Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen–induced rhinoconjunctivitis

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Background: Seasonal allergic rhinoconjunctivitis affects millions of persons. The efficacy of allergen sublingual immunotherapy (SLIT) was demonstrated in previous short-term studies.

Objectives: We sought to evaluate the sustained efficacy of 2 dosing regimens of a pre- and coseasonal treatment with 300 IR (index of reactivity) 5-grass-pollen SLIT tablets (Oralair) compared with placebo assessed by using the average adjusted symptom score (AAdSS) at season 3 in adults with grass pollen–induced rhinoconjunctivitis.

Methods: Six hundred thirty-three patients were treated for either 2 or 4 months before and then during the grass pollen season with active or placebo treatment for 3 consecutive seasons. The primary outcome was the AAdSS, a symptom score adjusted for rescue medication use, after 3 consecutive treatment seasons. Secondary outcomes were symptoms and rescue medication score, quality-of-life, and safety assessments.

Results: The mean AAdSS was reduced by 36.0% and 34.5% at season 3 in the 2- and 4-month pre- and coseasonal active treatment groups, respectively, compared with that in the placebo group ($P < .0001$ for both). Reductions were observed in total symptom scores and ISSs and the medication score, with a marked improvement in quality of life for both active groups compared with the placebo group at season 3. Most treatment-emergent adverse events were local reactions expected with SLIT, decreasing in number and intensity in each treatment season.

Conclusions: Sustained efficacy of 2- and 4-month pre- and coseasonal treatment with the 300 IR tablet over 3 pollen seasons was demonstrated, with reduction in symptoms and rescue medication use. The treatment was well tolerated. Adverse events decreased in number and intensity over the 3 seasons. (J Allergy Clin Immunol 2011;128:559-66.)

Key words: *Rhinoconjunctivitis, sublingual immunotherapy, grass pollen, allergen, pre- and coseasonal treatment*

Respiratory allergy occurs in more than 500 million persons around the world.[1,2] In developed countries allergic rhinitis affects between 10% and 25% of the general population,[3] with an average of 23% in European countries.[4] The risk of asthma is higher in patients with rhinitis.[5] Allergies to grass, weed, and tree pollen characteristically result in seasonal rhinitis symptoms, which correlate with the presence of allergen exposure in the environment. The primary approach to the control of symptoms is the identification and avoidance of the causal allergens, which is often impossible for pollen. Pharmacotherapy and immunotherapy are the main treatment modalities.

Allergen immunotherapy is considered appropriate when allergic rhinitis symptoms cannot be controlled sufficiently by avoidance of the allergen or an optimal symptomatic medication regimen. Allergen immunotherapy acts on the main cause of the allergic reaction by modifying or downregulating the immune response. Sublingual immunotherapy (SLIT) tablets containing freeze-dried allergen extracts of 5 grasses (cocksfoot *[Dactylis glomerata]*, meadow grass *[Poa pratensis]*, rye grass *[Lolium perenne]*, sweet vernal grass *[Anthoxanthum odoratum]*, and timothy grass *[Phleum pratense]*) have been developed by Stallergenes S.A. (Antony, France) and approved for use in 23 European countries under the trade name Oralair.

Short-term studies in adult and pediatric patients demonstrated the efficacy in the first pollen season after starting therapy with Oralair.[6,7] This study evaluated the sustained efficacy and the safety of pre- and coseasonal treatments with a 300 IR (index of reactivity) 5-grass SLIT tablet in patients with grass pollen–induced rhinoconjunctivitis compared with that of placebo, as assessed by the average adjusted symptom score (AAdSS)[8,9] over 3 consecutive pollen seasons. Efficacy parameters were reported at each season.

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Abbreviations used
AAdSS: Average adjusted symptom score
AdSS: Adjusted symptom score
AE: Adverse event
ANCOVA: Analysis of covariance
ARMS: Average rescue medication score
ARTSS: Average rhinoconjunctivitis total symptom score
ISS: Individual symptom score
LS: Least squares
RMS: Rescue medication score
RTSS: Rhinoconjunctivitis total symptom score
SLIT: Sublingual immunotherapy
TEAE: Treatment-emergent adverse event

METHODS

Study design

We performed a randomized, multicenter, double-blind, placebo-controlled, 5-year, ongoing phase III study with 3-season treatment and 2-year follow-up phases. Six hundred thirty-three men and women 18 to 50 years of age with seasonal grass pollen–induced allergic rhinoconjunctivitis for at least the 2 previous pollen seasons were enrolled. The study was conducted in Austria, Canada, Czech Republic, Denmark, France, Germany, Italy, Poland, Russia, and Slovakia. The use of antihistamines, nasal corticosteroids, and oral corticosteroids as rescue medication was allowed by using a stepwise regimen defined in the study protocol. The protocol was reviewed and approved by local regulatory authorities and independent ethics committees in each country and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice–International Conference on Harmonisation guidelines. Written informed consent was obtained from all patients before starting any study procedure.

Treatment was initiated 4 months before the expected start of the pollen season. Patients received either placebo or 300 IR 5-grass-pollen tablets (Oralair) sublingually once daily for 2 months or 4 months before and then during the pollen season (the 2-month and 4-month groups, respectively) for 3 consecutive pollen seasons in years 1 to 3 (2007, 2008, and 2009 seasons). The 2-month group also received placebo for 2 months before the start of active treatment during the time that the 4-month group was receiving active treatment to maintain the blinding. The primary end point was the AAdSS assessed for the third pollen season. The fourth and fifth pollen seasons (years 4 and 5) are treatment free, with follow-up periods currently ongoing (Fig 1). The secondary end points discussed in this publication were symptom and medication scores, individual symptom scores (ISSs), symptom and medication-free days, quality of life, and safety.

Baseline characteristics

Sensitization status to either 5-grass-pollen allergens only (monosensitization) or to 5-grass-pollen allergens and at least another allergen (polysensitization) was derived from a skin prick test at screening. Asthma status and severity were recorded at every visit. A retrospective rhinoconjunctivitis total symptom score (RTSS) was calculated from the most severe rhinoconjunctivitis symptoms of the previous pollen season, as reported by the patient.

Symptom and medication scores

Symptom and medication scores have been discussed previously.[8,10] The following 6 rhinoconjunctivitis symptoms were assessed daily by the patient over each pollen season: sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes. The severity of these symptoms was evaluated by using a 4-level descriptive scale: 0, absent (no sign/symptom evident); 1, mild (sign/symptom clearly present but minimal awareness and easily tolerated); 2, moderate (definite awareness of sign/symptom, bothersome but tolerable); and 3, severe (sign/symptom hard to tolerate and causes interference with daily activities, sleeping, or both).

For each of the 6 ISSs, an average for each pollen season was calculated, resulting in ISSs per pollen season. The sum of the daily 6 ISSs provided the daily RTSSs, which ranged from 0 to 18. The average rhinoconjunctivitis total symptom score (ARTSS) was defined as the average of the daily RTSSs for the considered pollen period during treatment (for study years 1, 2, and 3).

The rescue medication score (RMS) was recorded daily by the patients. The following scale was used: 0, no rescue medication; 1, antihistamine (oral and/or eye drops); 2, nasal corticosteroid; and 3, oral corticosteroid. If a patient took 2 or more categories on the same day, the higher score was used for the RMS. The RMS on a particular day was only valid if the RTSS was valid for that same day. Daily RMSs were summarized as the average rescue medication score (ARMS) during a pollen season while receiving treatment (for study years 1, 2, and 3).

The daily adjusted symptom score (AdSS) corresponds to adjustment of the daily RTSS for rescue medication use. When a patient takes rescue medication on a particular day, the observed symptom severity is biased. To adjust for rescue medication use, we assume that the true severity of the symptoms is at least as high as on the preceding rescue medication–free day. Because rescue medication can be taken early in the morning or late in the evening on a particular day, the adjustment applies to the day of rescue medication use and the following day. The AdSS is defined by using the following algorithm:

1. On the first day, AdSS and RTSS are equal:

$$\mathrm{AdSS}_1 = \mathrm{RTSS}_1.$$

2. If a patient did not take rescue medication on day *(d-1)* and day *d*, then:

$$\mathrm{AdSS}_d = \mathrm{RTSS}_d.$$

3. If a patient took rescue medication on day *d*, then:

$$\begin{aligned}\mathrm{AdSS}_d &= \text{maximum}\,(\mathrm{RTSS}_d,\ \mathrm{AdSS}_{d-1}) \text{ and } \mathrm{AdSS}_{d+1}\\ &= \text{maximum}\,(\mathrm{RTSS}_{d+1},\ \mathrm{AdSS}_d).\end{aligned}$$

If RTSS_d was missing, AdSS_d was missing. If a patient took rescue medication at day *d* and RTSS_{d-1} was missing, then:

$$\mathrm{AdSS}_d = \mathrm{RTSS}_d.$$

The AAdSS is the average of the nonmissing daily AdSSs over the pollen season and ranges from 0 to 18.

The proportion of symptom and medication-free days, defined as days on which the patient had no symptoms and did not take any symptomatic medication, was calculated as follows:

$$\begin{aligned}&100 \times (\text{number of symptom} - \text{ and medication} - \text{free days})/\\ &\qquad(\text{number of days in the considered pollen period}).\end{aligned}$$

The patient's quality of life was assessed by using the self-administered disease-specific Rhinoconjunctivitis Quality of Life Questionnaire.[11]

Pollen season measurements

The expected site-specific start and end dates of the 2007, 2008, and 2009 grass pollen seasons were determined before the study's start by Dr S. Jäger (ENT University Clinic, Vienna, Austria), taking into account historical pollen data, pollen counts, and pollen graphs during the previous pollen seasons for the various study sites. The expected dates were used to define when to start and end treatment at the site level. The actual start and end dates for the grass pollen period of each study year were established based on the pollen counts measured at pollen traps in the regions where sites were located during each pollen season.

The pollen period for statistical analysis was defined as starting on the first of 3 consecutive days with a grass pollen count of at least 30 grass pollen grains per cubic meter of air and the end as the last day of 3 consecutive days with a grass pollen count of 30 grass pollen grains or above per cubic meter of air. The daily pollen counts were available at the end of each grass pollen season during the study in all 3 years, so that the start, end, duration, and intensity of the various pollen seasons at each site could be discriminated according to the definition detailed above.

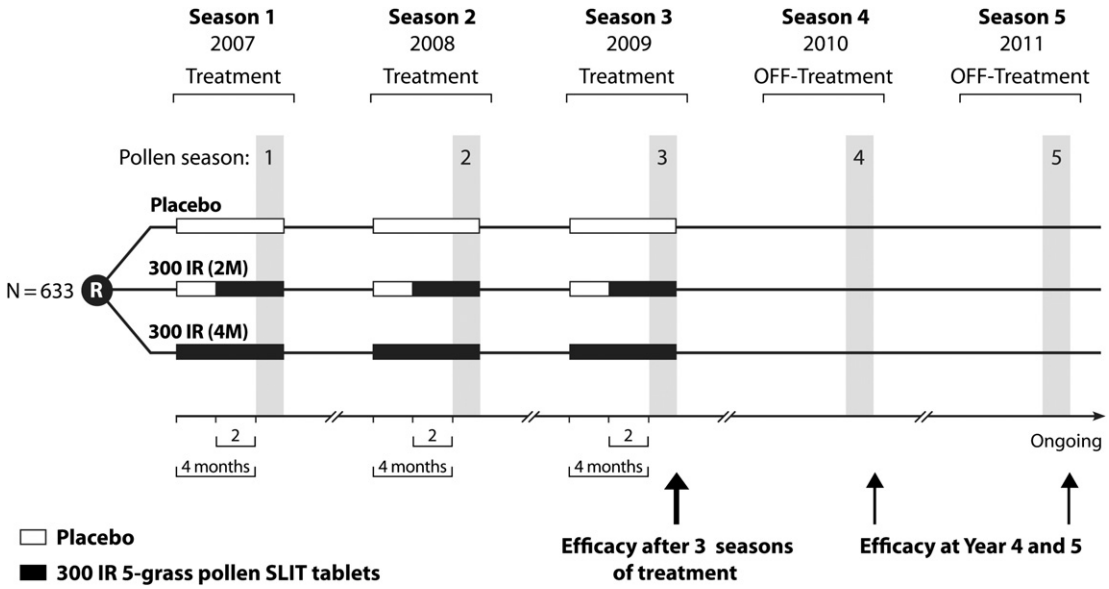

FIG 1. Study design. The *circled R* represents randomization to the 3 treatment arms. The actual time of the pollen season in each year is represented by the *shaded bar*.

Multinational multiple-center studies allow an overall balance between those with high and low pollen counts, and because the 3 treatment groups were randomized within each center, this ensured that the grass pollen levels were comparable.

Safety measurements

Adverse events, physical examination, and vital signs were recorded throughout the study. Blood specimens for routine laboratory safety testing were taken at screening and at the end of each pollen season. Treatment-emergent adverse events (TEAEs) were defined as starting on or after the first administration at each treatment period (seasons 1, 2, and 3), including the days of first and last administration of the investigational product. Adverse events are presented separately for the groups having received 2 or 4 months of active treatment and the placebo group. The 2-month treatment group had a shorter preseasonal treatment period, and these patients received placebo for the 2 months before the start of their active treatment; they are presented separately as the 2-month placebo period and 2-month active period. The placebo group used for efficacy comparisons received placebo during the entire 4 months before and then during the pollen season and is indicated for safety as the 4-month placebo group.

Statistical analysis

All efficacy analyses were performed on the corresponding full analysis set, which was defined as all patients who received at least 1 dose of investigational product and had at least 1 AdSS measurement during the pollen period while receiving treatment (for each treatment season). For all analyses, the probability of a type I error was set at 5% ($\alpha = .05$). All inferential tests were 2-sided. All statistical analyses were performed with SAS software, version 9.1.3 (SAS Institute, Inc, Cary, NC).

The primary efficacy variable, the AAdSS during the third pollen period, was analyzed by using an analysis of covariance (ANCOVA) with treatment and pooled centers (the number of centers was 47, and they were grouped into 20 pools) as main effects and age, sex, sensitization and asthma status as covariates. A point estimate and 95% CI for the difference in the adjusted means between the active treatment group and the placebo group were calculated from the ANCOVA. For the analysis of the AAdSS, a step-down approach (the 4-month group vs the placebo group and then the 2-month group vs the placebo group) was used to control the overall type I error rate at 5%.

Step 1: If the 300 IR (4-month) treatment group and the placebo treatment group were significantly different by using a 5% level of significance, then move to step 2. If there was no significance, no further statistical significance was declared.

Step 2: If the 300 IR (2-month) treatment group and the placebo treatment group were significantly different by using a 5% level of significance, then move to step 3. If there was no significance, no further statistical significance was declared.

Step 3: Declare statistical significance between the 300 IR (4-month) treatment group and the 300 IR (2-month) treatment group if the *P* value was .05 or less. *P* values are from the ANCOVA and correspond to the pairwise comparisons between the 300 IR (4-month) and placebo groups and then between the 300 IR (2-month) and placebo groups by using the appropriate contrasts.

The ARTSSs, ARMSs, the 6 ISSs were analyzed as for the primary efficacy variable. Descriptive statistics were used for the proportion of symptom- and medication-free days.

With an α value of .05 and a common SD of 3.6, the results of a previous study[6] suggested that a sample size of 144 patients per group would have a power of 80% to detect a mean difference of 1.2 (ie, an average difference of 0.20 per symptom [1.2/6] between placebo and 300 IR treatment in the AAdSS during the third pollen period). On the basis of the first 2 years of this study, the screening failure rate was 13%, and the dropout rate for each of the 3 treatment years was 12%. With these data, the 729 screened patients allowed having 633 randomized patients and at least 144 patients per group for the sustained clinical effect. The retention rate was higher than expected, resulting in a 98% power to detect the expected difference of −1.2 between the 300 IR and placebo groups.

RESULTS

Population and baseline characteristics

Of 633 patients randomized in the study, 219 received placebo, 207 received 300 IR tablets for a pre- and coseasonal treatment of 4 months before and then during the pollen season, and 207 received 300 IR tablets for a pre- and coseasonal treatment of 2 months before and then during the pollen season. The full analysis set of the first year comprises 581 patients. At study year 3, 465 patients entered the treatment period (Fig 2). Discontinuations from the study were uncommon and decreased steadily over the

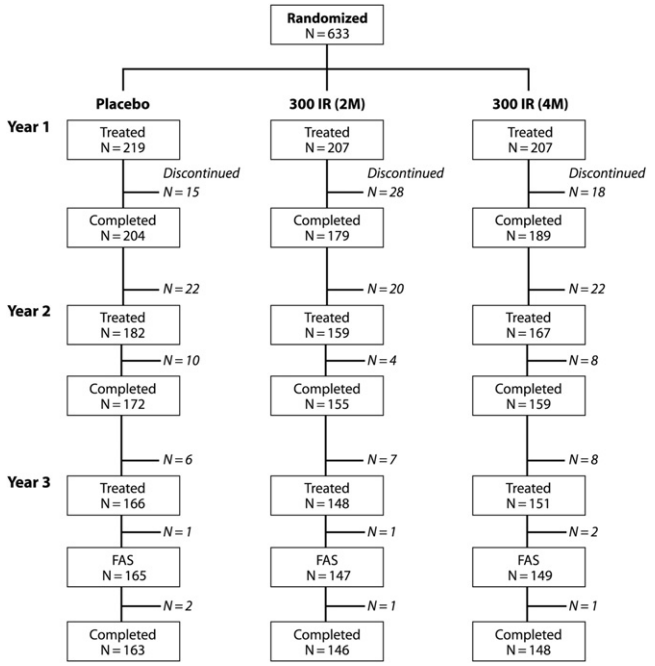

FIG 2. Subject disposition during the 3 treatment years. *FAS,* Full analysis set (only for year 3).

TABLE I. Demographic and baseline characteristics of the FAS population

	Placebo (n = 205)	300 IR tablets (2-month group [n = 188])	300 IR tablets (4-month group [n = 188])	Total (n = 581)
Sex (%)				
Men	59.5	59.0	64.9	61.1
Women	40.5	41.0	35.1	38.9
Age (y)				
Mean (SD)	30.2 (8.56)	30.4 (7.57)	30.9 (8.25)	30.5 (8.14)
Range	18-49	18-51	18-49	18-51
BMI (kg/m^2)				
Mean (SD)	23.99 (4.11)	24.20 (3.62)	24.28 (3.75)	24.15 (3.84)
Range	15.6-42.4	17.3-35.1	17.2-39.0	15.6-42.4
Patients with asthma (%)	15.6	11.7	14.9	14.1
Sensitization status (%)				
Monosensitized	39.5	41.5	39.4	40.1
Polysensitized	60.5	58.5	60.6	59.9
RRTSS				
Mean (SD)	14.1 (1.76)	13.9 (1.75)	14.1 (1.67)	14.0 (1.73)

BMI, Body mass index; *FAS*, full analysis set; *RRTSS*, retrospective rhinoconjunctivitis total symptom score.

first 3 years of the study from 61 patients during the first treatment period to 22 during the second and only 8 in the third periods. The main reasons for discontinuation were adverse events (4.3%, 1.6%, and 0% in years 1, 2, and 3, respectively) and withdrawn consent (3.2%, 1.0%, and 0.9% in years 1, 2, and 3, respectively). The frequency of patient discontinuations was similar in the 3 treatment groups. Patients dropped out because of adverse events more frequently in the 2 active arms and because of other reasons more frequently in the placebo arm. The overall treatment duration was 166, 172, and 171 days (average of 5.5 months per year) for study years 1, 2, and 3, respectively. Overall, the compliance was 97% or greater in years 1 to 3. Of the 64 discontinued patients after completion of the first treatment period, 18 were from 1 study center in the Czech Republic, where the investigator chose not to continue.

Demographic and baseline characteristics were well balanced among the 3 treatment groups (Table I). Asthma and sensitization status did not change during the 3 years, with an average of 13.7% of patients having asthma and the majority of patients expressing polysensitization to grass pollen and another allergen (59.2%). The mean retrospective RTSS was 14.0 (95% CI, 13.9-14.2), confirming the severity of the patient's disease.

On the basis of the actual pollen data recorded, the second grass pollen season (2008) was the highest and the third (2009) was the lowest of the 3 years.

AAdSS (primary efficacy result) over the third pollen season

After 3 seasons of treatment, the mean AAdSS over the third pollen season (primary efficacy end point) was reduced by 34.8% (4-month group) and 37.7% (2-month group; relative least-squares [LS] mean differences) compared with that seen in the placebo group. The absolute differences of each active group compared with the placebo group were as follows: −1.81 [95% CI, −2.61 to −1.02] for the 4-month group and −1.96 [95% CI, −2.79 to −1.16] for the 2-month group. They were statistically significant ($P < .0001$, Table II). Over the 3 treatment periods, the treatment effect was similar in monosensitized and polysensitized patients independent of treatment schedule (data not shown).

TABLE II. Primary efficacy end point: AAdSS over the third pollen season in the FAS population

	Placebo (n = 165)	300 IR tablets (4-month group [n = 149])	300 IR tablets (2-month group [n = 147])
Mean (SD)	5.28 (3.942)	3.46 (3.625)	3.38 (3.210)
LS means*	5.21	3.39	3.24
Comparison with placebo group			
Point estimate		−1.81	−1.96
95% CI	—	−2.61 to −1.02	−2.76 to −1.16
P value	—	<.0001	<.0001
Relative LS mean difference	—	−34.8	−37.7

FAS, Full analysis set.
*Based on ANCOVA.

Secondary efficacy results at season 3

All symptom and medication scores were also lower in the third pollen season in patients receiving 300 IR tablets compared with those receiving placebo. The relative LS mean differences for ARTSS were reduced by 33.9% (4-month group) and 36.6% (2-month group) and for ARMS by 33.4% (4-month group) and 34.8% (2-month) compared with that seen in the placebo group

TABLE III. Secondary efficacy end points: ARTSSs, ARMSs, and average ISSs over the third pollen season in the FAS population

Measure	Group	LS mean (SE)	Difference to placebo in LS means			
			Point estimate	95% CI	*P* value	Relative difference
ARTSS	Placebo	4.03 (0.289)	—	—	—	—
	300 IR tablets (4-month group)	2.67 (0.297)	−1.37	−2.03 to −0.71	<.0001	−33.9%
	300 IR tablets (2-month group)	2.56 (0.307)	−1.48	−2.14 to −0.81	<.0001	−36.6%
ARMS	Placebo	0.47 (0.041)	—	—	—	—
	300 IR tablets (4-month group)	0.31 (0.042)	−0.16	−0.25 to −0.06	.0011	−33.4%
	300 IR tablets (2-month group)	0.31 (0.043)	−0.16	−0.26 to −0.07	.0007	−34.8%
Sneezing	Placebo	0.78 (0.060)	—	—	—	—
	300 IR tablets (4-month group)	0.62 (0.062)	−0.16	−0.30 to −0.02	.0207	−20.8%
	300 IR tablets (2-month group)	0.56 (0.064)	−0.22	−0.36 to −0.08	.0020	−27.9%
Rhinorrhea	Placebo	0.76 (0.059)	—	—	—	—
	300 IR tablets (4-month group)	0.51 (0.061)	−0.25	−0.38 to −0.11	.0004	−32.3%
	300 IR tablets (2-month group)	0.43 (0.063)	−0.33	−0.47 to −0.20	<.0001	−43.9%
Nasal pruritus	Placebo	0.68 (0.056)	—	—	—	—
	300 IR tablets (4-month group)	0.44 (0.057)	−0.24	−0.36 to −0.11	.0003	−35.0%
	300 IR tablets (2-month group)	0.44 (0.059)	−0.24	−0.37 to −0.11	.0003	−35.3%
Nasal congestion	Placebo	0.65 (0.061)	—	—	—	—
	300 IR tablets (4-month group)	0.37 (0.063)	−0.28	−0.42 to −0.14	.0001	−42.9%
	300 IR tablets (2-month group)	0.42 (0.065)	−0.24	−0.38 to −0.09	.0011	−36.2%
Ocular pruritus	Placebo	0.76 (0.061)	—	—	—	—
	300 IR tablets (4-month group)	0.50 (0.063)	−0.26	−0.40 to −0.12	.0002	−34.5%
	300 IR tablets (2-month group)	0.50 (0.065)	−0.26	−0.40 to −0.12	.0003	−34.0%
Watery eyes	Placebo	0.41 (0.048)	—	—	—	—
	300 IR tablets (4-month group)	0.23 (0.050)	−0.18	−0.29 to −0.07	.0014	−44.3%
	300 IR tablets (2-month group)	0.21 (0.051)	−0.19	−0.30 to −0.08	.0007	−47.4%

(Table III). Results were similar for both the 4-month and 2-month groups. The mean proportion of symptom- and medication-free days was higher in both active groups compared with that seen in the placebo group (4-month group, 37.9%; 2-month group, 36.9%; and placebo group, 26.4%).

The improvement in efficacy with 300 IR tablets was demonstrated for each of the 6 ISSs. The means of all 6 ISSs were significantly reduced versus placebo over the third pollen season by values ranging from 21% (sneezing) to 47% (watery eyes) in patients receiving active treatment, irrespective of the preseasonal schedule (Table III).

AAdSS over time

AAdSSs were assessed over each pollen season and demonstrated a progressively greater reduction compared with placebo for the 3 pollen seasons. Compared with the placebo group, the mean AAdSS was reduced by 20% at season 1, 34% at season 2, and 37% at season 3. There was no significant difference between the 2 active groups.

Quality of life

The Rhinoconjunctivitis Quality of Life Questionnaire showed an improvement in the 2 active arms compared with the placebo arm for the 3 pollen seasons. The LS means difference showed significant changes for the 4-month and 2-month groups versus the placebo group: −0.31 (95% CI, −0.50 to −0.12; $P = .0015$) in the 4-month group and −0.46 (95% CI, −0.64 to −0.27; $P < .0001$) in the 2-month group at study year 1; −0.39 (95% CI, −0.61 to −0.17; $P = .0005$) in the 4-month group and −0.45 (95% CI, −0.67 to −0.22; $P < .0001$) in the 2-month group at study year 2; and −0.43 (95% CI, −0.64 to −0.19; $P = .0003$) in the 4-month group and −0.41 (95% CI, −0.63 to −0.18; $P = .0004$) in the 2-month group at study year 3.

Safety

Treatment with 300 IR tablets administered 4 or 2 months before and during the pollen season for 3 consecutive years was safe, and tolerability improved over the 3 years. In general, the incidence and severity of TEAEs decreased each year in all 3 treatment groups (Table IV). In the first study year the percentages of patients reporting a TEAE was greater than 80% for all 3 groups but had decreased to values of greater than 62% at year 2 to greater than 54% by year 3.

Most of the differences in TEAEs between the active and placebo treatment groups were due to local events related to the study treatment intake, with the most frequently reported at year 1 being the following: oral pruritus (>30% in the active groups vs 11.4% in the placebo group), throat irritation (>15% in the active groups vs 3.7% in the placebo group), and mouth edema (>6% in the active groups vs 1.4% in the placebo group). The incidence and severity of these local reactions decreased in consecutive treatment years in patients receiving active treatment (>57% in year 1, >43% in year 2, and >36% in year 3; Fig 3).

A total of 35 patients discontinued from the study because of TEAEs. During the first study year, the number of discontinuations from the study because of TEAEs was higher in the active groups compared with that seen in the placebo group (7.2% vs 1.4%). In contrast, there were no discontinuations caused by TEAEs in the third study year. Overall, serious TEAEs occurred in 11 subjects in the first study year (1 in the placebo group, 3 in

TABLE IV. Overview of TEAEs during the first 3 study years in the safety population

Description	No. (%) of subjects			
	300 IR tablets (4-month group)	Placebo	300 IR tablets (2-month group)	
			Placebo period	Active period
Year 1	n = 207	n = 219	n = 207	n = 207
≥1 TEAE	183 (88.4)	174 (79.5)	62 (30.0)	158 (76.3)
≥1 Application-site TEAE	149 (72.0)	89 (40.6)	23 (11.1)	119 (57.5)
≥1 Serious TEAE	7 (3.4)	1 (0.5)	1 (0.5)	2 (1.0)
≥1 Drug-related TEAE	147 (71.0)	55 (25.1)	22 (10.6)	118 (57.0)
≥1 Serious drug-related TEAE	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
A TEAE leading to discontinuation	13 (6.3)	2 (0.9)	2 (1.0)	12 (5.8)
Year 2	n = 167	n = 182	n = 159	n = 159
≥1 TEAE	123 (73.7)	94 (51.6)	39 (24.5)	101 (63.5)
≥1 Application-site TEAE	99 (59.3)	32 (17.6)	20 (12.6)	79 (49.7)
≥1 Serious TEAE	1 (0.6)	1 (0.5)	2 (1.3)	0 (0)
≥1 Drug-related TEAE	98 (58.7)	17 (9.3)	16 (10.1)	75 (47.2)
≥1 Serious drug-related TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
An AE leading to discontinuation	5 (3.0)	1 (0.5)	1 (0.6)	1 (0.6)
Year 3	n = 151	n = 166	n = 148	n = 148
≥1 TEAE	95 (62.9)	77 (46.4)	31 (20.9)	81 (54.7)
≥1 Application-site TEAE	75 (49.7)	30 (18.1)	11 (7.4)	58 (39.2)
≥1 Serious TEAE	1 (0.7)	3 (1.8)	1 (0.7)	1 (0.7)
≥1 Drug-related TEAE	68 (45.0)	6 (3.6)	6 (4.1)	55 (37.2)
≥1 Serious drug-related TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
An AE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AE, Adverse event.

the 2-month group, and 7 in the 4-month group), with 3 (all in the 4-month group) considered related to the study treatment by the investigator (1 severe local allergic reaction and 1 because of angioedema, both leading to permanent discontinuation from the study, and 1 case of diarrhea, which did not), all of which resolved. There were no serious TEAEs related to study medication in the third study year. There were no relevant differences in any of the safety laboratory tests, physical examinations, or vital sign measurements between the treatment groups.

DISCUSSION

This is the first study of a pollen allergy immunotherapy to be specifically designed and statistically powered as a 3-season treatment study with a long-term follow-up. It demonstrated the efficacy and safety of 300 IR tablets for grass pollen–induced rhinoconjunctivitis over 3 seasons of therapy. Active treatment was started 2 or 4 months before the pollen season and continued during the pollen season for 3 consecutive years. AAdSSs were lower in both active groups in the third pollen season compared with those in the placebo group, and the differences were statistically significant. The 300 IR tablets demonstrated efficacy from the first pollen season onward in both active groups. The higher efficacy compared with that seen in the previous pollen season was supported by a reduction in all symptom-related scores and RMSs. Likewise, the proportion of symptom- and medication-free days was higher in the active groups compared with that in the placebo group. There was no significant difference between the 2-month and 4-month groups for any of the efficacy parameters.

The AAdSS has been accepted by the European Medicines Agency as a suitable primary end point to be used in allergen immunotherapy studies.[8] The AAdSS refines the RTSS by adjusting for rescue medication use, and thus symptom severity and treatment effect are described more accurately. The AAdSS adjustment is performed when unadjusted data are considered to underestimate symptom severity (ie, the score on the day preceding a day with rescue medication use is only carried forward if the RTSS on the day with rescue medication use was lower).[9] This avoids speculation as to the magnitude of effect of the rescue medication on symptom severity. Biased data are only replaced by values actually observed on the preceding day, thus reducing the subjectivity and increasing robustness.

The pre- and coseasonal treatment concept has previously been shown to be efficacious from the first treatment season onward,[6,7] and follow-up results in a study with SLIT drops were indicative of a disease-modifying effect on seasonal allergic rhinitis.[12] These results support the current findings and provide additional evidence that the efficacy of treatment with the 300 IR tablets is in the same range, as reported with another grass tablet administered in a year-long treatment,[13-15] but the preseasonal and coseasonal treatment have the advantage of being shorter. A positive effect on adherence can be expected. The decrease in the ARTSS at season 3 in the active groups versus the placebo group of 36.6% and 33.7% (relative LS mean differences) for the 2-month and 4-month groups, respectively, compares favorably with the 29% observed by Durham at al.[15] Although the assessment methods in our study are different than those used in that study, in both studies a decrease in rescue medication use was seen (relative LS mean differences of about 35% for the 2-month and 4-month groups and 40% in the other study). The improvement versus placebo in quality of life of 30% for the 2-month and 4-month groups and of 23% as reported by Durham et al shows that grass tablet immunotherapy has a positive effect on the patient's life. The current study is still ongoing and will assess the posttreatment efficacy and disease-modifying effect during the fourth and fifth pollen seasons (treatment-free years). The discontinuation rate was low (around 10% across all treatment groups in the first year and lower in years 2 and 3) and marginally lower than what has been reported (13%) for the other grass tablet immunotherapy study.[13-15]

Safety findings were those generally expected for this study population over the time period studied. The incidence and severity of TEAEs decreased with each treatment year. Another study with grass tablet immunotherapy also showed a generally good safety profile, although the safety at each separate year was not reported.[14]

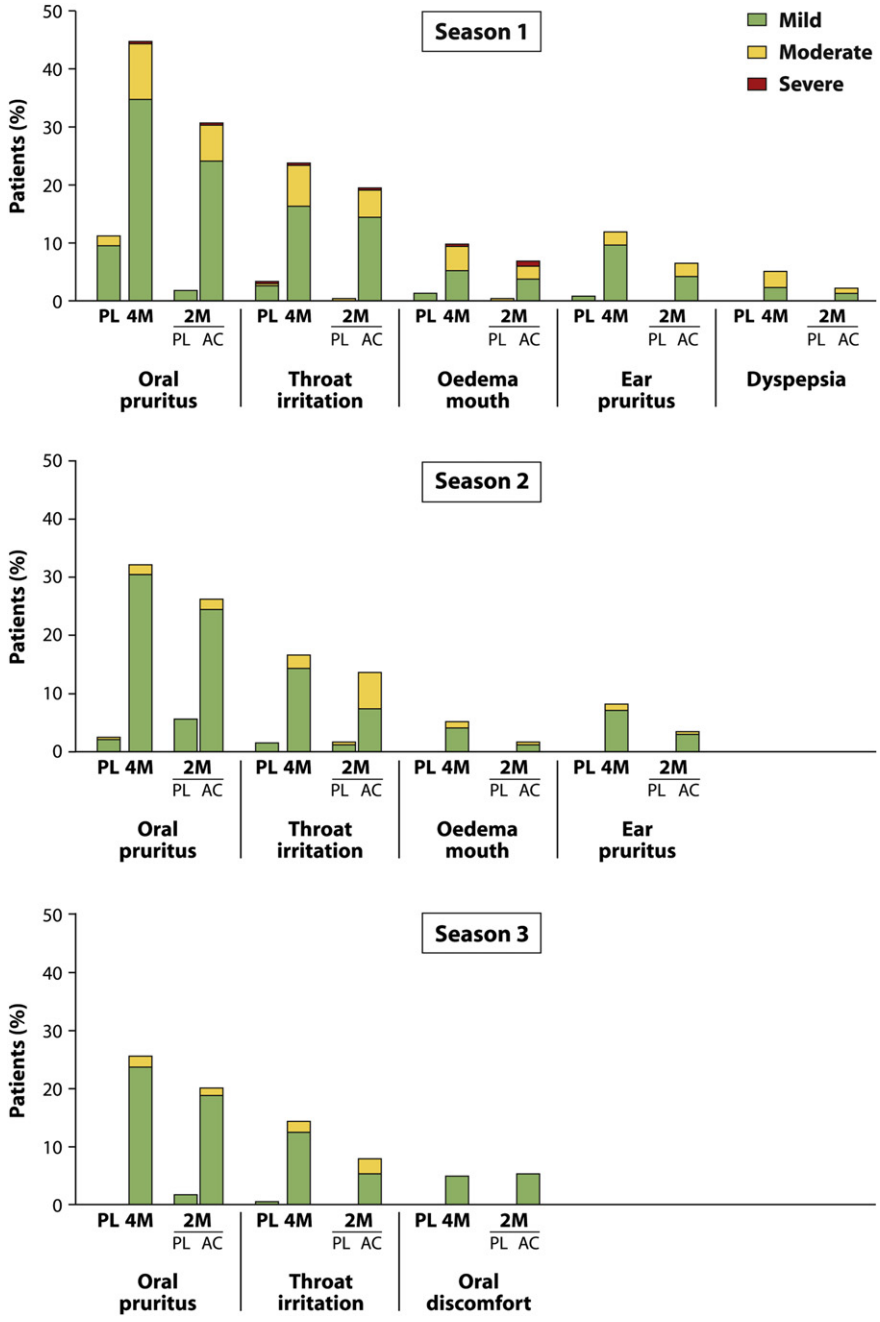

FIG 3. Most common (≥5%) treatment-related adverse events by intensity: incidence for seasons 1 to 3. Treatment-related adverse events are those considered by the investigator to be at least possibly related to the study treatment. TEAEs are events starting on or after the first administration at each treatment period, including the days of first and last administration of the investigational product. Adverse events are presented separately for the groups having received 2 or 4 months of active treatment and the placebo group. The 2-month treatment group had a shorter preseasonal treatment period, and these patients received placebo for the 2 months before the start of their active treatment; therefore they are presented separately as a 2-month placebo period and a 2-month active period. The placebo group used for efficacy comparisons received placebo during the entire 4 months before and then during the pollen season and is indicated for safety as 4 months of placebo. *AC*, Active treatment; *PL*, placebo.

In conclusion, treatment with the 300 IR 5-grass-pollen tablets was well tolerated and effective in reducing rhinoconjunctivitis symptoms and symptomatic medication use at each year up to season 3. These results suggest that there is no need for a continuous year-long therapy. The sustained clinical efficacy of treatment was supported by the reduction in other symptom-related scores and the marked increase in symptom- and medication-free days.

We thank all of the investigators for their commitment to this study.

Clinical implications: The 5-grass-pollen 300 IR tablets administered in a discontinued, seasonal treatment schedule showed sustained efficacy after 3 treatment seasons. In patients with seasonal allergic rhinoconjunctivitis, a continued treatment schedule is not necessary.

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