

Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis

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Background: Allergen immunotherapy (desensitization) by injection is effective for seasonal allergic rhinitis and has been shown to induce long-term disease remission. The sublingual route also has potential, although definitive evidence from large randomized controlled trials has been lacking.

Objective: The aim was to confirm the efficacy of a rapidly dissolving grass allergen tablet (GRAZAX, ALK-Abelló, Hørsholm, Denmark) compared with placebo in patients with seasonal rhinoconjunctivitis.

Methods: A longitudinal, double-blind, placebo-controlled, parallel-group study that included 51 centers from 8 countries. Subjects were randomized (1:1) to receive a grass allergen tablet or placebo once daily. A total of 634 subjects with a history of grass pollen-induced rhinoconjunctivitis for at least 2 years and confirmation of IgE sensitivity (positive skin prick test and serum-specific IgE) were included in the study.

Subjects commenced treatment at least 16 weeks before the grass pollen season, and treatment was continued throughout the entire season.

Results: The primary efficacy analysis showed a reduction of 30% in rhinoconjunctivitis symptom score ($P < .0001$) and a reduction of 38% in rhinoconjunctivitis medication score ($P < .0001$) compared with placebo. Side effects mainly comprised mild itching and swelling in the mouth that was in general well tolerated and led to treatment withdrawal in less than 4% of participants. There were no serious local side effects and no severe systemic adverse events.

Conclusion: Sublingual immunotherapy with grass allergen tablets was effective in grass pollen-induced rhinoconjunctivitis. The tablet was well tolerated with minor local side effects.

Clinical implications: The grass allergen tablet represents a safe alternative to injection immunotherapy suitable for home use. (J Allergy Clin Immunol 2006;118:434-40.)

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The prevalence of seasonal allergic rhinitis is increasing.¹ At least 20% of the European population has the disease, and approximately half of these people are allergic to grass pollen. A general practice-based community study in United Kingdom revealed that more than 40% of patients receiving usual therapy with antihistamine tablets and/or nasal corticosteroid sprays were dissatisfied with their treatment.² In patients with severe hayfever unresponsive to usual therapy, allergen immunotherapy has been shown to be highly effective. Immunotherapy reduces symptoms and use of relief medication and markedly improves patients' quality of life within the first treatment year.^{3,4} In contrast with symptomatic treatment with antiallergic drugs, immunotherapy is the only available therapy that treats the underlying cause of the disease, with proven long-term benefits. Thus, immunotherapy has been shown to induce long-term remission for at least 3 years after its discontinuation.⁵ In children with seasonal pollinosis, immunotherapy reduced 2-fold to 3-fold the risk of progression of rhinitis to asthma.^{6,7} Several studies in children have confirmed that immunotherapy may prevent the onset of new sensitizations to other inhalant allergens.⁷⁻⁹ A disadvantage of the subcutaneous route is the

Abbreviations used

SQ-T: Standardized quality tablet
VAS: Visual analog scale

occasional risk of side effects, including systemic allergic reactions, which confines the use of injection immunotherapy to specialist centers with access to adrenaline and other resuscitative measures.

In contrast with the injection route, sublingual immunotherapy has a very favorable safety profile, thereby enhancing the benefit-risk ratio in favor of a broader indication for allergen immunotherapy for use in the patients' home. Although, sublingual immunotherapy has been shown to be effective in a recent meta-analysis, the studies assessed were, in general, small, and there was considerable heterogeneity among studies.^{8,10,11} Thus, the efficacy profile for the sublingual route is not as well documented as injection-based immunotherapy, and large controlled studies are needed to define the role of the sublingual approach in allergic rhinitis and asthma as well as in the prevention of asthma.^{11,12}

Historically, an initial up-dosing treatment phase has been an important element of injection immunotherapy to optimize treatment to the tolerance of each patient while minimizing any untoward effects. However, up-dosing complicates the treatment regimen with the need for frequent clinic visits for the first 8 to 16 weeks. A new tablet-based sublingual immunotherapy (GRAZAX, ALK-Abelló, Hørsholm, Denmark) without up-dosing has recently been investigated in subjects with grass pollen allergy.¹³ In a preliminary dose-finding study of 855 patients, there was a dose-dependent efficacy with a reduction in symptoms of 16% and decrease in relief medication of 29% with the 75,000 standardized quality tablet (SQ-T) daily dose (GRAZAX) given from approximately 8 weeks before the season compared with placebo therapy.¹⁴ The results suggested that the length of the pre-seasonal treatment period might influence the magnitude of the clinical effect, because those subjects who received more than 8 weeks of therapy improved more than subjects who received less than 8 weeks. For this reason and on the basis of the favorable safety profile for the 75,000 SQ-T dose, this dose was selected for the current study in which the pre-seasonal treatment period was extended to a minimum of 16 weeks before the onset of the pollen season.

METHODS

The study was initiated in the autumn 2004 and was randomized, parallel-grouped, double-blinded, and placebo-controlled. A total of 634 patients from 51 centers in 8 countries (Austria, Denmark, Germany, Italy, The Netherlands, Spain, Sweden, and United Kingdom) were randomized 1 to 1 receiving either an orodispersible grass allergen tablet 75,000 SQ-T (GRAZAX; approximately 15 µg major allergen *Phleum p 5*) or a placebo tablet similar in taste, smell, and appearance once daily. The placebo tablet did not contain

TABLE I. Daily scoring of rescue medication

Step	Rhinoconjunctivitis	Score/dose
1	Desloratadine 5 mg once daily	6
2	Budesonide nasal spray (as much as 32 µg; 2 puffs per nostril twice daily)	1 per spray
3	Prednisone (as much as 50 mg once daily)	1.6 per 5 mg

histamine or other active ingredients. The treatment started 16 weeks before the expected start of the grass pollen season and continued throughout the grass pollen season 2005. Double-blind treatment continued for another 2 years, followed by 2 years of follow-up. Results from the first treatment season are presented here.

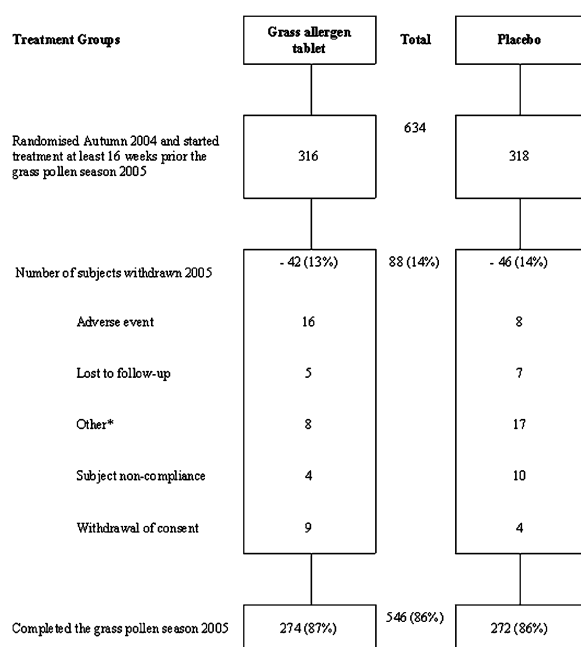
Written informed consent was obtained before entering the study, and the study was performed in accordance with the Declaration of Helsinki¹⁵ and Good Clinical Practice. The ethics committees in each of the participating countries approved the study.

Inclusion criteria were as follows: 18 to 65 years old; at least 2-year clinical history of significant grass pollen-induced allergic rhinoconjunctivitis; specific IgE against *Phleum pratense* CAP class ≥ 2 ; positive skin prick test against *Phleum pratense* (Soluprick SQ, ALK-Abelló), wheal diameter ≥ 3 mm; and FEV₁ higher than 70% of predicted value. Exclusion criteria were as follows: significant asthma outside the grass pollen season; FEV₁ lower than 70% of predicted value; allergic rhinitis requiring medication caused by allergens other than grass during the treatment period (patients with positive skin tests to other allergens in the absence of symptoms were permitted); conjunctivitis, rhinitis, or asthma at the screening or randomization visits; history of anaphylaxis; immunosuppressive treatment; receipt of immunotherapy with grass pollen allergen within the previous 10 years or any other allergen within the previous 5 years; and pregnancy.

Each day the subjects rated their rhinoconjunctivitis symptoms on a scale from 0 to 3 (0 = no symptoms, 1 = slight symptoms, 2 = moderate symptoms, 3 = severe symptoms). The symptoms rated were runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes. In case of allergic symptoms, subjects had free access to relief medication (desloratadine, budesonide nasal spray, and oral prednisone) in a stepwise fashion depending on the persistence and severity of their symptoms. Relief medication was scored according to predetermined criteria (Table I). The scoring scale was not seen by the subjects. The final medication and symptom scores were calculated as the mean of the total daily scores recorded throughout the whole 2005 pollen season.

Well days, defined as days without intake of rescue medication and a symptom score of 2 or less, were calculated for the entire grass pollen season. Rhinoconjunctivitis symptoms were also evaluated through daily scoring on a visual analog scale (VAS). Throughout the grass pollen season, the subjects registered their overall severity of rhinoconjunctivitis symptoms daily by answering the question, "How has your hay fever been today?" by indicating a point on a continuous VAS ranging from no symptoms (0) to severe symptoms (100).

Finally, rhinoconjunctivitis symptoms were globally evaluated by asking the subjects the following question: "Compared to your symptoms in previous grass pollen seasons, how have you felt overall in this grass pollen season?" The possible response categories were much better, better, the same, worse, or much worse. For the statistically analysis, categorical data were pooled into a binary endpoint of improved or not improved (improved = much better/better, and not improved = the same/worse/much worse). This analysis permitted the computation of a responder analysis because the observations were within-subject and based on the patients' retrospective comparison with their previous baseline seasons. All



*3 pregnancies, 1 unrelated death (subarachnoid haematoma), 1 lack of efficacy, 8 withdrawals due to site closure, 2 moved far away from study site, 2 just stopped showing up, 3 were withdrawn due to conflicting allergic symptoms not related to grass pollen, 4 stopped for personal reasons and 1 was withdrawn as she worked at a study site.

FIG 1. Consort flow diagram.

other data were collected at 7 visits in the clinic, and, in addition, the subjects were reporting data for the efficacy analyses into an electronic diary on a daily basis.

Statistics

The first ranked primary efficacy endpoint was the average rhinoconjunctivitis symptom score during the grass pollen season, and the power calculation was based on this endpoint. Data of average rhinoconjunctivitis symptom score in the grass pollen season necessary for the calculations were estimated from the previous dose-ranging study.¹⁴ The values used were mean symptom score, 2.91, and SD, 2.25. A reduction of at least 25% in symptom score can be discovered with a 5% significance level and a power of 95% with a sample size of 268 subjects in each arm. With an estimated dropout of 10%, approximately 300 subjects were to be included in each treatment arm. Comparison of the 2 treatment groups was by analysis of variance with the efficacy endpoint as response variable, treatment group as a fixed effect, and pollen region as random effect. Each treatment group was adjusted for different error variation. A *P* value < .05 was considered statistically significant. Reductions were calculated as:

$$\left(\frac{\text{Active} - \text{Placebo}}{\text{Placebo}} \right) \times 100.$$

Analyses of difference between active and placebo first day and first week of the grass pollen season were performed post hoc. All other analyses were predefined.

To secure continuous double-blinding in the following treatment years, the statistical analysis of the presented results were handled by a Contract Research Organization. Unblinded efficacy and safety assessments on subject level were available only for a biostatistician at the Contract Research Organization. All personnel associated with the

TABLE II. Subject demographics

	Treatment group			
	Grass allergen tablet		Placebo	
No. of subjects	316		318	
Sex (N)				
Men	179	57%	193	61%
Women	137	43%	125	39%
Age (y)				
Mean (SD)	33.8	9.6	34.5	10.0
Ethnic origin (N)				
African	2	1%	4	1%
Asian	8	3%	3	1%
White	299	95%	308	97%
Other	7	2%	3	1%
Country (N)				
Austria	13	4%	12	4%
Denmark	60	19%	62	19%
Germany	77	24%	75	24%
Italy	34	11%	36	11%
Netherlands	19	6%	21	7%
Spain	24	8%	22	7%
Sweden	32	10%	31	10%
United Kingdom	57	18%	59	19%
Grass pollen allergy (severity)				
Moderate	137	43%	144	45%
Severe	179	57%	174	55%

study remained blinded. Hence, beside the predefined tables only blinded subject listings were available for the preparation of this paper.

All analyses presented were performed on all randomized subjects. No imputation of data was performed in case of missing data, but all available data were used to their full extent.

RESULTS

A total of 634 subjects were randomized, and 546 (86%) subjects completed the first treatment year. In total, 88 (14%) subjects withdrew, and of these withdrawals, 24 (4%) withdrew because of adverse events. The pattern of withdrawal was similar between treatment groups, but with nominally more withdrawals because of adverse events in subjects treated with the grass allergen tablet. A diagram of the study flow is presented in Fig 1.

The study population was made up of 372 (59%) male subjects and 262 (41%) female subjects. A total of 281 (44%) subjects had moderate and 353 (56%) subjects had severe grass pollen allergy. The average history of grass pollen allergy was 16 years. The average subject was 34.2 years old, and overall subject characteristics and anthropometrics were similar between treatment groups (Table II).

Grass pollen counts were obtained from 33 pollen stations available in the participating countries. The average grass pollen season lasted 57.8 days (SD, 13.9; range, 16-86 days). The length of preseasonal treatment ranged from 16 to 35 weeks.

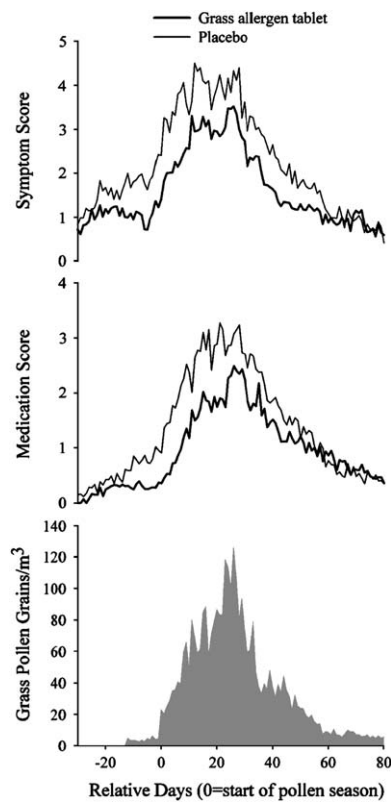


FIG 2. Daily averaged grass pollen counts, scoring of symptoms, and scoring of rescue medication. *P* value presented for the comparison of the 2 treatment groups tested by ANOVA with the score as response variable, treatment group as a fixed effect, and pollen region as random effect. Reduction was calculated as $\left(\frac{\text{Active} - \text{Placebo}}{\text{Placebo}} \right) \times 100$.

Efficacy

The average daily rhinoconjunctivitis symptom and medication score are illustrated in Fig 2. A higher score indicates a higher level of symptoms or use of medication. Subjects treated with the grass allergen tablet scored statistically significantly lower than subjects treated with placebo ($P < .0001$). The reduction over placebo was 30% in symptom score and 38% in medication score over the entire grass pollen season. The significant reductions over placebo were present from the start of the grass pollen season ($P < .0001$; first day reduction, 43% in symptom score, 68% in medication score; first week reduction, 38% in symptom score, 62% in medication score). In Table III, average scores and the reported medication usage are presented for the entire grass pollen season.

A well day was defined as a day when the subject did not need any rescue medication and had a symptom score no greater than 2. Subjects treated with the grass allergen tablet on average had 27 (53%) well days during the grass pollen season versus 23 (44%) well days for placebo. The difference was highly statistically significant ($P < .0001$).

A statistically significant lower mean daily VAS score ($P < .0001$) of 31% in the grass pollen season was reported

TABLE III. Average daily scores and medication usage during the grass pollen season

	Treatment group	
	Grass allergen tablet	Placebo
No. of subjects for the entire season	282	286
Entire-season rhinoconjunctivitis symptom score		
Mean (SD)	2.4 (1.6)	3.4 (2.2)*
Median	2.1	3.2
Nose symptom score		
Mean (SD)	1.7 (1.2)	2.3 (1.5)
Median	1.4	2.2
Eye symptom score		
Mean (SD)	0.7 (0.6)	1.1 (0.8)
Median	0.5	0.9
Entire-season rhinoconjunctivitis medication score		
Mean (SD)	1.5 (1.9)	2.4 (2.5)*
Median	0.8	1.7
	N (%)	T N (%) T
Any rhinoconjunctivitis medication	191 (68%)	3284 229 (80%) 4278
Desloratadine (5 mg)	186 (66%)	2966 224 (78%) 3957
Budesonide nasal spray (32 µg)	107 (38%)	1186 164 (57%) 1970
Prednisone (5 mg)	13 (5%)	137 21 (7%) 115

T, Total number of days with use of rescue medication by all subjects.

*Statistically significant difference between treatment groups ($P < .0001$).

TABLE IV. Global evaluation of treatment effect

	Treatment group	
	Grass allergen tablet N (%)	Placebo N (%)
No. of subjects	316	318
Overall assessment of 2005 compared with previous seasons		
N	278	275
Much better	96 (35)	45 (16)
Better	132 (47)	106 (39)
The same	41 (15)	89 (32)
Worse	7 (3)	25 (9)
Much worse	2 (1)	10 (4)
Improved	228 (82)	151 (55)
Not improved	50 (18)	124 (45)

by subjects treated with the grass allergen tablet (mean score, 12; SD, 10.8) compared with subjects treated with placebo (mean score, 18; SD, 13.1).

At the end of the grass pollen season 2005, the subjects answered the question, "Compared to your rhinoconjunctivitis symptoms in previous grass pollen seasons, how have you felt overall in this grass pollen season?" In Table IV, the scoring is summarized. Data were pooled into the binary endpoint of improved or not improved. Results demonstrate that 82% of the patients who received active treatment responded, compared with 55% on placebo, an overall improvement in the response rate of 49% ($P < .0001$).

TABLE V. Summary of treatment-emergent adverse events

	Treatment group			
	Grass allergen tablet		Placebo	
	N (%)	E	N (%)	E
No. of subjects	316		318	
All adverse events	265 (84)	824	205 (64)	507
Causality				
Probable related	212 (67)	419	27 (8)	39
Possible related	74 (23)	104	47 (15)	67
Unlikely related	165 (52)	301	183 (58)	401
Severity				
Mild	243 (77)	593	177 (56)	321
Moderate	118 (37)	208	75 (24)	159
Severe*	16 (5)	23	21 (7)	26

N, Number of subjects; E, number of events.

*Ten of the severe events were assessed by the investigator to be treatment-related. Because of the continuous blinding of the study, it is unknown whether they received active treatment. The severe related events were 2 oral pruritus, 4 edema mouth, 1 fatigue, 1 pharyngeal edema, 1 oral discomfort, and 1 nausea.

Safety

The overall frequency and severity of adverse events are tabulated in Table V. A total of 265 (84%) subjects treated with grass allergen tablets and 205 (64%) treated with placebo reported at least 1 adverse event. Approximately half of the reported events were assessed unlikely related to the study drug. More adverse events were reported by subjects treated with grass allergen tablets compared with placebo. Although subjects receiving the grass allergen tablet reported 523 adverse events assessed probably or possibly related to the drug, the placebo subjects reported only 106 adverse events assessed as probably or possibly related to the study drug.

No serious adverse events with possible or probable relation to the study drug were reported. The 24 (4% of 634 subjects) who had adverse events that resulted in withdrawal all responded to medication equivalent to the study reliever medication or simple painkillers, and there was no use of adrenaline.

The majority of the most frequently reported adverse events were application site-related, indicating drug relationship. For instance, oral pruritus was reported by 46% of actively treated subjects versus 4% of placebo treated subjects (Table VI). Other common adverse events such as headache, nasopharyngitis, and influenza were equally reported in both groups. A total of 24 subjects were withdrawn because of an adverse event, but only in 5 cases the withdrawals were treatment-related and initiated by the investigator. In Table VII, the 5 cases are described in detail.

DISCUSSION

Comparison of efficacy between the grass allergen tablet and placebo showed highly statistically significant

TABLE VI. Treatment-emergent adverse events reported by $\geq 5\%$ of subjects

	Treatment group	
	Grass allergen tablet	Placebo
	N (%)	N (%)
No. of subjects	316	318
Oral pruritus	145 (46)	13 (4)
Nasopharyngitis	47 (15)	60 (19)
Edema mouth	58 (18)	2 (1)
Influenza	23 (7)	24 (8)
Ear pruritus	38 (12)	3 (1)
Throat irritation	30 (9)	3 (1)
Headache	9 (3)	19 (6)

improvements in favor of the active treatment for all endpoints tested. The grass allergen tablet resulted in a 30% decrease in rhinoconjunctivitis symptoms in the face of an additional 38% reduction in the use of reliever medication (antihistamines and intranasal corticosteroid) compared with placebo. There was a 31% improvement in the visual analogue scores for symptoms during the pollen season and an overall 49% higher response rate for the actively treated group, as judged by the global assessments of hayfever severity compared with previous years. Localized itching and swelling in the mouth, although common, largely required no treatment, and was well tolerated as reflected by a withdrawal rate because of adverse events of 5% in the subjects treated with the grass allergen tablet.

This study had both the rhinoconjunctivitis symptom score and rhinoconjunctivitis medication score as primary endpoints. In view of the size of the study and the strict randomization protocol, it is unlikely that the observed differences between the groups could be explained by any mismatching at baseline. Although it could be argued that inclusion of a baseline observational year would have confirmed matching for symptom and rescue medication use, any advantage has to be weighed against the inevitable increased dropout rate associated with a more prolonged study. Further, the groups were well matched for all other variables, including grass sensitivity as defined by skin prick testing and specific IgE levels and their duration of disease. In the statistical test, hierarchy symptom score was ordered first and medication score second. Because both null hypotheses were clearly rejected at the 5% test level ($P < .0001$), improvement for both rhinoconjunctivitis symptom score and rhinoconjunctivitis medication score was confirmed. The efficacy results for the 75,000 SQ-T dose were superior to the level established in the previous dose-finding study.¹⁴ This is probably caused by a longer preseasonal treatment period. Comparison with subcutaneous immunotherapy is difficult because the treatment regimens are completely different, but currently published results from large placebo-controlled, randomized, double-blind trials indicate that the efficacy in first treatment season is similar.¹⁶ The

TABLE VII. Treatment-related adverse event withdrawals initiated by the investigator

Adverse event	Description
Angioedema on the base of the tongue	Twelve days after treatment start, the subject reported mild angioedema on the base of the tongue. The event was reported the following 8 days, each time lasting 6 hours and recovering without treatment.
Inferior lip angioedema, pharyngeal hyperemia, cough, and mild dyspnea	On the first day of treatment, 5 minutes after taking the trial drug, the subject had inferior lip angioedema, pharyngeal hyperemia, cough, and mild dizziness. Spirometry showed no lung function impairment. The subject received antihistamine and recovered from all events. The event lasted 70 minutes.
Pharynx edema and changes in voice	From first day of treatment, the subject reported moderate oral pruritus immediately after tablet intake. On day 18, the subject came for an unscheduled visit because of worsening of oral pruritus and "strange feeling in the mouth." An oral examination was performed by the investigator, and edema of pharynx was reported. Furthermore, the subject and the investigator found a mild change of the subject's voice. The subject was treated with prednisolone (40 mg) and cetirizine (10 mg) and recovered. The events lasted 6 to 8 hours.
Swelling in throat	Eight days after start of treatment, the subject developed mild swelling under the tongue. The swelling recovered after 22 days. On day 29, the subject in addition developed moderate swelling in the throat. The subject recovered without treatment.
Angioedema of lips (externally)	From first day of treatment, the subject reported mild tingling in the mouth after tablet intake lasting for 30 minutes. On day 11, the subject developed moderate angioedema externally on the lips. The event lasted 3 hours, and the subject recovered without treatment.

observed effect sizes for the grass allergen tablet of greater than 30% over placebo compare favorably with those observed in a recent Cochrane meta-analysis of treatments for allergic rhinitis in which effect sizes compared with placebo were, respectively, 5%, 7%, and 18% for leukotriene pathway modifiers, antihistamines, and intranasal corticosteroids.¹⁷

The effect of the grass allergen tablet was present already at the start of the pollen season. This was obtained by starting the treatment 16 weeks before the expected start of the pollen season. Previous studies suggest that 8 to 10 weeks of preseasonal treatment may be sufficient,^{14,18} but because it is difficult to predict the exact start of the pollen season, 10 to 16 weeks may be optimal.

In the current study, no anaphylaxis, no use of adrenaline, and no severe systemic adverse events have been reported. The favorable benefit-risk ratio of the grass allergen tablet will potentially make specific immunotherapy available to a broader group of patients as a home-based treatment.

Other currently available treatments for allergic rhinitis can only reduce symptoms, with relapse within days when discontinued. Allergen immunotherapy, on the other hand, is the only treatment that addresses the root cause of the disease, with long-term modification of both allergen-specific T-cell responses^{19,20} and B-cell antibody responses,¹⁹ and persistent clinical improvement that lasts for years after discontinuation.⁵ As previously observed with subcutaneous immunotherapy,²¹ high-dose sublingual grass immunotherapy has been shown to suppress allergen-induced late-phase skin responses and to be accompanied by increases in allergen-specific IgG with blunting of seasonal increases in allergen-specific IgE.²² The grass allergen tablet can be considered a baseline treatment because it provides symptom prevention and in addition reduces the use of symptom relieving medication. The

ongoing extension of this study for an additional 4 years will provide data to evaluate the long-term benefits of this treatment during its continued administration for a further 2 years and for 2 years after its discontinuation.

In conclusion, treatment with the grass allergen tablet was well tolerated and clinically effective as treatment of seasonal allergic rhinoconjunctivitis already from the first treatment season. For all efficacy endpoints, differences between the grass allergen tablet and placebo were pronounced, highly statistically significant, and in favor of specific immunotherapy with the grass allergen tablet. The study confirms proof of concept of home treatment with grass allergen tablets in a heterogeneous population from several countries. The grass allergen tablet might represent a new baseline treatment of grass pollen allergy.

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