Sublingual immunotherapy with once-daily grass allergen tablets: A randomized controlled trial in seasonal allergic rhinoconjunctivitis

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Background: Specific immunotherapy is the only treatment modality that has the potential to alter the natural course of allergic diseases. Sublingual immunotherapy has been developed to facilitate access to this form of treatment and to minimize serious adverse events.
Objective: To investigate the efficacy and safety of sublingual grass allergen tablets in seasonal allergic rhinoconjunctivitis.
Methods: A multinational, multicenter, randomized, placebo-controlled trial conducted during 2002 and 2003. Fifty-five centers in 8 countries included 855 participants age 18 to 65 years who gave a history of grass pollen–induced allergic rhinoconjunctivitis and had a positive skin prick test and elevated serum allergen-specific IgE to *Phleum pratense*. Participants were randomized to 2500, 25,000, or 75,000 SQ-T grass allergen tablets (GRAZAX; ALK-Abelló, Hørsholm, Denmark) or placebo for sublingual administration once daily. Mean duration of treatment was 18 weeks.
Results: Average rhinoconjunctivitis scores during the season showed moderate reductions of symptoms (16%) and medication use (28%) for the grass allergen tablet 75,000 SQ-T ($P = .0710$; $P = .0470$) compared with placebo. Significantly better rhinoconjunctivitis quality of life scores ($P = .006$) and an increased number of well days ($P = .041$) were also observed. Efficacy was increased in the subgroup of patients who completed the recommended preseasonal treatment of at least 8 weeks before the grass pollen season (symptoms, 21%, $P = .0020$; and medication use, 29%, $P = .0120$). No safety concerns were observed.
Conclusion: This study confirms dose-dependent efficacy of the grass allergen tablet. Although further studies are required, the greater tolerability of the tablet may permit immunotherapy to be available to a much broader group of patients with impaired quality of life caused by grass pollen allergy.
Clinical implications: For patients with grass pollen allergy, sublingual immunotherapy is well tolerated and can reduce symptoms and improve quality of life. (J Allergy Clin Immunol 2006;117:802-9.)

Key words: *Specific immunotherapy, sublingual immunotherapy, grass allergen tablets*

Allergic rhinoconjunctivitis represents a global health problem.[1] A recent community-based survey in 6 countries in Western Europe revealed an average prevalence of 23% (range, 17% to 29%).[2] Allergy to grass pollen is one of the most common inhalant allergies leading to impaired quality of life and increased expenditures in the healthcare system.[1] The current recommended treatment for allergic rhinitis is the use of topical nasal corticosteroids and antihistamines.[1] However, these measures have been shown to be at best only partially effective in more than 40% of patients with hay fever evaluated in a general practice setting.[3] In patients who fail to respond to these measures, controlled trials have documented the efficacy of subcutaneously administered allergen-specific immunotherapy.[4-7] Clinical improvement has been shown to persist for at least 3 to 6 years after discontinuation of this treatment.[7-9] Thus, specific immunotherapy[10] is today the only treatment modality able to induce prolonged remission and prevent disease progression.

Regardless of the success of the subcutaneous route for specific immunotherapy, the inconvenience of frequent hospital/clinic visits, the discomfort associated with injections, and the risk of IgE-mediated severe systemic adverse events has prompted investigation of alternative methods of administration.

Early trials of oral administration of immunotherapy have failed to show clinical benefit, probably because of the rapid inactivation of allergen within the gastrointestinal tract.[11] The use of enteric-coated oral formulations did not prove to be a better alternative. However, a review from 2002 concluded that sublingual immunotherapy (SLIT) showed promise with regard to efficacy,[12] and

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Abbreviations used
AE: Adverse event
RQLQ: Rhinoconjunctivitis Quality-of-Life Questionnaire
RU: Relative units
SLIT: Sublingual immunotherapy

a recent meta-analysis confirmed that SLIT can produce a significant reduction of symptoms and antiallergic medication requirements compared with placebo.[13] SLIT has also been shown to decrease or prevent the development of more severe allergic disease and protect against the development of new allergies.[14]

The orodispersible grass allergen tablet (GRAZAX; ALK-Abelló, Hørsholm, Denmark) is a new oral formulation for sublingual administration and has been developed to ease the patient's access to immunotherapy by allowing self-administration at home. The active ingredient is a standardized allergen extract derived from the pollen of timothy grass (*Phleum pratense*). However, because extensive cross-reactivity of allergenic components of grass pollens from different species has been shown,[15] the clinical use of the grass allergen tablet is anticipated to be for the treatment of IgE-mediated grass pollen allergy in general, as confirmed for the subcutaneous preparation.

The purpose of the trial was to investigate the efficacy and safety of 3 doses of grass allergen tablets in grass pollen–induced allergic rhinoconjunctivitis. Outcomes included rhinoconjunctivitis symptom and medication scores, quality of life, and number of well days during the pollen season. Relevant immunologic parameters were also measured.

METHODS

Participants

This multinational, multicenter, double-blind, randomized, parallel group, placebo-controlled trial was performed with the approval of local ethics committees and written informed consent from all participants. A total of 855 participants were enrolled into 2 cohorts from 55 centres in Europe and Canada. Participants were recruited from allergy clinics and by local advertising. Cohort I was enrolled in 2002 and received trial medication, and were asked to recorded symptom and rescue medication scores during the pollen season, to permit a power calculation of the number of participants required to detect a 20% reduction in symptoms and/or rescue medication use during the pollen season. All completed and protocol-compliant participants from the baseline phase were continued in the treatment phase in 2003, together with cohort II.

Criteria for inclusion were as follows: signed informed consent, participants 18 to 65 years of age who gave a clinical history of troublesome symptoms of allergic rhinoconjunctivitis during the grass pollen season of a duration of at least 2 years, a positive skin prick test to *P pratense* (Soluprick SQ; ALK-Abelló; wheal diameter $\geq$3 mm), raised serum allergen-specific IgE to *P pratense*, and no significantly abnormal findings on physical examination. Reasons for exclusion included the following: a clinical history of significant asthma outside the grass pollen season; FEV_1 less than 70% of the predicted value; significant allergic rhinitis (requiring medication) caused by allergens other than grass during the planned treatment period; significant recurrent acute sinusitis or chronic sinusitis; conjunctivitis, rhinitis, or asthma at the screening or randomization visits; a history of anaphylaxis or angioedema; presence of serious underlying conditions; immunosuppressive treatment; hypersensitivity to excipients of trial medications or rescue medications; or having received immunotherapy with grass pollen allergen within the previous 10 years or any other allergen within the previous 5 years. Pregnant women and those at risk of pregnancy were also excluded.

Eligible participants received a randomization number according to a computer-generated schedule. Participants were not stratified. The allocation sequence was generated by the sponsoring company and blinded for the investigators, who knew whether they participated in cohort I or II. Whether investigators/patients participated in cohort I or II was defined by country. Cohort I countries were Belgium, Denmark, Germany, and Sweden. Cohort II countries were Austria, Norway, the United Kingdom, and Canada. No major differences were observed between the 2 cohorts, and the pooled pollen counts for the 2 cohorts were comparable. Any differences between regions were independent of whether the regions were in cohort I or cohort II, so the results for both were combined in the analysis. The treatment schedule and assessments were performed double-blind and maintained blind until the database was locked. On the basis of the baseline season, we calculated that inclusion of 125 participants per group would give us sufficient power to detect a 20% (α = 0.05;2-sided) decrease in rhinoconjunctivitis symptom score.

Procedures

Active treatment involved an orodispersible, fast-dissolving grass allergen tablet (ALK-Abelló A/S) containing a standardized grass allergen extract from timothy grass (*P pratense*).[16,17] Participants received placebo, 2500, 25,000 or 75,000 SQ-T. Respectively, this corresponded to approximately 0, 0.5, 5, or 15 μg *P pratense* major allergen (Phl p 5). Tablets were to be placed beneath the tongue and swallowing avoided for 1 minute after administration. Study medication was given once daily for approximately 8 weeks before and during the grass pollen season in 2003. The trial included 6 visits to the clinic and a telephone follow-up. Compliance was monitored via patient-recorded tablet intake using electronic diaries.

Individuals with continuing symptoms of allergic rhinitis were allowed additional single-blind rescue medication (loratadine or placebo). If this was ineffective or if asthma symptoms were present, participants were given (stepwise) further, active, open-label rescue medication (budesonide nasal spray and oral prednisone for rhinoconjunctivitis symptoms and salbutamol inhaler, fluticasone inhaler, and oral prednisone for asthma symptoms).

Grass pollen counts were measured daily by European Pollen Information Ltd (Vienna, Austria) and Aerobiology Research Laboratories Ltd (Nepean, Ontario, Canada) and expressed as grains per cubit meter of air. The pollen season was defined as the first day of 3 consecutive days with a pollen count equal to or above 10, to the last day before 3 consecutive days with a pollen count less than 10. A period of 15 days with the highest moving average was defined as the peak pollen season.

Participants kept symptom and medication diaries from the screening visit before the pollen season until the postseason visit. Nose (running, blockage, sneeze, itching), eye (gritty/red/itching, watery) and lung (cough, wheeze, chest tightness/dyspnea, exercise-induced) symptoms were each scored on a scale of 0 to 3 and totalled daily. Daily medication for relief of rhinoconjunctivitis and asthma was recorded. The rhinoconjunctivitis symptom and medication scores were investigated in the primary efficacy analysis.

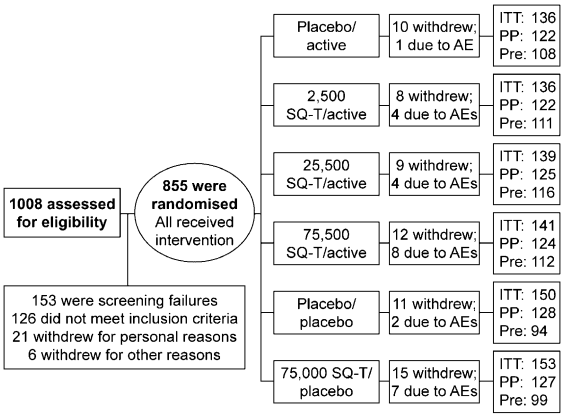

FIG 1. Trial profile. Participants received double-blind trial medication once daily (placebo, 2500, 25,000, 75,000 SQ-T grass-pollen tablets) and single-blind Step 1 rescue medication as needed (loratadine or placebo; depicted as /active or /placebo). Sixty-five participants withdrew after randomization for the following reasons: adverse events (26), physician or sponsor decision (4), consent withdrawn (5), noncompliance (5), lack of or insufficient efficacy (4), protocol deviation (3), intake of excluded medication (2), lost to follow-up (9), and other (7). *ITT,* Intention-to-treat analysis set, defined as all randomized participants (n = 855); *PP,* per-protocol analysis set, defined as randomized participants who had completed the trial and taken sufficient trial medication (at least 80%) and provided sufficient diary data (at least 30% in 50% of the weeks; n = 748); *Pre,* preseasonal analysis set; participants with at least 8 weeks treatment before the grass pollen season (n = 640).

The effect of allergic rhinoconjunctivitis on the participants' quality of life was determined by a well validated disease-specific Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ).[18] Well days were defined as those without use of any rescue medication and with a rhinoconjunctivitis symptom score $\leq$2.

Relevant immunologic parameters (IgE, IgG, and blocking components to IgE-allergen binding) to *P pratense* allergen extract were measured in serum samples taken from the participants before, during, and after the treatments.

The concentration of *P pratense* specific IgE antibodies (kU/L) in patient serum samples was measured by using an ADVIA Centaur Immunoassay System (Bayer Healthcare, New York, NY) as described by Petersen.[19] The inhibitory capacity of non-IgE serum components for the reaction between IgE and *P pratense* allergens, termed IgX, was estimated as a ratio between IgE measured using a modification of the Petersen 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.

The concentration of *P pratense* specific IgG antibodies (relative units [RU]) was determined by direct ELISA. ELISA plates (Maxisorp, Nunc, Denmark) were coated with 10 μg/well *P pratense* extract overnight, then washed and incubated with triplicate serial 3-fold dilutions made of each serum sample. After additional washing, bound IgG was estimated by horseradish peroxidase–labeled mouse antihuman IgG (Zymed, San Francisco, Calif).

Statistical analyses

Results were analyzed by using SAS version 8.02 (SAS Institute, Cary, NC). All statistical analyses and CIs were 2-sided, and a significance level of 5% was used. Group comparisons regarding symptom and medication scores, dose-response, and number of well days were analyzed by ANOVA. RQLQ scores were analyzed in a repeated measurement model. All estimates were adjusted for pollen region.

TABLE I. Clinical data of participants

	Placebo/ active	2500 SQ-T/ active	25,000 SQ-T/ active	75,000 SQ-T/ active	Placebo/ placebo	75,000 SQ-T/ placebo
N	136	136	139	141	150	153
Sex (M/F)	89/47	84/52	92/47	84/57	89/61	95/58
Mean age (y)	33	34	34	37	36	36
Range	18-61	18-61	19-59	19-62	18-64	18-66
Grass allergy*	18.2 (10.9)	17.2 (11.2)	17.4 (10.4)	19.2 (12.1)	22.6 (12.9)	20.5 (12.9)
IgE class†	3.46	3.53	3.47	3.46	3.11	3.45
Other allergies‡	18.4 (11.7)	17.8 (11.9)	17.1 (11.2)	20.4 (13.5)	18.4 (14.7)	20.4 (14.4)

*History of grass allergy in years; mean (SD).
†Specific IgE to grass pollen; CAP allergy class; mean.
‡History of other allergies in years; mean (SD).

Baseline comparability, immunologic responses, and safety assessments were evaluated by summary statistics and shift tables.

RESULTS

A total of 855 participants were randomized, and 790 (92%) completed the trial (Fig 1). Individual characteristics were similar among treatment groups at baseline (Table I). The average duration of treatment was 18 weeks (range, 1-174 days) starting approximately 8 weeks before and continuing during the grass pollen season. Adherence with treatment was high in all dose groups (94% to 98%), with no significant difference between groups.

The primary efficacy analysis demonstrated a moderate improvement in symptom score of 16% (P = .0710) and in medication score of 28% (P = .0470) with the 75,000 SQ-T grass allergen tablet compared with placebo (Table II). Numbers were similar for the peak pollen season (16%, P = .0470; 28%, P = .0390; Table II). A clear dose-response relationship for rhinoconjunctivitis symptom and medication scores was observed, but no significant changes were found when the 2 lower doses were compared with placebo (Fig 2).

Analysis of the effect of the recommended preseasonal treatment was performed by selecting all participants receiving trial medication for at least 8 weeks before the start of the grass pollen season in a preanalysis set (n = 640; Fig 1). Data were subsequently pooled from the two 75,000 SQ-T groups (n = 211) as well as the corresponding placebo groups (n = 202) with Step 1 rescue medication as a fixed effect to achieve additional power. The results supported the primary analysis and indicated that additional benefits were accrued with preseasonal treatment. The reduction in symptom and medication scores for patients in the 75,000 SQ-T group who achieved the recommended preseasonal treatment duration of at least 8 weeks reached 21% (P = .002) and 29% (P = .012), respectively (Table II).

A descriptive comparison of the average daily rhinoconjunctivitis symptom and medication scores is shown in

TABLE II. Efficacy analysis of average rhinoconjunctivitis symptom and medication scores

	Adjusted mean of 75,000 SQ-T (SE)	Adjusted mean of placebo (SE)	Estimated difference (% reduction)*	95% CI of estimated difference	*P* value
Entire grass-pollen season†					
Symptom score	2.474 (0.180)	2.935 (0.180)	−0.462 (16%)	[−0.963; 0.040]	.071
Medication score	1.463 (0.205)	2.046 (0.206)	−0.582 (28%)	[−1.156; −0.008]	.047
Peak grass pollen season†					
Symptom score	3.584 (0.232)	4.243 (0.235)	−0.659 (16%)	[−1.308; −0.009]	.047
Medication score	1.887 (0.254)	2.638 (0.257)	−0.751 (28%)	[−1.463; −0.039]	.039
Pooled data‡					
Entire grass pollen season					
Symptom score	2.608 (0.132)	3.057 (0.133)	−0.449 (15%)	[−0.809; −0.090]	.014
Medication score	1.552 (0.154)	2.197 (0.155)	−0.644 (29%)	[−1.062; −0.227]	.003
Pooled data‡					
>8 Weeks preseasonal treatment					
Entire grass pollen season					
Symptom score	2.513 (0.155)	3.176 (0.159)	−0.663 (21%)	[−1.088; −0.238]	.002
Medication score	1.612 (0.184)	2.260 (0.189)	−0.648 (29%)	[−1.154; −0.143]	.012

SE, Standard error of adjusted mean.
*The % reduction was defined as the estimated difference relative to the adjusted mean of placebo.
†The analyses were performed on participants receiving active Step1 rescue medication (as defined in the statistical analysis plan).
‡The pooled analyses were based on data from the 75,000 SQ-T groups versus the placebo groups with Step1 rescue medication as a fixed effect.

Table III. For the rhinoconjunctivitis symptom score, a reduction of 16% of both mean and median values was seen in the 75,000 SQ-T group compared with placebo. During the peak pollen season, this difference increased to 30% for median values. The rhinoconjunctivitis medication score differed by 31% in the mean values of the 75,000 SQ-T relative to the placebo group, whereas 69% to 72% reductions were seen in the median values in the peak and entire pollen seasons. The divergence reflects the fact that many participants had a medication score of 0, and thus the medians were significantly lower than the means; this was most evident for the active treatment group. Data in Table III are descriptive only, and no adjustments for pollen region have been made.

Rhinoconjunctivitis Quality-of-Life Questionnaire scores were significantly improved with the 75,000 SQ-T grass allergen tablet compared with placebo, both at the first and second seasonal visit (17%, $P = .006$; 20%, $P = .020$). The number of well days was also significantly increased (by 18%, $P = .041$) for participants treated with the 75,000 SQ-T grass allergen tablet compared with placebo.

Changes in specific IgE and IgG (and inhibitory components [IgX]) analyzed in serum were time-dependent and dose-dependent, indicating that the treatment has an effect on the immune system (Figs 2 and 3). In the 75,000 SQ-T group, specific IgG to *P pratense* was increased after 8 weeks of treatment and reached a 3-fold increase at the posttreatment visit (Fig 3, *A*). For specific IgE, an initial increase was observed with an unchanged level at the posttreatment visit (Fig 3, *B*). In the placebo group, the expected seasonal increase in IgE was also observed. The induction of inhibitory components expressed as the increase in blocking antibody activity (specific IgX) in serum showed a clear time and dose response relationship detectable even in the low-dose group. No change was observed in the placebo group. The increases in IgG in subjects who received less than the recommended 8 weeks of preseasonal therapy were comparable with subjects who received at least 8 weeks of treatment (mean ± SD, 0.06 ± 0.05 RU).

Treatment with the grass allergen tablet was generally well tolerated. A total of 451 (53%) participants had adverse events (AEs) judged by the investigators as probably or possibly related to treatment. These were mainly located within the mouth or throat (eg, oral pruritus or throat irritation). They were primarily mild or moderate in intensity and of short duration (median duration of oral sensations was 10.5 and 4 days in the 2 75,000 SQ-T groups, respectively). The frequency of mild AEs, but not moderate or severe AEs, increased noticeably between the 2,500 SQ-T dose and the 25,000 SQ-T dose, but did not increase further with the 75,000 SQ-T dose (n = 232, 253, 391, and 385, for placebo through 75,000 SQ-T doses, respectively; Table IV). Only 26 participants (3%) withdrew because of adverse events (Table IV). One drug-related serious adverse event was reported (uvula edema in the 25,000 SQ-T group). However, this did not require treatment and did not lead to withdrawal. Only 18 participants (2%) withdrew from the trial because of probable or possible treatment-related adverse events. No life-threatening systemic reactions or deaths were seen in any group.

DISCUSSION

The trial was a large-scale, double-blind, placebo-controlled trial showing a clear dose-response relationship and clinical efficacy of sublingual immunotherapy.

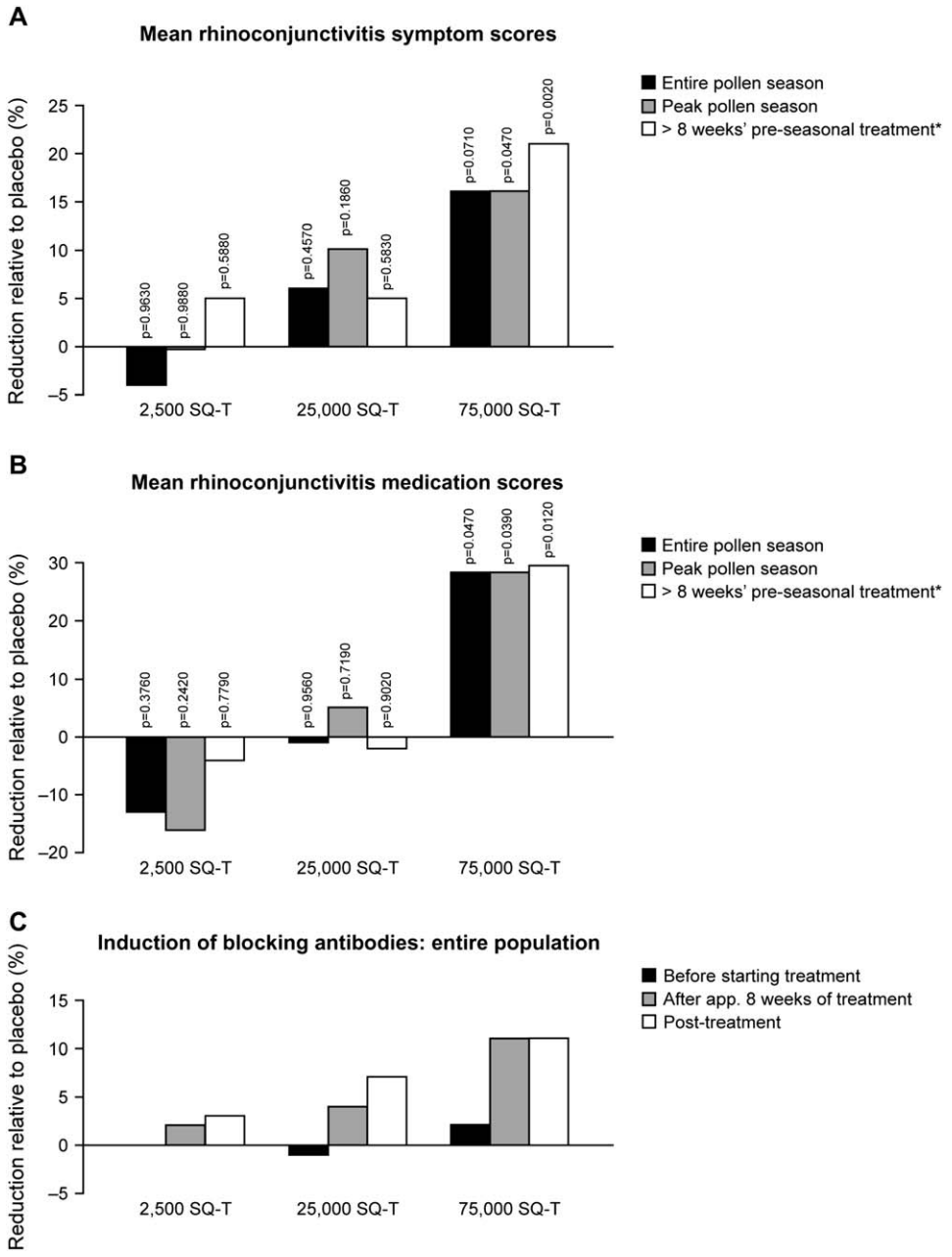

FIG 2. Percentage reduction in the active treatment groups relative to the placebo group. The analyses for the entire *(black bars)* and peak *(grey bars)* pollen season included participants receiving active Step 1 medication. *White bars* show analysis for subjects receiving trial medication for at least 8 weeks before the grass pollen season; *data for 75,000 SQ-T are pooled data, entire pollen season (ie, participants receiving similar trial medication with active or placebo Step 1 rescue medication were pooled). **A,** Mean rhinoconjunctivitis symptom scores. **B,** Mean rhinoconjunctivitis medication scores. **C,** Induction of blocking antibodies. IgX is a measure of the level of inhibitory components to specific IgE–*P pratense* allergen binding and is a ratio of 2 IgE measurements. The figure shows the increase in inhibitory components relative to placebo. *App.,* Approximately.

Overall, the comparison of efficacy among 3 doses of grass allergen tablets and placebo showed a dose-related response with highest reductions in the rhinoconjunctivitis symptom and medication scores for the 75,000 SQ-T tablet. All efficacy analyses were consistent and supported the clinical benefit at the 75,000 SQ-T dose, which was confirmed by additional analyses. Quality of life was significantly improved, as were the number of well days, after treatment with 75,000 SQ-T tablets. The trial demonstrated proof of concept of the grass allergen tablet in a heterogeneous population from several countries.

Alterations in IgE, IgG, and serum blocking activity were time-dependent and dose-dependent and had qualitative similarities with successful subcutaneous

TABLE III. Descriptive table of rhinoconjunctivitis symptom and medication scores; means and medians for the entire pollen season and the peak pollen season*

	75,000 SQ-T	Placebo	Difference	Percent reduction†
Rhinoconjunctivitis symptom score				
Entire pollen season				
Mean	2.48	2.96	0.48	16%
Median	2.13	2.53	0.40	16%
Peak pollen season				
Mean	3.57	4.28	0.71	17%
Median	2.93	4.18	1.25	30%
Rhinoconjunctivitis medication score				
Entire pollen season				
Mean	1.40	2.03	0.63	31%
Median	0.35	1.24	0.89	72%
Peak pollen season				
Mean	1.81	2.63	0.82	31%
Median	0.50	1.60	1.1	69%

*Descriptive comparison; no adjustment for pollen region.
†The % reduction was defined as the difference between the active group relative to the placebo group.

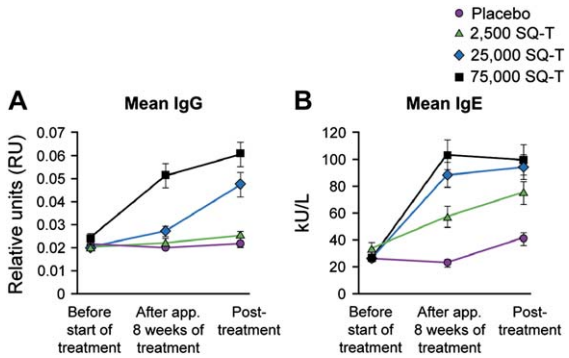

FIG 3. Immunologic changes after treatment with placebo or grass pollen tablets 2500, 25,000, or 75,000 SQ-T. The amounts of specific (**A**) IgG and (**B**) IgE to *Phleum pratense* allergen are given in RU and kU/L, respectively. *App*, Approximately.

immunotherapy.[20,21] Thus, there was an increase in both allergen-specific IgG and IgE antibodies with blunting of further seasonal increases in IgE. In addition, the observed parallel dose-response relationships for changes in IgX and rhinoconjunctivitis symptom and medication scores might express a potential for this IgG-associated blocking activity to be predictive of clinical efficacy.

The risk of severe systemic reactions, including anaphylaxis, has been a key concern in relation to subcutaneous immunotherapy. Encouragingly, no treatment-related severe systemic adverse event requiring intervention with adrenaline occurred during this large-scale multicenter trial. Similarly, no severe systemic adverse events (early or delayed) have been reported in the literature for sublingual immunotherapy in the past 15 years.[22]

Adherence to any treatment is influenced by the number and severity of adverse events and the efficacy obtained, and relates to the treatment's complexity and convenience for the patient. The adherence to trial medication in this trial was high; that is, the participants clearly accepted and consented to the treatment regimen. In addition, only 18 participants (2%) withdrew from the trial because of probable or possible treatment-related adverse events.

Although the overall effect of immunotherapy on the primary end point for the entire population was moderate (16% for symptoms), the result compares favorably with a recent Cochrane meta-analysis that compared efficacy of different pharmacologic agents for allergic rhinitis.[23] Compared with placebo, the computed effect size for antihistamines was 7%; for leukotriene antagonists, 5%; and for topical steroids, 17%. In our study, the planned duration of preseasonal treatment of at least 8 weeks was based on suggestions from the literature.[1,24,25] However, because of the unpredictable onset of the grass pollen season, some participants did not receive treatment for 8 weeks before the season commenced. A protocol-correct analysis of our data indicated that participants who had received the 75,000 SQ-T grass allergen tablet for at least 8 weeks had greater and highly statistically significant reductions in rhinoconjunctivitis symptoms (21%) and medication scores (29%) compared with placebo. This suggests that the length of preseasonal treatment period may have an effect on the clinical outcome, and further studies are in progress to address this possibility.

It is possible that an awareness of treatment-related itching and minor swelling in the mouth in the actively treated group could have influenced the reporting of symptoms and biased the results. This was not the case, because there were frequent reports of local side effects also in the placebo group. Furthermore, the mean weekly symptom scores in participants who received the 75,000 SQ dose were virtually identical in subjects who reported local side effects compared with subjects who did not report such effects (data not shown).

In summary, this study provides proof of concept for the use of the grass allergen tablet in seasonal allergic rhinoconjunctivitis. It is likely that a more prolonged preseasonal treatment phase will enhance efficacy, and such studies are currently in progress. The grass tablet represents a new baseline treatment involving a once-daily tablet which is simple and safe and addresses underlying allergic mechanisms. Preventing symptoms while reducing the need for symptomatic medication the grass allergen tablet should help to make immunotherapy available to a broad range of patients whose quality of life is impaired by grass pollen allergy. The remarkably low dropout rate observed in this study supports the view that there is likely to be a high degree of adherence to treatment. In the long term, specific immunotherapy has been shown to induce long-term remission[7] and to decrease or prevent the development of more severe manifestations of allergic disease—for example, progression from rhinitis to asthma, and/or the development of new allergies (shown in children with grass or birch pollen allergy).[14,26,27] Whether treatment with the grass allergen tablet provides these benefits needs to be tested in more long-term placebo-controlled trials.

TABLE IV. Summary of adverse events

	Placebo/active n (%) E	2500 SQ-T/active n (%) E	25,000 SQ-T/active n (%) E	75,000 SQ-T/active n (%) E	Placebo/placebo n (%) E	75,000 SQ-T/placebo n (%) E
Patients, N	136	136	139	141	150	153
All AEs	100 (73.53) 363	118 (86.76) 398	126 (90.65) 608	130 (92.20) 571	115 (76.67) 395	137 (89.54) 633
SAEs*	0 (0.00) 0	2 (1.47) 2	0 (0.00) 0	1 (0.71) 1	1 (0.67) 1	2 (1.31) 3
Relation of AEs to treatment						
Probable/possible	3 (25.74) 82	44 (32.35) 102	101 (72.66) 287	110 (78.01) 317	38 (25.33) 73	123 (80.39) 427
Severity						
Mild	83 (61.03) 232	93 (68.38) 253	109 (78.42) 391	120 (85.11) 385	98 (65.33) 247	123 (80.39) 427
Moderate	60 (44.12) 117	61 (44.85) 128	69 (49.64) 194	62 (43.97) 162	58 (38.67) 128	81 (52.94) 188
Severe	12 (8.82) 14	12 (8.82) 17	15 (10.79) 23	17 (12.06) 24	13 (8.67) 20	13 (8.50) 18
AE withdrawals	1 (0.74) 1	4 (2.94) 4	4 (2.88) 6	8 (5.67) 12	2 (1.33) 2	7 (4.58) 16

E, Number of events. *SAE,* serious AE.
*One adverse event (uvula edema in 25,000 SQ-T group) was, after closure of the database, upgraded from nonserious to serious.

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