response variable, treatment group as a fixed effect, pollen region as random effect, and adjusting for different error variation in each treatment group. Specific IgE and IgG4 were Log10-transformed before doing comparisons between treatment groups. This was necessary in order to obtain approximately normally distributed residuals in the statistical analysis.
Results

A total of 546 participants completed the first year of the trial. Due to closure of a few trial centers, only 472 could be offered to continue in the extension. 351 participants accepted to participate in the extension period of the trial and continued treatment with grass allergen tablets or placebo after the grass pollen season 2005. A diagram of the trial flow is presented in Figure 1. 319 participants were in the trial when the grass pollen season 2006 started and 306 when the pollen season ended. The average length of treatment at the end of the grass pollen season 2006 was 22 months. Of the 45 withdrawals, 3 withdrew due to adverse events and 4 due to a perceived lack of effect. The number and reasons for withdrawal was similar between treatment groups.

All participants had a history of moderate (N=143, 41%) or severe (N=208, 59%) grass pollen allergy at inclusion. The average duration of grass pollen allergy was 17.8 (SD=10.4) years. Overall demographics were similar between the two treatment groups (Table 1). In addition, the demographics of the participants in the extension of the trial were similar to the demographics of the participants that did not participate in the extension (see Table E1 in the Online Repository). Importantly the symptom and medication scores for the participants that did and did not continue in the extension were also similar after the first season (see Figure E1 in the Online Repository). The p-values for a difference in treatment effect during the grass pollen season 2005 between subjects continuing and subjects not continuing were p=0.27 for the symptom score and p=0.81 for the medication score. Thus, the participants in the extension are considered a representative subset of the population originally included in the trial.
Grass pollen counts were obtained from 28 regional pollen stations in the participating countries. The average grass pollen season lasted 59 days (range: 30-116 days). No major differences were seen between the grass pollen seasons 2005 and 2006.

**Efficacy**

The average daily rhinoconjunctivitis symptom and medication score for the entire grass pollen season 2006 are illustrated in Figure 2 together with the weighted average of daily grass pollen counts. A higher score indicates a higher level of symptoms or use of medication. Participants treated with grass allergen tablets scored statistically significantly lower than participants treated with placebo during the entire grass pollen season 2006 (p<0.0001). The mean difference relative to placebo was 36% in symptom score and 46% in medication score in favor of the grass allergen tablets (Table 2). For comparison, results after the first treatment season (2005) are also shown; the corresponding differences to placebo were 30% (p<0.0001) and 38% (p<0.0001) (see also (24)). The subgroup of patients that completed both treatment years had similar reductions in symptom and medication scores as the entire population in 2005 (33% and 36% respectively).

There was a statistically significant difference for all six individual symptom scores relative to placebo (gritty feeling/red/itchy eyes 37%, watery eyes 51%, runny nose 34%, blocked nose 32%, sneezing 32% and itchy nose 35%; all p-values<0.002) during the second grass pollen season.

The percentage of days without symptoms and use of rescue medication was calculated (Table 2). Participants treated with grass allergen tablets had on average 46% symptom and
medication free days during the grass pollen season (corresponding to 20 days in 2006 (17
days in 2005)), versus 32% in the placebo group (15 days in 2006 (13 days in 2005)). The
difference of 45% was highly statistically significant (p<0.0001). The median numbers of
symptom and medication free days was 9 in the placebo group versus 18 in the grass allergen
tablet group.

Quality of life was assessed by means of Juniper’s rhinoconjunctivitis quality of life
questionnaire (RQLQ) (28). A significant better quality of life (i.e. a lower RQLQ score) was
reported in the group treated with grass allergen tablets relative to the placebo group (Table
2). The difference in overall score was 0.41, corresponding to 33% (p<0.0001).

The participants’ global assessment of rhinoconjunctivitis symptoms during the grass pollen
season was performed at the end of the season by asking "how do you assess the severity of
your rhinoconjunctivitis symptoms, when they were the most severe during this grass pollen
season?" The adjusted mean score for the active group was 5.78 versus 8.35 in the placebo
group (Table 2). The difference of 31% was highly statistically significant (p<0.0001). The
alterations in the global evaluation from 2004 to 2005 and 2006 are illustrated in Figure 3.
The differences in the grass allergen tablet group relative to placebo were numerically higher
than in the first treatment season (Table 2), with a trend towards statistical significance
(p=0.0789) for the global evaluation during the second treatment season.

The immunological endpoints, specific IgE, specific IgG4 and IgE-blocking antibodies, were
measured after the grass pollen season (2006) and compared to the measurements performed
after the first grass pollen season (in a subset of serum samples) (Figure 4). For the placebo
group there were small seasonal variations in the levels of *Phleum pratense* specific IgE during the grass pollen seasons (Figure 4A). In the immunotherapy group there was an initial significant rise in specific IgE of more than 3-fold after 2 months of treatment which decreased over time. After 22 months of treatment the level of specific IgE approached the level measured at the screening visit, although remained statistically significantly different from the level observed in the placebo group. An increase in the level of IgE-blocking antibodies was seen in the grass allergen tablet group during the first 10 months and then a further elevation was observed at 22 months, whereas IgE-blocking antibodies in the placebo group did not change over the same time period. The increase in IgE-blocking antibodies observed in the actively treated group was significantly higher compared with placebo-treated subjects both from 10 to 22 months of treatment (p=0.0003) and from 19 to 22 months of treatment (p<0.0001).

*Phleum pratense* specific IgG4 was measured in serum samples obtained at screening, after the first treatment season (10 months) and after the second treatment season (22 months) (Figure 5). The levels did not change in the placebo group, whereas there was a rapid increase in IgG4 in the grass allergen tablet group of 1 unit on the Log10-scale (corresponding to a 10-fold increase) from treatment initiation to 10 months of treatment, followed by a slower increase of 0.4 units on the Log10-scale (corresponding to a 2-fold increase) from 10 to 22 months of treatment. These increases were statistically significant both from 0 to 10 months of treatment (p<0.0001) and from 10 to 22 months of treatment (p=0.0001). From treatment initiation to 22 months of treatment an increase of 1.4 units were observed corresponding to a 23-fold increase.
Safety

The overall frequency and severity of adverse events with start and stop date during the second treatment year are tabulated in Table 3. Adverse events ongoing at the time of this interim analysis were not included. A total of 67 (41%) participants treated with placebo and 97 (51%) treated with grass allergen tablets reported at least 1 adverse event during the second year of the trial. More than 90% of the reported events were assessed unlikely related to the trial medication in both groups. Participants receiving grass allergen tablets reported 14 adverse events with probable or possible relation to the trial medication; the same number of probably or possibly related adverse events was reported in the placebo group. Of the 28 related adverse events, only 4 types of events (oral pruritus: 4 events, conjunctivitis: 4 events, nasopharyngitis: 2 events, and allergic rhinitis: 2 events) occurred in more than one subject. No serious adverse events with possible or probable relation to the trial medication were reported.

In contrary to the first treatment year, there was no predominance of application site related adverse events in the grass allergen tablet group during the second treatment year. Whereas oral pruritus was reported by 46% of actively treated participants versus 4% in the placebo group during the first year (24) only 3 participants overall reported 4 events of oral pruritus during the second treatment year. Ear pruritus and tongue swelling were not reported at all during the second treatment year. Only 3 participants (2 from the placebo group, 1 from the active group) withdrew due to in total 5 adverse events (mild headache; mild burning pain in left groin, moderate viral infection and moderate lymph nodes increasing; and mild bilateral knee pain/arthritis).
Discussion

The present data are from an extension of a trial where approximately 65% of the completers from the original trial chose to continue double-blinded treatment during the extension. Different analyses were performed to investigate whether the population that continued in the extension of the trial was representative for the entire population during the first year of the trial. The analyses demonstrated that both demographics and symptom and medication scores for the first year of treatment were virtually identical in the extension population compared to the participants that elected not to continue in the extension.

Treatment with grass allergen tablets resulted in a 36% decrease in rhinoconjunctivitis symptoms and on top of that an additional 46% reduction in the use of symptomatic medication relative to placebo. This is a numerically greater improvement as compared to the treatment effect after the first year of treatment and suggests a sustained benefit of sublingual immunotherapy treatment over more than one season. Note that no major differences were observed between the pollen counts in the two seasons. This is in line with the recommended treatment regimen for subcutaneous immunotherapy (4;9;10). Although the continuing treatment regimen has been widely adapted for sublingual treatment with named patient products (11), this is the first large-scale, double-blinded, placebo-controlled trial to support this approach for sublingual immunotherapy. The treatment effects during the second year were numerically higher than those observed during year one although did not achieve statistical significance compared to year one, possibly because the trial was not originally powered to detect differences between treatment years. None-the-less a trend for a significant effect between years one and two was observed for global evaluation scores (p=0.08).
The participants receiving grass allergen tablets reported significantly improved quality of life relative to the placebo group (by means of the RQLQ (28)) and in the global assessment of the most severe rhinoconjunctivitis symptoms during the previous season, there was a statistically significant difference in the adjusted mean score of 31%. The descriptive comparison to the global assessment after the grass pollen season 2005 suggested a difference in treatment effect in year 2 above that observed in year 1 (Figure 3); however, the p-value in the comparative analysis was 0.08.

Specific immunotherapy is the only treatment modality that addresses the cause of allergic disease, with alterations of allergen specific T-cell (29;30) and B-cell responses (29) during subcutaneous immunotherapy that are associated with persistent clinical improvement that potentially lasts for years after discontinuation (12). The immunological endpoints in this trial imply that a progressive treatment-related effect also occurs during sublingual immunotherapy with grass allergen tablets. The patterns over time seen in *Phleum pratense* specific IgE and IgE-blocking antibodies resembled that previously observed for both subcutaneous (31; 32) and sublingual (31; 33; 34) immunotherapy.

Specific IgG4 increased significantly in the grass allergen tablet group over the two seasons to 23-times the level at screening. Two years of treatment with subcutaneous immunotherapy has shown to induce a >100-fold increase in IgG4 (32), thus the kinetics may differ for the two administration routes. The link between immunological changes and clinical efficacy is not clarified as yet, but the present data suggests that the clinical effect is not directly dependent on the size of the increase in immunoreactive IgG4 since the clinical effect with the grass
allergen tablet was similar to that reported for subcutaneous immunotherapy in a comparable group of patients with the same grass allergen extract (35).

Treatment with grass allergen tablets was well-tolerated during the second treatment season with significantly fewer related adverse events than in the first year of treatment. More than 90% of the adverse events were considered unlikely related to trial medication and the withdrawal rate due to adverse events was below 1% overall. Although sublingual immunotherapy is considered a safe and effective therapeutic option for patients with allergic rhinitis and asthma and has been approved by the World Health Organization since 1988 (36), long-term data on the effect on rhinoconjunctivitis symptoms in particular are sparse. In an open-trial with 4-5 years of treatment with sublingual house dust mite immunotherapy, a highly significant decrease in asthma medication was observed that remained during the 4-5 years follow-up (18). The ongoing extension of this trial for an additional 3 years will provide data to evaluate the persistent benefits of this treatment during its continued administration for a further year and for 2 years after its discontinuation. The individual treatment allocations will remain blinded during the entire trial period.

In conclusion, treatment with grass allergen tablets was well tolerated and clinically effective as treatment of seasonal allergic rhinoconjunctivitis. Grass allergen tablets should be considered a baseline treatment because it provides symptom prevention and in addition reduces the use of symptom relieving medication. Sublingual immunotherapy with grass allergen tablets showed a long-term and progressive effect on immunological parameters including IgE, IgG4 and IgE-blocking antibodies.
For all efficacy endpoints, differences between grass allergen tablets and placebo were pronounced, highly statistically significant, and in favor of specific immunotherapy with grass allergen tablets with a trend for further improvement during the second year.
Acknowledgements

**References**


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Table 1: Demographics at screening

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Placebo</th>
<th>Grass Allergen Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants, N (%)</td>
<td>162 (100)</td>
<td>189 (100)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, N (%)</td>
<td>97 (60)</td>
<td>118 (62)</td>
</tr>
<tr>
<td>Women, N (%)</td>
<td>65 (40)</td>
<td>71 (38)</td>
</tr>
<tr>
<td>Age (Years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>35.9 (9.61)</td>
<td>35.4 (9.77)</td>
</tr>
<tr>
<td>Median</td>
<td>35.0</td>
<td>35.0</td>
</tr>
<tr>
<td>[Q5%; Q95%]</td>
<td>[22.0; 55.0]</td>
<td>[22.0; 56.0]</td>
</tr>
<tr>
<td>Ethnic Origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian, N (%)</td>
<td>155 (96)</td>
<td>180 (95)</td>
</tr>
<tr>
<td>Other, N (%)</td>
<td>7 (4)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Severity of Grass Pollen Allergy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate, N (%)</td>
<td>71 (44)</td>
<td>72 (38)</td>
</tr>
<tr>
<td>Severe, N (%)</td>
<td>91 (56)</td>
<td>117 (62)</td>
</tr>
<tr>
<td>Grass Pollen Allergy (Years):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>160</td>
<td>187</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>17.4 (10.4)</td>
<td>18.1 (10.4)</td>
</tr>
<tr>
<td>Median</td>
<td>17.0</td>
<td>17.0</td>
</tr>
<tr>
<td>[Q5%; Q95%]</td>
<td>[3.00; 37.5]</td>
<td>[3.00; 36.0]</td>
</tr>
</tbody>
</table>

N: number of participants; SD: standard deviation; %: percent of the FAS 2006
Table 2: Efficacy endpoints during the entire grass pollen seasons 2005 and 2006

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Year</th>
<th>Placebo</th>
<th>Active</th>
<th>Difference</th>
<th>95% CI</th>
<th>% Diff.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Score</td>
<td>2005*</td>
<td>3.37</td>
<td>2.36</td>
<td>1.01</td>
<td>[0.69;1.33]</td>
<td>30%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>3.76</td>
<td>2.40</td>
<td>1.36</td>
<td>[0.86;1.86]</td>
<td>36%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medication Score</td>
<td>2005*</td>
<td>2.23</td>
<td>1.38</td>
<td>0.85</td>
<td>[0.50;1.20]</td>
<td>38%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>3.19</td>
<td>1.74</td>
<td>1.45</td>
<td>[0.75;2.16]</td>
<td>46%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Symptom and Medication Free Days</td>
<td>2005</td>
<td>31.05</td>
<td>42.47</td>
<td>-11.43</td>
<td>[-16.17;-6.68]</td>
<td>-37%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medication Free Days</td>
<td>2006</td>
<td>31.69</td>
<td>45.86</td>
<td>-14.17</td>
<td>[-21.02;-7.31]</td>
<td>-45%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RQLQ Overall Score‡</td>
<td>2005</td>
<td>1.40</td>
<td>1.03</td>
<td>0.37</td>
<td>[0.23;0.50]</td>
<td>26%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>1.26</td>
<td>0.85</td>
<td>0.41</td>
<td>[0.23;0.59]</td>
<td>33%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Global Evaluation¤</td>
<td>2005</td>
<td>8.95</td>
<td>7.09</td>
<td>1.86</td>
<td>[2.46;1.26]</td>
<td>21%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>8.35</td>
<td>5.78</td>
<td>2.57</td>
<td>[1.77;3.38]</td>
<td>31%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*: previously published in (24); ‡: RQLQ: Rhinoconjunctivitis quality of life questionnaire; ¤: Global evaluation: A global assessment of rhinoconjunctivitis symptoms was performed at the end of the season by asking "how do you assess the severity of your rhinoconjunctivitis symptoms, when they were the most severe during this grass pollen season?"; CI: confidence interval; % diff. = [(Placebo-Active)/Placebo] × 100; p-value presented for the comparison of the 2 treatment groups tested by ANOVA with the score as response variable, treatment group as a fixed effect, pollen region as random effect and adjusting for different error variation in each treatment group.
### Table 3: Summary of adverse events during the second treatment year

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo</th>
<th>Grass Allergen Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>E</td>
</tr>
<tr>
<td><strong>Full Analysis Set 2006</strong></td>
<td>162</td>
<td>189</td>
</tr>
<tr>
<td><strong>All Adverse Events</strong></td>
<td>67 (100%)</td>
<td>158</td>
</tr>
<tr>
<td><strong>Causality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>9 (13%)</td>
<td>11</td>
</tr>
<tr>
<td>Probable</td>
<td>2 (3%)</td>
<td>3</td>
</tr>
<tr>
<td>Unlikely</td>
<td>63 (94%)</td>
<td>144</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>47 (70%)</td>
<td>81</td>
</tr>
<tr>
<td>Moderate</td>
<td>41 (61%)</td>
<td>68</td>
</tr>
<tr>
<td>Severe</td>
<td>8 (12%)</td>
<td>9</td>
</tr>
<tr>
<td><strong>Seriousness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non serious</td>
<td>66 (99%)</td>
<td>153</td>
</tr>
<tr>
<td>Serious</td>
<td>5 (7%)</td>
<td>5</td>
</tr>
</tbody>
</table>

N: number of participants; %: percent of participants with adverse events; E: number of events.

All the serious adverse events were considered unlikely related to the trial medication.
Figure Legends:

Figure 1: Trial flow diagram

Figure 2: Daily averaged scoring of symptoms, scoring of rescue medication, and weighted grass pollen counts.

Figure 3: Difference in global evaluation of rhinoconjunctivitis symptoms between grass allergen tablet and placebo treatment from screening (at the end of the grass pollen season 2004) to the end of the grass pollen seasons 2005 and 2006. The global assessment was performed by asking "how do you assess the severity of your rhinoconjunctivitis symptoms, when they were the most severe during this grass pollen season? 6 rhinoconjunctivitis symptoms (4 nose and 2 eye symptoms) were scored on a scale from 0 (no symptoms) to 3 (severe symptoms).

Figure 4: *Phleum pratense* specific IgE (A) and IgE-blocking antibodies (B) measured during the first treatment year (0-10 months) in Danish sites (N=102) and during the second treatment year (19-22 months) for all sites (N=313). The approximate locations of the grass pollen seasons (GPS) are symbolized by the grey boxes on the x-axes. A) The levels of specific IgE shown for the placebo and the active group. There were statistically significant difference between placebo and the active group for all visits except visit 1 (all p-values ≤ 0.005). Mean and confidence intervals are calculated on the log\(_{10}\)-transformed data. The values are then re-transformed, using the modified Cox-method (37), to the original scale, thus the depicted values does not correspond to a true mean and confidence interval on the original scale. B) The level of IgE-blocking antibodies was determined as a ratio of specific IgE in the presence and absence of competing serum immunoglobulins. Shown here are the changes over time in the level of IgE-blocking antibodies for the placebo and active group.
Figure 5: *Phleum pratense* specific IgG₄ was measured after the second treatment season in samples from the screening (0 months of treatment), after the first treatment season (10 months) and after the second treatment season (22 months). The analysis included only a subset of the trial participants (Danish sites only, N=70). The approximate locations of the grass pollen seasons (GPS) are symbolized by the grey boxes on the x-axes. Mean and confidence intervals are calculated on the log₁₀-transformed data. The values are then re-transformed, using the modified Cox-method (37), to the original scale, thus the depicted values does not correspond to a true mean and confidence interval on the original scale. AU: arbitrary units.