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

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Background: This is an interim analysis of a randomized, double-blind, placebo-controlled phase III trial with 3 years of daily treatment with grass tablet immunotherapy (GRAZAX; ALK-Abelló A/S, Hørsholm, Denmark) or placebo, followed by 2 years of follow-up to assess the persistent efficacy.

Objective: We sought to evaluate the efficacy and safety of specific immunotherapy with grass allergen tablets compared with placebo after treatment covering 2 consecutive grass pollen seasons.

Methods: The interim analyses included 351 adult participants with moderate-to-severe allergic rhinoconjunctivitis caused by grass pollen. Participants were treated with active (n = 189) or placebo (n = 162) tablets for an average of 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 ($P < .0001$; median reduction, 44%) and 46% in rhinoconjunctivitis medication score ($P < .0001$; median reduction, 73%) in the active group relative to the placebo group. Mean rhinoconjunctivitis quality of life was 33% better ($P < .0001$; 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 immunologic changes and highly significant efficacy over 2 years of continued treatment. (J Allergy Clin Immunol 2008;121:512-8.)

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

An estimated 45 million persons in Europe have grass pollen allergy,[1] and many patients believe that the allergy affects their quality of life.[2] A survey of adult patients with hay fever prescribed a nonsedating 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 with symptomatic treatment of allergy in view of its potential to target the immunologic process underlying allergic diseases and induce long-term remission.[4] Based on results from subcutaneous immunotherapy,[5] international clinical guidelines recommend that immunotherapy maintenance treatment is continued for 3 to 5 years,[4] and studies have further demonstrated a maintained clinical effect in the years after termination of treatment.[6-9] There are increasing data to support that this might also be true for the sublingual route.[10-12]

A fast-dissolving, once-daily grass immunotherapy tablet (approximately 15 μg of major allergen Phleum p 5; GRAZAX; ALK-Abelló A/S, Hørsholm, Denmark) 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.[13-15] In view of the need of long-term data on sublingual immunotherapy, this trial[14] was extended to cover long-term and persistent efficacy. This article reports the interim results after the second grass pollen season, when the participants had received daily treatment for approximately 22 months.

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Abbreviation used
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire

METHODS

Clinical trial design

A randomized, parallel-group, double-blind, placebo-controlled, multicenter trial was performed. The trial is an extension of a previously published trial in which participants received double-blind treatment from the autumn of 2004 until the end of the grass pollen season of 2005.[14] Three hundred fifty-one participants from 43 sites in 7 countries continued treatment with grass allergen tablets or placebo and will continue treatment until the end of the grass pollen season of 2007. The participants will provide data for an additional 2 grass pollen seasons, and thus the participants will be followed for a total of 5 years. This article covers the period from September 2005 through August 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[16] and Good Clinical Practice. The ethics committees in each of the participating countries approved the trial.

The main inclusion criteria were as follows: male or female sex; age 18 to 65 years; a clinical history of moderate-to-severe grass pollen–induced rhinoconjunctivitis of 2 years or more requiring treatment during the grass pollen season, which remain troublesome despite treatment with antiallergic drugs; a positive skin prick test response (wheal diameter ≥3 mm) to *Phleum pratense*; a positive specific IgE result against *P pratense* (≥IgE class 2); an FEV_1 of 70% of predicted value or greater; no clinical history of symptomatic seasonal allergic rhinitis, asthma, or both because of 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, asthma, or both caused by an allergen to which the participant is regularly exposed.

The treatment started 4 to 8 months before the anticipated start of the grass pollen season of 2005, and by the time of this interim analysis, all participants had received treatment for approximately 22 months.

For each pollen region, the season was defined as the first of 3 consecutive days with grass pollen counts of 10 grains/m^3 or greater to the last day before 3 consecutive days with a grass pollen count of less than 10 grains/m^3.

The primary efficacy end points 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; 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) to 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 per puff) up to 2 puffs per nostril twice daily, 1 point per puff; and prednisone (5 mg per tablet), 1.6 points per tablet. The scores presented are averages of the daily scores for each participant for the entire grass pollen season. Other efficacy end points included quality of life assessed by using Juniper's Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ),[17] symptom- and medication-free (healthy) days, and global evaluations of the most severe rhinoconjunctivitis symptom during the 2006 season (maximal score, 18).

Immune response assay

Changes in immunologic blood markers (specific IgE, IgE-blocking antibodies, and IgG4) were investigated for the Danish sites only in 2005 but for all sites in 2006. *P pratense*–specific IgE levels were measured by using an ADVIA Centaur Immunoassay System (Bayer Healthcare, Tarrytown, NY), as described by Petersen et al.[18] The inhibitory capacity of IgE-blocking antibodies for the reaction between IgE and *P pratense* allergens was estimated as a ratio between IgE measured by using a modification of the protocol of Petersen et al (excluding the first washing step, thus allowing non-IgE antibodies to compete with IgE for the allergen) and IgE measured by using the conventional protocol.[15,19] The *P pratense*–specific IgG4 assay was performed similarly to the IgE assay, with few modifications. Anti-human IgE was replaced with a murine monoclonal anti-human IgG4, and sera were diluted to counteract for the amount of nonspecific IgG4 in the serum samples. The amount of specific IgG4 in the serum samples was estimated to a dilution of a standard serum pool (arbitrary unit) to obtain a standardized measure. Adverse events were assessed and comprised the safety evaluation.

Statistics

Comparison of the 2 treatment groups was done by means of ANOVA, with the efficacy end point as the response variable, treatment group as a fixed effect, pollen region as a random effect, and adjustment for different error variation in each treatment group. Specific IgE and IgG4 values were $\log_{10}$ transformed before doing comparisons between treatment groups. This was necessary to obtain approximately normally distributed residuals in the statistical analysis.

RESULTS

Five hundred forty-six participants completed the first year of the trial. Because of closure of a few trial centers, only 472 could be offered to continue in the extension. Three hundred fifty-one accepted participation in the extension period of the trial and continued doubled-blind treatment after the grass pollen season of 2005. A diagram of the trial flow is presented in Fig 1. Three hundred nineteen participants were in the trial when the grass pollen season of 2006 started, and 306 were in the trial when the pollen season ended. The average length of treatment at the end of the grass pollen season of 2006 was 22 months. Of the 45 withdrawals, 3 withdrew because of adverse events and 4 because of a perceived lack of effect. The numbers of patients withdrawing and reasons for withdrawal were 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 years (SD, 10.4 years).

Overall demographics were similar between the 2 treatment groups (Table I). In addition, the demographics of the participants in the extension of the trial were similar to the demographics of the participants who did not participate in the extension (see Table E1 in the Online Repository at www.jacionline.org). Importantly, the symptom and medication scores for the participants who did and did not continue in the extension were also similar after the first season (see Fig E1 in the Online Repository at www.jacionline.org). There was no difference in treatment effect between subjects continuing and subjects not continuing in the trial (P = .27 for symptom score and P = .81 for 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. The average grass pollen season lasted 59 days (range, 30-116 days). No major differences were seen between the grass pollen seasons of 2005 and 2006.

Efficacy

The average daily rhinoconjunctivitis symptom and medication score for the entire grass pollen season of 2006 are shown in Fig 2. A higher score indicates a higher level of symptoms or use of

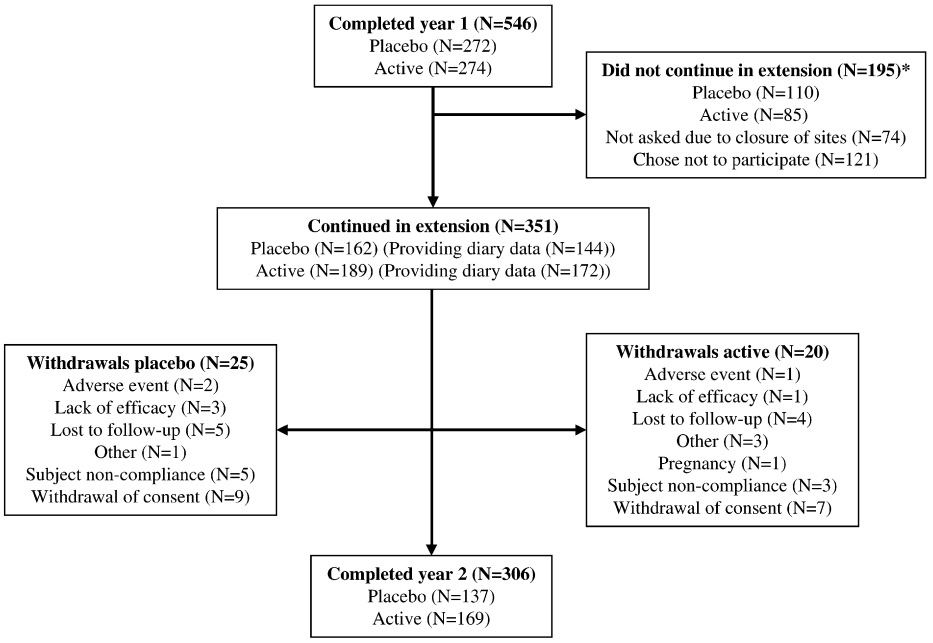

FIG 1. Trial flow diagram.

TABLE I. Demographics at screening

Treatment group	Placebo	Grass allergen tablet
No. of participants (%)	162 (100)	189 (100)
Sex		
Men [N (%)]	97 (60)	118 (62)
Women [N (%)]	65 (40)	71 (38)
Age (y)		
Mean (SD)	35.9 (9.61)	35.4 (9.77)
Median	35.0	35.0
5% quantile; 95% quantile	22.0; 55.0	22.0; 56.0
Ethnic origin		
White [N (%)]	155 (96)	180 (95)
Other [N (%)]	7 (4)	9 (5)
Severity of grass pollen allergy		
Moderate [N (%)]	71 (44)	72 (38)
Severe [N (%)]	91 (56)	117 (62)
Grass pollen allergy (y)		
N	160	187
Mean (SD)	17.4 (10.4)	18.1 (10.4)
Median	17.0	17.0
5% quantile; 95% quantile	3.00; 37.5	3.00; 36.0

%, Percentage of the full analysis set 2006.

medication. Participants treated with grass allergen tablets scored statistically significantly lower than participants treated with placebo during the entire grass pollen season of 2006 ($p < .0001$). The mean difference relative to placebo was 36% in symptom score and 46% in medication score in favor of the grass allergen tablets (Table II). For comparison, results after the first treatment season (2005) were 30% ($P < .0001$) and 38% ($P < .0001$), respectively.[14] The subgroup of patients who 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 6 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 $P < .002$) during the second grass pollen season.

The percentage of days without symptoms and use of rescue medication was calculated (Table II). 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 ($P < .0001$). The median numbers of symptom- and medication-free days was 9 in the placebo group versus 18 in the grass allergen tablet group.

A significantly better quality of life (ie, a lower RQLQ score) was reported in the group treated with grass allergen tablets relative to the placebo group (Table II). The difference in overall score was 0.41, corresponding to 33% ($P < .0001$).

The participants' global assessment of rhinoconjunctivitis symptoms during the grass pollen season was performed at the end of the season by asking the following: "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 II). The difference of 31% was highly statistically significant ($P < .0001$). The alterations in the global evaluation from 2004 to 2005 and 2006 are shown in Fig 3.

The differences in the grass allergen tablet group relative to the placebo group were numerically higher during the second treatment season compared with the first treatment season (Table II), with a trend toward statistical significance ($P = .0789$).

For the placebo group, there were small seasonal variations in the levels of *P pratense*–specific IgE during the grass pollen seasons (Fig 4, *A*).[20] In the immunotherapy group there was an

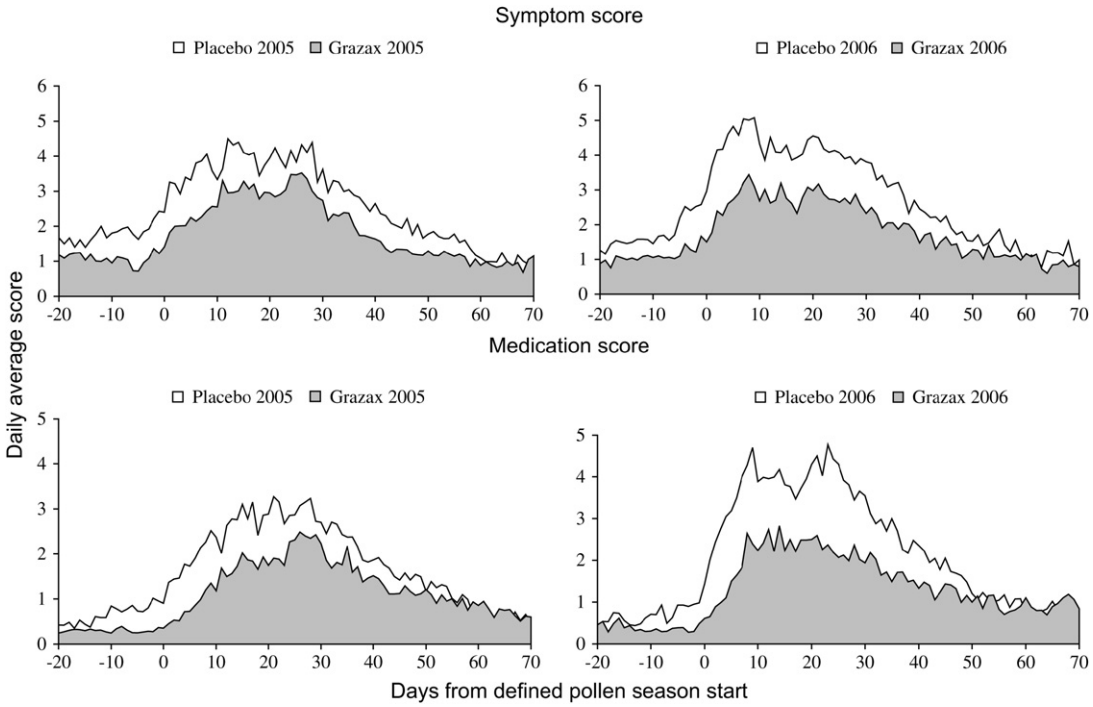

FIG 2. Daily averaged scoring of symptoms and medication in both treatment years (2005 and 2006).

TABLE II. Efficacy end points during the entire grass pollen seasons of 2005 and 2006

End point	Year	Adjusted mean		Difference	95% CI	% Diff	*P* value
		Placebo	Active				
Symptom score	2005*	3.37	2.36	1.01	0.69 to 1.33	30%	<.0001
	2006	3.76	2.40	1.36	0.86 to 1.86	36%	<.0001
Medication score	2005*	2.23	1.38	0.85	0.50 to 1.20	38%	<.0001
	2006	3.19	1.74	1.45	0.75 to 2.16	46%	<0.0001
Symptom- and medication-free days (%)	2005	31.05	42.47	−11.43	−16.17 to −6.68	−37%	<.0001
	2006	31.69	45.86	−14.17	−21.02 to −7.31	−45%	<.0001
RQLQ overall score	2005	1.40	1.03	0.37	0.23-0.50	26%	<.0001
	2006	1.26	0.85	0.41	0.23-0.59	33%	<.0001
Global evaluation†	2005	8.95	7.09	1.86	2.46-1.26	21%	<.0001
	2006	8.35	5.78	2.57	1.77-3.38	31%	<.0001

The *P* value is presented for the comparison of the 2 treatment groups tested by means of ANOVA, with the score as response variable, treatment group as a fixed effect, pollen region as a random effect, and adjustment for different error variation in each treatment group.
% Diff, $([Placebo - Active]/Placebo) \times 100$.
*Previously published in Dahl et al.[14]
†For global evaluation, assessment was performed at the end of the season by asking the following question: "How do you assess the severity of your rhinoconjunctivitis symptoms when they were the most severe during this grass pollen season?"

initially significant increase in specific IgE levels 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 it 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 increase 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 that seen in placebo-treated subjects both from 10 to 22 months of treatment ($P = .0003$) and from 19 to 22 months of treatment ($P < .0001$).

P 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; Fig 5). The levels did not change in the placebo group (n = 32), whereas there was a rapid increase in IgG4 levels in the grass allergen tablet group (n = 38) of 1 unit on the $\log_{10}$ 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 $\log_{10}$ 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 ($P < .0001$) and from 10 to 22 months of treatment ($P = .0001$). From treatment initiation to 22 months of treatment, an increase of 1.4 units was observed, corresponding to a 23-fold increase.

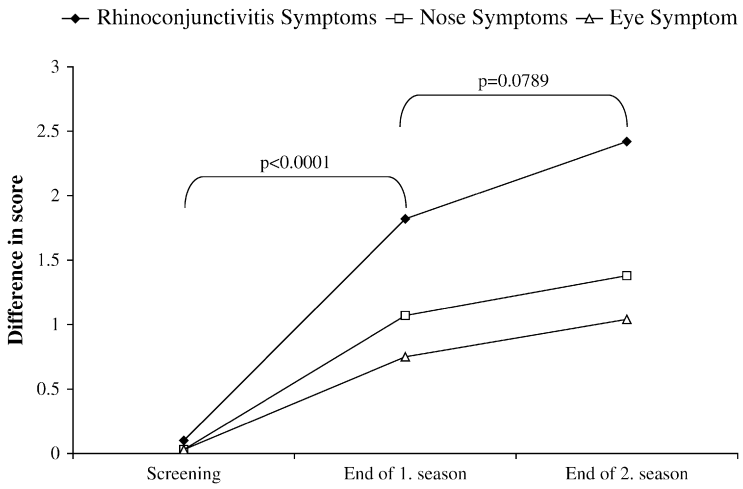

FIG 3. Difference in global evaluation of rhinoconjunctivitis symptoms. Assessment was performed by asking the following: "How do you assess the severity of your rhinoconjunctivitis symptoms when they were the most severe during this grass pollen season?" Six rhinoconjunctivitis symptoms (4 nose and 2 eye symptoms) were scored on a scale from 0 (no symptoms) to 3 (severe symptoms).

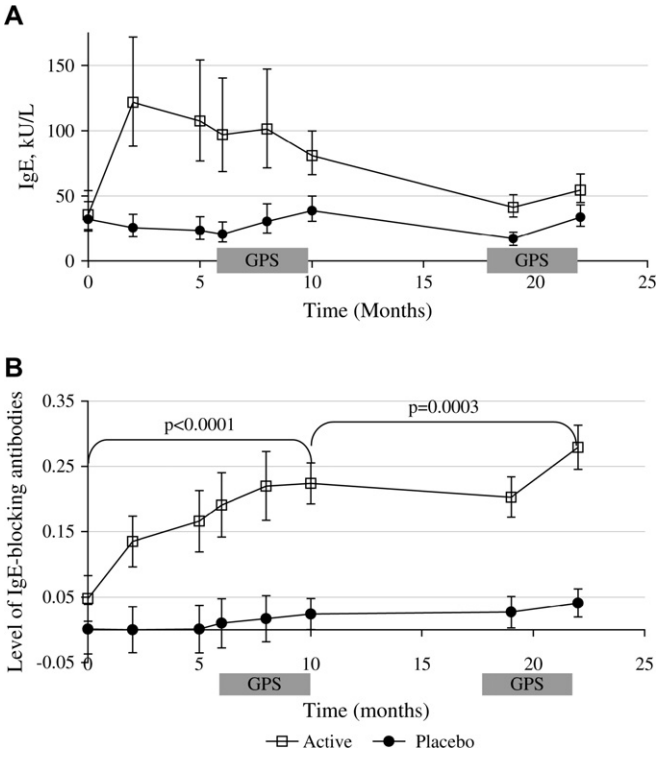

FIG 4. *P pratense*–specific IgE **(A)** and IgE-blocking antibodies **(B)** during the first year only in Danish sites (n = 102) and during the second year in all sites (n = 313). There were statistically significant differences between the placebo and active groups for all visits, except visit 1 (all $P \leq .005$). Means and CIs are calculated on the $\log_{10}$-transformed data. The values are then retransformed by using the modified Cox method[20] to the original scale. *GPS,* Approximate locations of the grass pollen seasons.

Safety

The overall frequency and severity of adverse events with start and stop dates during the second treatment year are tabulated in Table III. 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 as unlikely to be related to the trial medication in both groups. The same number of probably or possibly related adverse events was reported in the grass allergen tablet and placebo groups. Of these 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 1 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,[14] 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 and 1 from the active group) withdrew because of adverse events (mild headache; mild burning pain in the left groin, moderate viral infection, and moderate lymph node increase; and mild bilateral knee pain/arthritis).

DISCUSSION

The present data are from an extension of a trial in which approximately 65% of 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 with the participants who elected not to continue in the extension.

Treatment with grass allergen tablets resulted in a 36% decrease in rhinoconjunctivitis symptoms and, in addition, an additional 46% reduction in the use of symptomatic medication relative to

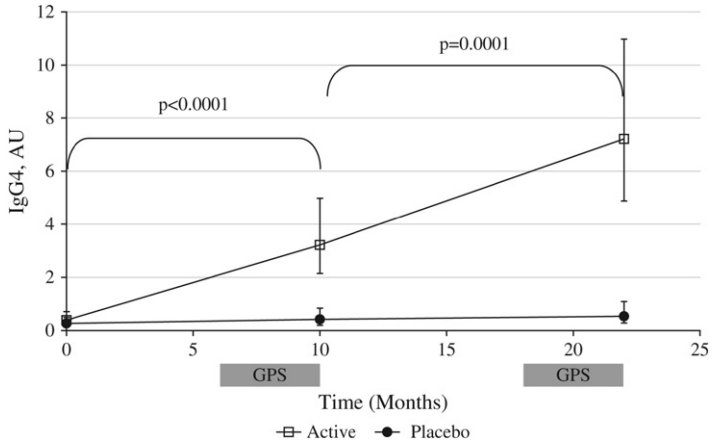

FIG 5. *P pratense*–specific IgG4. The analysis included only Danish sites (n = 70). Means and CIs are calculated on the $\log_{10}$-transformed data. The values are then retransformed with the modified Cox method[20] to the original scale. *GPS,* Approximate locations of the grass pollen seasons; *AU,* arbitrary units.

placebo. This suggests a sustained benefit of grass tablet immunotherapy treatment over more than one season. Note that no major differences were observed between the pollen counts in the 2 seasons. This is in line with the recommended treatment regimen for subcutaneous immunotherapy.[21] Although the continuing treatment regimen has been widely adapted for sublingual treatment with named patient products,[22] this is the first large-scale, double-blinded, placebo-controlled trial to support this approach for sublingual immunotherapy. The treatment effects during the first year were 30% in rhinoconjunctivitis symptom scores and 38% in rhinoconjunctivitis medication scores, but the reductions in the second year (36% and 46%, respectively) did not achieve statistical significance compared with year 1, possibly because the trial was not originally powered to detect differences between treatment years. The participants receiving grass allergen tablets reported significantly improved quality of life relative to the placebo group (by means of the RQLQ[23]) 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 with the global assessment after the grass pollen season of 2005 suggested a difference in treatment effect in year 2 above that observed in year 1 ($P = .08$, Fig 3).

Specific immunotherapy is the only treatment modality that addresses the cause of allergic disease, with alterations of allergen-specific T-cell[24,25] and B-cell[24] responses during subcutaneous immunotherapy that are associated with persistent clinical improvement that potentially lasts for years after discontinuation.[6] The immunologic end points 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 *P pratense*–specific IgE and IgE-blocking antibodies resembled that previously observed for both subcutaneous[26,27] and sublingual[26,28,29] immunotherapy.

Specific IgG4 levels increased significantly in the grass allergen tablet group over the 2 seasons to 23 times the level at screening. Two years of treatment with subcutaneous immunotherapy has been shown to induce a greater than 100-fold increase in IgG4 levels,[27] and thus the kinetics might differ for the 2 administration routes. The link between immunologic changes and clinical efficacy is not clarified as yet, but the present data suggest that the clinical effect is not directly dependent on the size of the increase in immunoreactive IgG4 level because 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.[30]

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 because of adverse events was less than 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,[31] long-term data on the effect on

TABLE III. Summary of adverse events during the second treatment year

	Treatment group					
	Placebo			Grass allergen tablet		
	N	Percent	E	N	Percent	E
Full analysis set 2006	162			189		
All adverse events	67	100%	158	97	100%	205
Causality						
Possible	9	13%	11	6	6%	7
Probable	2	3%	3	6	6%	7
Unlikely	63	94%	144	90	93%	191
Severity						
Mild	47	70%	81	72	74%	124
Moderate	41	61%	68	44	45%	76
Severe	8	12%	9	5	5%	5
Seriousness						
Nonserious	66	99%	153	96	99%	204
Serious	5	7%	5	1	1%	1

All the serious adverse events were considered unlikely related to the trial medication. The 6 cases were (1) riding accident, (2) snowboard accident, (3) road traffic accident, (4) abscess of the left hand, (5) viral infection, and (6) nephrolithiasis.
N, Number of participants; %, percentage of participants with adverse events; *E*, number of events.

rhinoconjunctivitis symptoms, in particular, are sparse. In an open trial with 4 to 5 years of treatment with sublingual house dust mite immunotherapy, a highly significant decrease in asthma medication was observed that remained during the 4 to 5 years of follow-up.[12] 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 blind during the entire trial period.

In conclusion, use of grass allergen tablets was well tolerated and clinically effective as a treatment from seasonal allergic rhinoconjunctivitis. Grass allergen tablets should be considered a baseline treatment because they provide symptom prevention and in addition reduce the use of symptom-relieving medication. Sublingual immunotherapy with grass allergen tablets showed a long-term and progressive effect on immunologic parameters, including IgE, IgG4, and IgE-blocking antibodies.

For all efficacy end points, differences between grass allergen tablets and placebo were pronounced, highly statistically significant, and in favor of specific immunotherapy with grass allergen tablets.

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Clinical implications: Grass allergen tablets are effective in reducing rhinoconjunctivitis symptoms and medication use, thereby improving quality of life during the grass pollen season. A progressive immune modulation occurred during 2 years.

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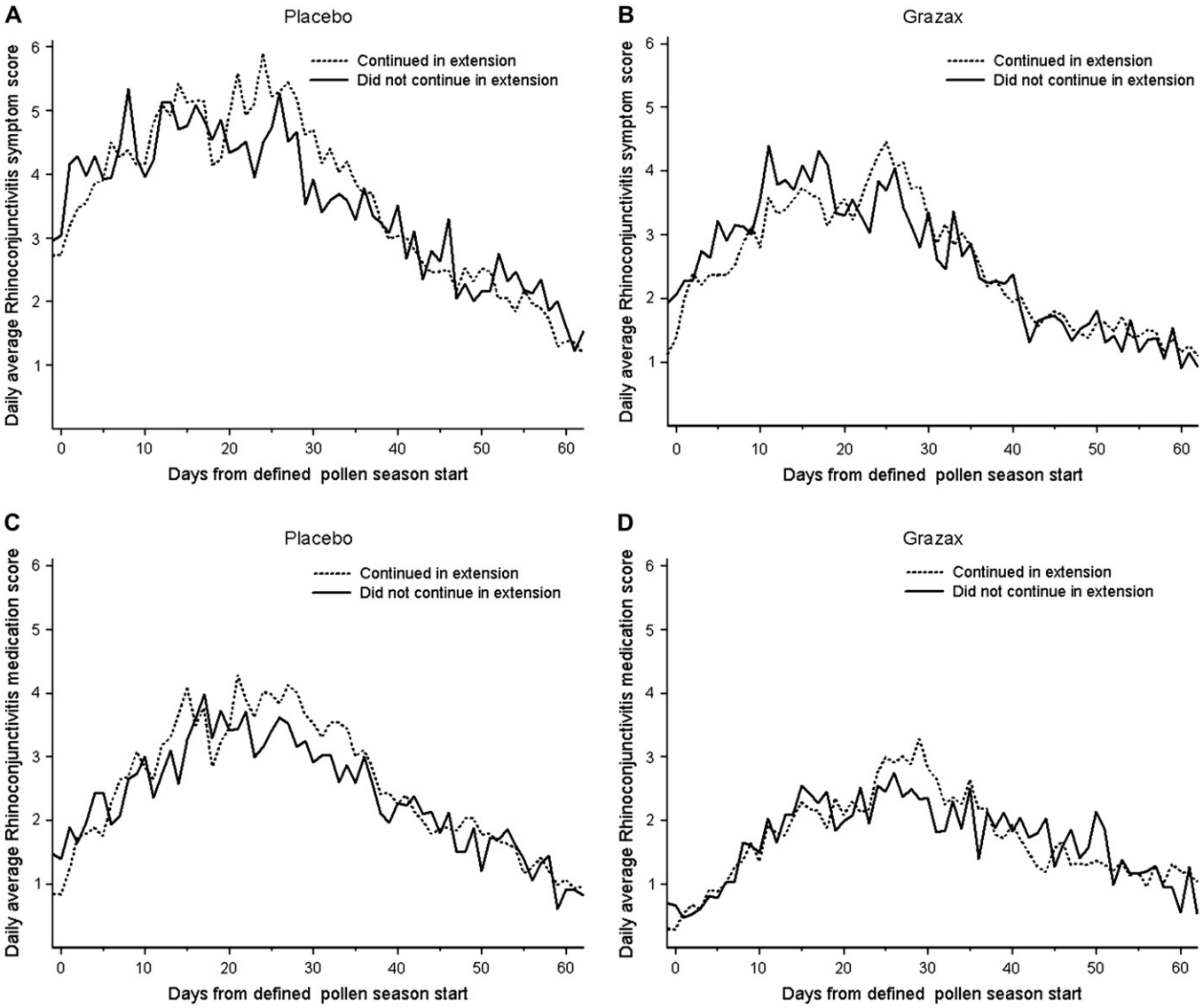

FIG E1. The symptom and medication scores during the grass pollen season of 2005 for the participants who continued in the extension and the participants who did not continue in the extension were compared to evaluate whether the extension population could be considered representative for the entire full analysis set for the year 2005. On the figure, the rhinoconjunctivitis symptom scores are shown for the placebo **(A)** and GRAZAX **(B)** groups, as are the medication scores for the placebo **(C)** and GRAZAX **(D)** groups. No differences in scores between those continuing and those not continuing can be seen. The treatment effect was analyzed and showed no statistically significant difference in treatment effect during the grass pollen season of 2005 between subjects continuing and subjects not continuing in the trial ($P = .27$ for the symptom score and $P = .81$ for the medication score). Thus the participants in the extension can be considered a representative subset of the population originally included in the trial.

TABLE E1. The demographics of the participants in the extension of the trial were similar to the demographics of the participants who did not participate in the extension

	Participating in the extension		Not participating in the extension	
Treatment group	**Placebo**	**Grass allergen tablet**	**Placebo**	**Grass allergen tablet**
No. of participants (%)	162 (100)	189 (100)	156 (100)	127 (100)
Sex				
Men [N (%)]	97 (60)	118 (62)	96 (62)	61 (48)
Women [N (%)]	65 (40)	71 (38)	60 (38)	66 (52)
Age (y)				
Mean (SD)	35.9 (9.61)	35.4 (9.77)	33.0 (10.2)	31.6 (8.90)
Median	35.0	35.0	31.5	30.0
Q5%; Q95%	22.0; 55.0	22.0; 56.0	20.0; 53.0	21.0; 49.0
Ethnic origin				
White [N (%)]	155 (96)	180 (95)	153 (98)	119 (94)
Other [N (%)]	7 (4)	9 (5)	3 (2)	8 (6)
Severity of grass pollen allergy				
Moderate ([N (%)]	71 (44)	72 (38)	73 (47)	65 (51)
Severe [N (%)]	91 (56)	117 (62)	83 (53)	62 (49)
Grass pollen allergy (y)				
N	160	187	156	126
Mean (SD)	17.4 (10.4)	18.1 (10.4)	14.7 (10.6)	13.6 (9.18)
Median	17.0	17.0	13.5	11.5
Q5%; Q95%	3.00; 37.5	3.00; 36.0	2.00; 34.0	2.00; 30.0