

Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: The importance of allergen-specific serum IgE

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Background: Previous trials have demonstrated the efficacy, safety, and optimal dosage of the 5-grass pollen sublingual tablet for adults and children with grass pollen-induced allergic rhinoconjunctivitis.

Objectives: We sought to evaluate the efficacy and safety of 300 index of reactivity (IR) 5-grass pollen sublingual tablet in US adults.

Methods: Adults with grass pollen allergy and Rhinoconjunctivitis Total Symptom Scores of 12 or greater (scale, 0-18) during the previous grass pollen season were randomized in a double-blind, placebo-controlled study to receive 300IR 5-grass pollen sublingual tablet or placebo starting 4 months before and continuing through the pollen season. The primary efficacy end point was the daily Combined Score (CS; scale, 0-3), which integrates symptoms and rescue medication use.

Results: Four hundred seventy-three participants were randomized. The mean daily CS over the pollen period was significantly lower in the active treatment group versus the placebo group (least-squares mean difference: -0.13 ; 95% CI, -0.19 to -0.06 ; $P = .0003$; relative reduction: 28.2%; 95% CI, 13.0% to 43.4%). In placebo-treated participants, the daily CS least-squares mean was 0.32 in the subgroup with baseline timothy grass-specific serum IgE of less than 0.1 kU/L ($n = 23$) and 0.46 in those with baseline timothy grass-specific serum IgE

of 0.1 kU/L or greater (n = 204). The most frequent reported adverse events were oral pruritus, throat irritation, and nasopharyngitis. There were no reports of anaphylaxis, and no actively treated participant received epinephrine.

Conclusion: In US adults with grass pollen-induced allergic rhinoconjunctivitis, preseasonal and coseasonal treatment with 300IR 5-grass pollen sublingual tablet demonstrated clinically meaningful efficacy, especially in study subjects with measurable timothy grass-specific serum IgE. Use of 300IR 5-grass pollen sublingual tablet was safe and well tolerated. A requirement for a measurable level of allergen-specific serum IgE should be considered in future studies in this field. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Double-blind, placebo-controlled trial, allergy, allergic rhinoconjunctivitis, grass pollen, specific immunotherapy, sublingual immunotherapy tablet, combined score, grass-specific IgE

Approximately 30 million Americans have allergic rhinoconjunctivitis (ARC),¹ much of which is caused by grass pollen allergy.² Untreated or inadequately treated ARC can cause sleep³ and mood disorders⁴ and impair social functioning⁵ and work performance.⁶

Current treatment options include antihistamines and intranasal corticosteroids. These provide temporary relief of allergy symptoms but are not disease modifying. A large proportion of patients are “not very satisfied” with pharmacologic therapies, and the most common reasons for stopping treatment include lack of efficacy (37%), effectiveness beginning to wear off (35%), lack of 24-hour relief (32%), and bothersome side effects (25%).⁷ Subcutaneous immunotherapy (SCIT) is a guideline-recommended therapeutic option for patients in whom symptomatic medications are ineffective, unwanted, or contraindicated.⁸ Despite the clear benefits of SCIT, only 5% of the US population with allergic rhinitis, asthma, or both receive this treatment.⁹ Its use is limited by the risk of near-fatal or fatal anaphylaxis, as well as the discomfort and inconvenience of frequent injections.¹⁰⁻¹²

The favorable safety profile and convenience of sublingual immunotherapy (SLIT) are likely factors for the substantial and growing increase in its use in Europe.^{12,13} Recent studies have demonstrated the efficacy of SLIT tablet in the treatment of grass pollen-associated ARC in adults and children.¹⁴⁻¹⁹ The purpose of this trial was to assess the efficacy and safety profile of 300 index of reactivity (IR) 5-grass pollen sublingual tablet in US adults with grass pollen-induced ARC.

METHODS

Study design

This was a double-blind, placebo-controlled, parallel-group, randomized, multicenter study conducted at 51 sites in the United States (ClinicalTrials.gov

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Abbreviations used

AdSS:	Adjusted Symptom Score
ARC:	Allergic rhinoconjunctivitis
CS:	Combined Score
FAS:	Full analysis set
IR:	Index of reactivity
LS:	Least-squares
RMS:	Rescue Medication Score
RQLQ:	Rhinoconjunctivitis Quality of Life Questionnaire
RSS:	Individual Rhinoconjunctivitis Symptom Score
RTSS:	Rhinoconjunctivitis Total Symptom Score
SCIT:	Subcutaneous immunotherapy
SLIT:	Sublingual immunotherapy
SPT:	Skin prick test
TEAE:	Treatment-emergent adverse event
WAO:	World Allergy Organization

no. NCT00955825). Written informed consent was obtained from all participants before study entry. The study was conducted in accordance with International Conference on Harmonisation good clinical practice and approved by the appropriate institutional review boards and the US Food and Drug Administration.

Study subjects were enrolled between December 2008 and August 2009 for a 6-month preseasonal and coseasonal treatment phase and a 2-week follow-up phase (Fig 1).

Eligible participants were randomized 1:1 to active treatment or placebo by using a computer-generated list (block size of 4; for details on randomization, see the [Methods](#) section in this article's Online Repository at www.jacionline.org).

Participants

The study enrolled men and women aged 18 to 65 years with documented grass pollen-related ARC for at least the 2 previous grass pollen seasons, a positive skin prick test (SPT) response to timothy grass (mean wheal diameter of 5 mm or greater than that elicited by the negative control; longest flare dimension, ≥ 10 mm), a Retrospective Rhinoconjunctivitis Total Symptom Score (RTSS; scale, 0-18) of 12 or greater during the previous grass pollen season, and an FEV₁ of 80% or greater of predicted value.

A panel of seasonal and perennial aeroallergens (including timothy and other grasses [Bermuda, Bahia, and Johnson grasses], trees and weeds, dust mites, molds, and dog and cat dander; Hollister-Stier Laboratories, Spokane, Wash), along with any other aeroallergens considered relevant by the investigator, was tested by SPT.

Participants were excluded from the study if they had (1) a positive SPT response to any other endemic grass allergens present in their region during the grass pollen period (including Bermuda, Bahia, and Johnson grasses); (2) clinically significant, confounding symptoms of allergy to other allergens that potentially overlapped the grass pollen period (eg, tree allergens, dust mites, and molds); or (3) asthma requiring treatment with medications other than inhaled β_2 -agonists.

Study treatment and rescue medication

Active treatment consisted of 300IR SLIT tablets containing a standardized 5-grass pollen allergen obtained by means of extraction of a mixture of 5 grass pollens in equal amounts (orchard grass, *Dactylis glomerata*; Kentucky bluegrass, *Poa pratensis*; perennial rye grass, *Lolium perenne*; sweet vernal grass, *Anthoxanthum odoratum*; and timothy grass, *Phleum pratense*). For details on the active treatment, see the [Methods](#) section in this article's Online Repository. Active and placebo tablets were identical in appearance and taste to ensure blinding.

Treatment was initiated approximately 4 months before the expected start of the grass pollen period at each study center and continued for its duration.

One 300IR or placebo tablet was to be taken sublingually at the same time every day from the randomization visit to the end of the treatment period. Participants were instructed to leave the tablet under the tongue until it had completely dissolved before swallowing. The first 3 doses were taken at the study site, and the participants were monitored for 30 minutes. The remainder of the treatment was taken at home. Self-injectable epinephrine was provided for use in the event of a severe systemic reaction, and study subjects were given instructions in its use. Rescue medications (oral and eye drop antihistamines and nasal corticosteroids) were supplied to participants who were instructed to use them according to a stepwise regimen for the management of severe or intolerable ARC symptoms. Participants were to consult the investigator if they remained symptomatic despite these treatments. Investigators could then provide study subjects with oral corticosteroids.

Participants were considered treatment compliant if the number of tablets taken was between 80% and 120% (inclusive) of the expected value.

Grass pollen season

Pollen counts were monitored and recorded at each study center during the 2009 grass pollen season. The pollen period was defined as starting on the first of 3 consecutive days with a grass pollen count (7-day moving average) of 10 grains/m³ of air or greater and ending on the last day of 3 consecutive days with a grass pollen count (7-day moving average) of 10 grains/m³ of air or greater. Pollen period start and end dates were determined before unblinding the data.

Outcome

Participants were provided with a daily record card for recording the 6 individual Rhinoconjunctivitis Symptom Scores (RSSs; sneezing, runny nose, itchy nose, nasal congestion, itchy eyes, and watery eyes) and rescue medication use during the previous 24 hours. The diary cards were to be completed at the same time every evening from approximately 3 weeks before the pollen season until its end by using a 4-point descriptor scale for each symptom: 0, no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms. The daily RTSS was the sum of the 6 individual RSSs. The daily Rescue Medication Score (RMS) was derived as follows: 0, no rescue medication taken; 1, use of antihistamine (oral drops, eye drops, or both); 2, use of nasal corticosteroid; and 3, use of oral corticosteroid. If a study subject took 2 or more rescue medications on the same day, the highest score was used for the RMS.

The primary efficacy criterion was the daily Combined Score (CS), a patient-specific measure that combines symptom (RTSS) and medication (RMS) scores per the World Allergy Organization (WAO) taskforce recommendations for standardization of clinical trials with allergen-specific immunotherapy for respiratory allergy.²⁰ The daily CS was calculated as follows:

$$CS = [(RTSS/6) + RMS]/2$$

and ranged from 0 to 3. Secondary efficacy criteria included the daily RTSS, the daily RMS, the daily Adjusted Symptom Score (AdSS; which adjusts the RTSS according to rescue medication use),²¹ each of the daily RSSs, quality of life, and patient's global evaluation of treatment efficacy. Quality of life was evaluated by using the overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score.²² The questionnaire was administered at screening and at the expected middle of the grass pollen period (visit 5). The RQLQ consists of 28 questions in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). In the patient global evaluation of treatment efficacy, which was completed at the end of the grass pollen season, each participant was asked to rate their overall symptoms relative to those of the previous season by using a 5-point Likert scale (1, marked worsening; 2, slight to moderate worsening; 3, no change; 4, slight to moderate improvement; and 5, marked improvement).

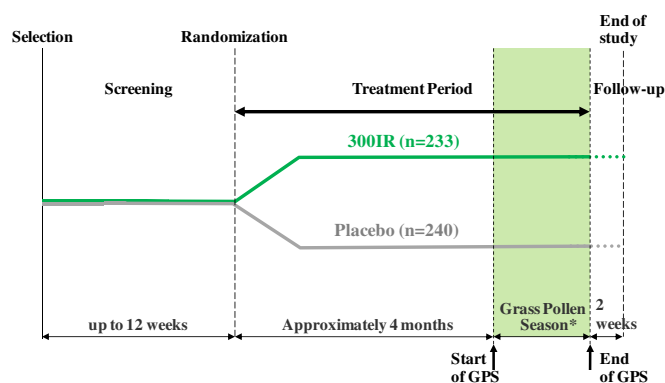


FIG 1. Study design. *Pollen season was defined as starting on the first of 3 consecutive days with a grass pollen count of at least 10 grains/m³ of air and ending on the last of 3 consecutive days with a grass pollen count of at least 10 grains/m³ of air. GPS, Grass pollen season.

Serum immunologic markers

Serum IgE (ImmunoCAP FEIA) and IgG₄ specific for timothy grass were assayed (Viracor-IBT Laboratories, Lee's Summit, Mo) before the pollen season, midway through the pollen season (visit 5), and at the end of the treatment period (visit 6).

Safety

The safety variables were adverse events, serious adverse events, data from physical examinations, and laboratory test results. Adverse events were monitored throughout the study and categorized according to the MedDRA dictionary (version 12.0).

Sample size

The study's original primary outcome measure was the average Adjusted Symptom Score, and the initial sample size calculation was based on this variable. Given an α value of .05, a 2-sided test, and a common SD of 3.603, the results of a prior study suggested that a sample size of 382 participants would provide 90% power to detect a mean difference of -1.2 between the active and placebo groups during the pollen period while on treatment. Such a value, assuming an average Adjusted Symptom Score of 6 for the placebo group (as observed in previous grass pollen allergen studies), corresponds to a 20% relative mean difference, the threshold recommended by the WAO taskforce as clinically relevant for efficacy.²⁰ Assuming a screening failure rate of 20% and a dropout rate of 10%, we planned to screen approximately 550 subjects and randomize 424 subjects.

On recommendation of health authorities and before unblinding of the data, the primary outcome variable was changed to the daily CS. On the basis of previous study results, a daily CS least-squares (LS) mean of 0.65 in the placebo group was assumed, and the expected mean difference between the 300IR and placebo groups during the pollen period was defined as -0.14 with a common SD of 0.50 to correspond to a relative difference of more than 20%. With at least 404 evaluable participants, the study had 80% power to detect such a difference.

Statistical analyses

Statistical analyses were performed with SAS software (version 9.1.3; SAS Institute, Cary, NC). The full analysis set (FAS) included all study subjects who received at least 1 dose of the investigational product and had at least 1 CS recorded while receiving treatment during the pollen period. The per-protocol set included all FAS participants with at least 14 days of valid CSs during the pollen period while receiving treatment and who completed the study without any major protocol deviations. The safety population included all participants who received at least 1 dose of the investigational product.

The primary efficacy end point (daily CS during the pollen period while receiving treatment) was analyzed for the FAS by using a repeated measures analysis of covariance model, including treatment group and valid days as main effects, patient as a random effect, and pooled study center, age, sex, asthma status, and sensitization status (monosensitized vs polysensitized) as covariates. Normality assumption and homogeneity of variance were assessed, and residual plots were displayed to confirm the appropriateness of the model. Additional prespecified analyses were performed to evaluate the effect of timothy grass-specific serum IgE at baseline on the primary efficacy end point.

The daily RTSS, RMS, AdSS,²¹ and RSSs were analyzed as per the primary efficacy criterion. The overall RQLQ score at the middle of the pollen period was analyzed by using an analysis of covariance with the same covariates plus the baseline overall RQLQ score. The patient global evaluation of treatment efficacy was analyzed by using a Cochran Mantel-Haenszel test (row mean score statistic) with pooled study center as a stratification variable. Unless otherwise specified, results are presented as means $\pm$ SDs. The threshold for statistical significance was set at a *P* value of less than .05, and all inferential tests were 2-sided.

RESULTS

Four hundred seventy-three participants were randomized to active treatment ($n = 233$) or placebo ($n = 240$, Fig 2). Because 35 study subjects did not have at least 1 CS during the pollen period while receiving treatment, the FAS consisted of 438 participants: 210 in the 300IR group and 228 in the placebo group.

The FAS included 53% women. The mean age was 37.2 years (SD, 11.46 years). Most participants (78%) were polysensitized (in decreasing order of frequency) to ragweed, trees (oak, ash, maple, and mountain cedar), house dust mites, animal danders, and molds, and 20% had intermittent asthma. The mean duration of ARC was 22.9 years (SD, 12.8 years). At study entry, demographic and disease characteristics were similar between the treatment groups (Table I).

The treatment duration in the FAS averaged 179.8 days (SD, 13.69 days), corresponding to an average of 126.6 days (SD, 10.81 days) before the pollen period and 42.8 days (SD, 15.31 days) during the pollen period. The mean (SD) values were similar in the 300IR and placebo groups.

The proportions of compliant participants in the 300IR and placebo groups (FAS) were 98.6% and 98.7%, respectively.

The median duration of the grass pollen season was 43 days (range, 11-70 days). The median average pollen count weighted by subject was 31.9 grains/m³ (range, 4.1-215.0 grains/m³). The interquartile range is 46.5 grains/m³ (quartile 1, 23.8 grains/m³; quartile 3, 70.3 grains/m³).

Efficacy outcomes

Throughout the pollen period, the mean daily CS was consistently lower in the 300IR group than in the placebo group and paralleled the grass pollen count (Fig 3, A). Overall, the difference between the 300IR group and the placebo group in daily CS LS means during the pollen period was statistically significant ($P = .0003$, Table II). The treatment effect, estimated as the difference in LS means of -0.13 (95% CI, -0.19 to -0.06), corresponds to a relative LS mean difference from placebo of -28.2% (95% CI, -43.4% to -13.0%). Sensitization status and asthma status were not significant covariates, indicating that they did not affect the primary efficacy results. The per-protocol set analysis results were consistent with those of the FAS.

Prespecified analyses of the mean daily CS were conducted in subgroups of study subjects based on their timothy grass-specific

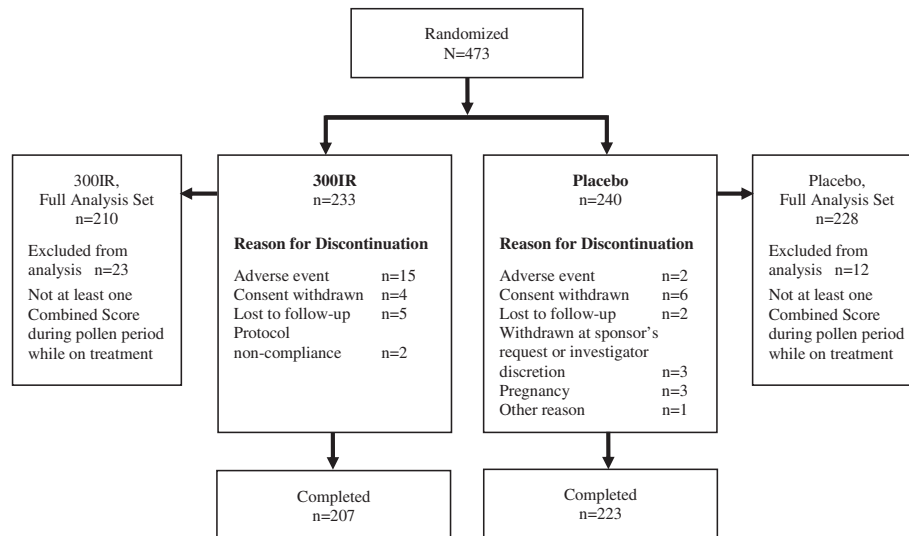


FIG 2. Participant disposition.

TABLE I. Baseline characteristics (FAS)

	300IR group (n = 210)	Placebo group (n = 228)
Age (y)	36.8 (11.27)	37.6 (11.64)
Sex (% female)	109 (51.9%)	125 (54.8%)
Current smoker	13 (6.2%)	19 (8.3%)
Former smoker	40 (19.0%)	31 (13.6%)
Duration of ARC (y)	22.3 (12.8)	23.4 (12.8)
Polysensitized participants*	166 (79.0%)	175 (76.8%)
Participants with asthma†	38 (18.3%)	50 (21.9%)
FEV ₁ (% predicted)	98.9 (11.09)	97.7 (10.31)
RRTSS	14.9 (1.95)	14.9 (1.91)
Timothy grass-specific IgE (kU/L)‡	2.14 (1.59-2.88)	2.60 (1.97-3.42)

Results describing continuous variables are expressed as means (SDs). Results describing categorical variables are expressed as number of participants and the percentage relative to the number of participants in the FAS with nonmissing data. RRTSS, Retrospective Rhinoconjunctivitis Total Symptom Score.
 *Sensitized to 5 grass pollens and at least 1 other tested allergen.
 †Data available for 208 participants in the active treatment group.
 ‡The value is presented as the geometric mean (95% CI). A value of 0.05 was imputed when the IgE level was less than the limit of detection (<0.1 kU/L).

serum IgE at baseline. The analysis of the daily CS in the 386 (89%) participants with baseline timothy grass-specific IgE of 0.1 kU/L or greater demonstrated a significant LS mean difference between the active and placebo groups of -0.14 (95% CI, -0.21 to -0.07 ; $P = .0002$; Table II and Fig 3, B). In the 49 (11%) participants without measurable timothy grass-specific serum IgE (ie, IgE <0.1 kU/L) at baseline, the daily CS LS mean difference was not significant (-0.02 ; 95% CI, -0.26 to 0.22 ; $P = .86$). In this subgroup, the daily CS LS mean in placebo-treated participants was 0.32 versus 0.46 in placebo-treated participants with timothy grass-specific serum IgE of 0.1 kU/L or greater.

The daily RTSS, RMS, and AdSS were significantly lower in the 300IR group than in the placebo group over the pollen period. Individual daily RSSs were also lower in the active treatment group. With the exception of the “itchy nose” RSS, all differences were statistically significant (Table III).

At baseline, before the pollen season, overall RQLQ scores in the 300IR and placebo groups were similar (mean scores, 0.69

and 0.63, respectively) and did not indicate quality of life impairment. At study visit 5, a visit designed to fall in the middle of the pollen season when pollen counts are at their peak and the disease burden is significant, participants completed the RQLQ again. A statistically significant difference was observed between the 300IR and placebo groups in overall RQLQ scores (LS mean scores, 1.25 and 1.58, respectively), with an estimated LS mean difference of -0.32 (95% CI, -0.55 to -0.10 ; $P = .0042$). Changes from baseline were less pronounced in the group receiving allergen immunotherapy, indicating a better overall quality of life with active treatment (Fig 4).

Participants who received 300IR sublingual tablet reported significantly higher ratings of treatment efficacy than those who received placebo ($P = .0017$). The proportion reporting treatment success (ie, ratings of marked improvement or slight to moderate improvement compared with the prior season) was also significantly higher in the 300IR group (74.8%) compared with the placebo group (63.2%; odds ratio, 1.19; 95% CI, 1.05 to 1.34; $P = .0081$).

Serum immunologic outcomes

Timothy grass-specific serum IgE increased in the 300IR group and were essentially unchanged in the placebo group. Geometric means at baseline, midway through the pollen season, and at the end of the pollen season were 2.141 kU/L (95% CI, 1.592-2.879 kU/L), 5.043 kU/L (95% CI, 3.625-7.016 kU/L), and 5.120 kU/L (95% CI, 3.658-7.167 kU/L) and 2.595 kU/L (95% CI, 1.970-3.418 kU/L), 2.497 kU/L (95% CI, 1.888-3.301 kU/L), and 3.285 kU/L (95% CI, 2.468-4.373 kU/L) in the 300IR and placebo groups, respectively. In the subgroup without measurable timothy grass-specific serum IgE at baseline, the geometric means remained less than the limit of detection midway through the pollen season and at its end.

Timothy grass-specific serum IgG₄ increased in the 300IR group and were essentially unchanged in the placebo group. Geometric means at baseline, midway through the pollen season, and at the end of the pollen season were 0.155 μ g/mL (95% CI, 0.133-0.180 μ g/mL), 0.292 μ g/mL (95% CI, 0.238-0.358 μ g/mL), and 0.289 μ g/mL (95% CI, 0.237-0.351 μ g/mL) and

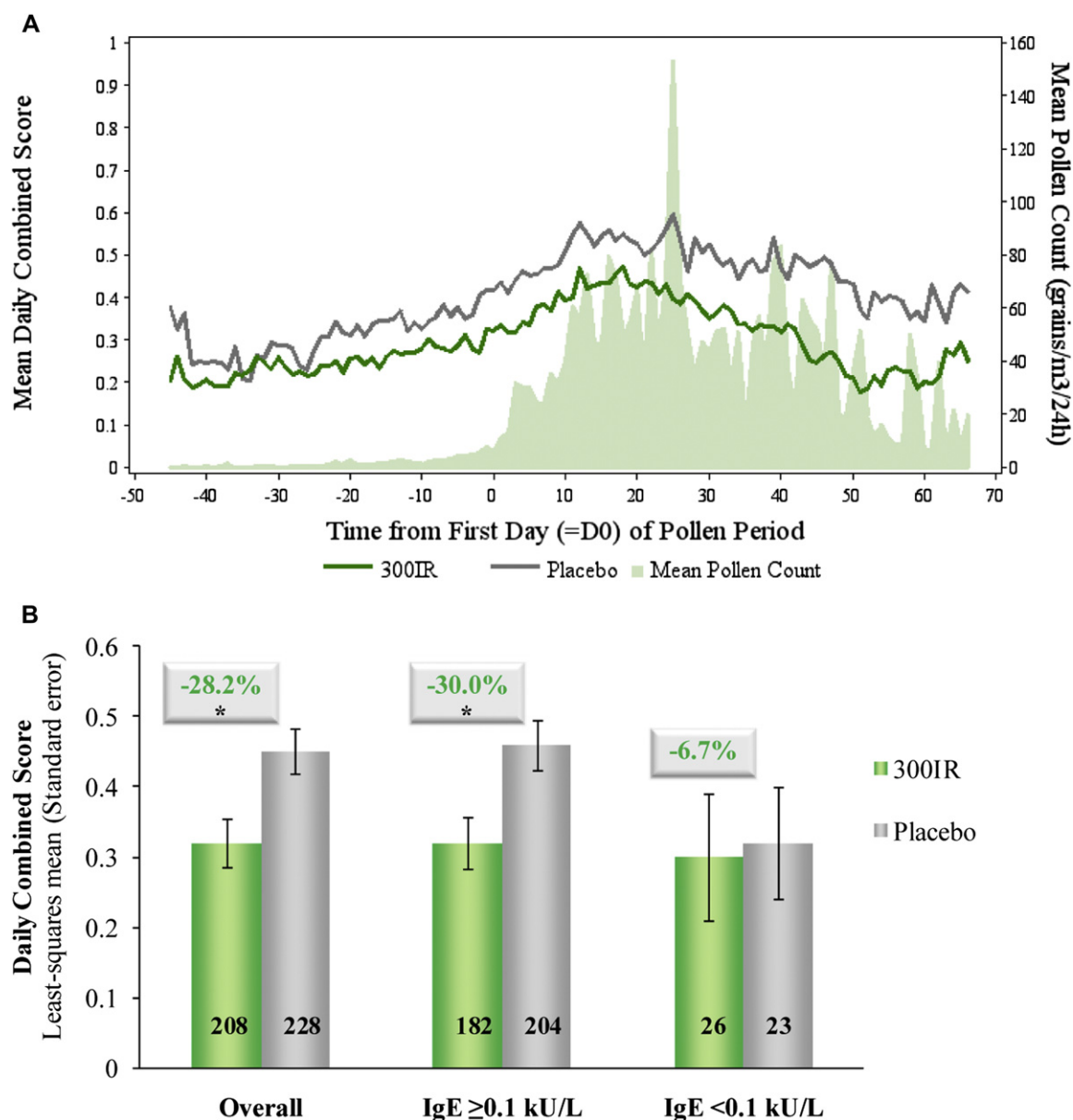


FIG 3. Daily CS (FAS). **A**, Mean daily CS and pollen count. **B**, Daily CS (LS mean $\pm$ SE) overall and in subgroups based on timothy grass-specific serum IgE at baseline. The number of participants per group is displayed in each bar. Note: IgE data were not obtained for 1 placebo-treated subject. * $P < .001$ versus placebo.

0.162 $\mu\text{g/mL}$ (95% CI, 0.141-0.185 $\mu\text{g/mL}$), 0.156 $\mu\text{g/mL}$ (95% CI, 0.136-0.178 $\mu\text{g/mL}$), and 0.166 $\mu\text{g/mL}$ (95% CI, 0.145-0.190 $\mu\text{g/mL}$) in the 300IR and placebo groups, respectively.

Safety

All 473 randomized participants were included in the safety analysis set. Overall treatment exposure was similar in the 2 groups and ranged from 3 to 205 days in the 300IR group (mean, 165.8 days [SD, 45.44 days]) and from 3 to 211 days in the placebo group (mean, 173.7 days [SD, 32.13 days]).

No death or intensive care unit admission occurred during the course of the study, and there were no reports of severe laryngopharyngeal edema, anaphylactic shock or anaphylaxis, or new-

onset autoimmune disorder. No participant in the active treatment group received epinephrine.

In the safety set, 5 serious treatment-emergent adverse events (TEAEs) were reported in 4 participants (palatal disorder [$n = 1$] and neuroendocrine carcinoma [$n = 1$] in the 300IR group, intestinal obstruction and gastroenteritis in the same participant [$n = 1$], and hematochezia [$n = 1$] in the placebo group). All serious TEAEs were considered by the investigators as not related or unlikely to be related to the investigational product. Eleven participants in the 300IR group prematurely withdrew from the study because of drug-related TEAEs, which were mostly application site reactions of mild or moderate severity.

The majority of participants in both groups reported at least 1 TEAE (Table IV). In the 300IR group, 20% of TEAEs occurred

TABLE II. Daily CS during the pollen period (FAS)

Population	Treatment	No.	LS mean (SE)	LS mean difference vs placebo			Relative difference (%)
				Point estimate	95% CI	P value	
Overall	300IR	208	0.32 (0.033)	−0.13	−0.19 to −0.06	<.001	−28.2
	Placebo	228	0.45 (0.032)				
Subgroup*							
IgE <0.1 kU/L	300IR	26	0.30 (0.092)	−0.02	−0.26 to 0.22	.86	−6.7
	Placebo	23	0.32 (0.081)				
IgE ≥0.1 kU/L	300IR	182	0.32 (0.037)	−0.14	−0.21 to −0.07	<.001	−30.0
	Placebo	204	0.46 (0.036)				

Statistical analysis was performed with repeated measures analysis of covariance.

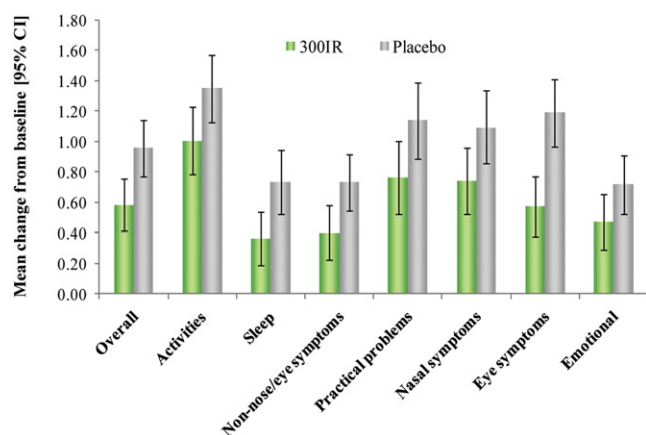
No., Number of participants with data.

*Patient subgroups by timothy grass-specific serum IgE levels at baseline.

TABLE III. Secondary efficacy analyses (pollen period, FAS)

	300IR, LS mean (SE)	Placebo, LS mean (SE)	300IR vs placebo, LS mean difference			
			Point estimate	95% CI	P value	Relative difference (%)
Daily RTSS	3.21 (0.315)	4.16 (0.299)	−0.95	−1.59 to −0.31	.004	−22.9
Daily RMS	0.11 (0.027)	0.20 (0.026)	−0.09	−0.15 to −0.04	<.001	−46.5
Daily AdSS	3.48 (0.347)	4.73 (0.330)	−1.25	−1.95 to −0.54	<.001	−26.3
Daily RSSs						
Sneezing	0.65 (0.061)	0.80 (0.058)	−0.15	−0.27 to −0.03	.02	−18.7
Runny nose	0.57 (0.062)	0.72 (0.059)	−0.15	−0.27 to −0.02	.02	−20.6
Itchy nose	0.49 (0.062)	0.59 (0.059)	−0.11	−0.23 to 0.02	.10	−17.6
Nasal congestion	0.71 (0.067)	0.85 (0.064)	−0.15	−0.28 to −0.01	.03	−17.4
Itchy eyes	0.48 (0.064)	0.70 (0.061)	−0.22	−0.35 to −0.09	<.001	−31.2
Watery eyes	0.31 (0.055)	0.49 (0.052)	−0.18	−0.29 to −0.07	.001	−37.1

Statistical analysis was performed with analysis of covariance as per the primary efficacy analysis. Observations for all variables were available for 208 participants in the active treatment group and 228 participants in the placebo group.

**FIG 4.** RQLQ scores: change from baseline to the expected middle of the grass pollen period (FAS). Vertical bars are 95% CIs.

on the first day of treatment intake, and half occurred within the first week. The most commonly reported TEAEs in this group were oropharyngeal in nature: oral pruritus, throat irritation, and nasopharyngitis. No exacerbations of asthma related to the 300IR sublingual tablet were reported.

DISCUSSION

This US study was conducted in adults with grass pollen-induced ARC. The primary efficacy end point was the daily CS,

TABLE IV. Incidence of all TEAEs and investigator-assigned drug-related TEAEs reported by participants in any treatment group (safety set)

	300IR (n = 233)		Placebo (n = 240)	
	Overall, no. (%)	Drug related, no. (%)	Overall, no. (%)	Drug related, no. (%)
Participants experiencing ≥1 TEAE*	191 (82.0)	128 (54.9)	184 (76.7)	54 (22.5)
Mild	150 (64.4)	113 (48.5)	96 (40.0)	40 (16.7)
Moderate	139 (59.7)	68 (29.2)	118 (49.2)	15 (6.3)
Severe	64 (27.5)	9 (3.9)	77 (32.1)	5 (2.1)

TEAEs occurred from the day the first dose of study medication was administered to study's end. TEAEs were considered related to the study drug if their relationship was "possible," "probable," "certain," or missing.

no., Number of participants with at least 1 event in given preferred term; %, percentage of participants with at least 1 event relative to the number of participants in each treatment group (n) in the safety set.

*Each participant could contribute up to 1 event per severity category.

which takes into account symptoms and rescue medication use consistent with WAO recommendations.²⁰ The 28.2% relative LS mean difference versus placebo in daily CS during the pollen period exceeded the 20% value recommended by the WAO taskforce for standardization of clinical trials with allergen-specific immunotherapy for respiratory allergy as clinically relevant for efficacy.^{20,23} Treatment effect size also compares favorably with those reported for antihistamines and inhaled corticosteroids.²⁴⁻²⁷ An additional strength of this study is the

consistency of the results across the efficacy end points. The positive findings on symptom scores (RTSS), medication scores (RMS), and a complementary approach to combining symptom scores and rescue medication use (AdSS), support the primary results. A comparison of these findings with those of SCIT for grass pollen–associated ARC would be valuable. However, no adequately powered, well-controlled study of grass pollen SCIT for ARC has included an efficacy end point combining symptom and rescue medication scores.

The clinical meaningfulness of the primary efficacy analysis is supported by patient-reported outcome measures related to quality of life and evaluation of treatment efficacy. A significant relative mean difference in overall RQLQ score was observed in the group of actively treated participants compared with the placebo group. Of note, in contrast to many studies of symptomatic treatments for ARC, rescue medication use was permitted in this study and was greater in placebo-treated participants. This likely reduced the degree of impairment in the placebo group compared with that seen in the 300IR group, resulting in the potential underestimation of the treatment effect. Therefore, the significant differences observed should be interpreted as the additive benefit of 300IR 5-grass pollen sublingual tablet on quality of life in study subjects who had access to symptomatic treatment. The favorable effect of active treatment on quality of life is further supported by the patient's global evaluation of treatment efficacy. The proportion of "treatment success" was significantly higher in the 300IR group compared with that seen in the placebo group.

To be consistent with US practice, and in contrast to previous studies of 300IR 5-grass pollen sublingual tablet which required both a positive SPT response to timothy grass and a timothy grass–specific serum IgE level of 0.7 kU/L or greater for inclusion,^{14,15,28} a positive ImmunoCAP FEIA result was not required in this study. However, serum samples were collected for analyses of immunologic markers at screening and at the end of the pollen season. Importantly, 11% of study subjects met the inclusion criteria for this study but had undetectable timothy grass–specific serum IgE (ie, IgE <0.1 kU/L) at screening.²⁹ This subgroup was essentially asymptomatic during the grass pollen season and therefore was unable to benefit from study therapy. This resulted in a dilution of the observed treatment effect of the investigational product and suggests that in the setting of a clinical trial, a minimum level of allergen-specific serum IgE is important in identifying a population sufficiently symptomatic to enable evaluation of treatment benefit. Our results are consistent with those of previous studies that demonstrated the high specificity of serum specific IgE tests.^{30,31} A retrospective study of monosensitized patients (grass, *Parietaria judaica*, *Olea europaea*, or house dust mite) found that higher serum specific IgE/total IgE ratios correlated with patient-reported response to allergen-specific immunotherapy, further supporting the clinical value of these measurements.³²

The proportion of polysensitized participants was higher in this study (78%) than in European studies (52%). However, sensitization status was not a significant predictor of outcome. In addition, interaction between treatment and sensitization status was not significant, indicating that treatment effect was independent of sensitization status. In North America, a 5-grass pollen allergen extract can be expected to better represent natural exposure and sensitization conditions encountered by patients

with grass pollen allergy than an extract of a single grass pollen. Specifically, a 5-grass pollen allergen mix provides coverage against a broad range of allergens, as identified among the family of temperate grasses and an expanded repertoire of T- and B-cell epitopes.³³

Timothy grass–specific serum IgE and IgG₄ increased in the 300IR group and were essentially unchanged in the placebo group. Although the clinical implications of this finding are not certain, an increase in serum IgG₄–associated inhibitory activity for IgE-facilitated allergen binding has been reported to correlate with clinical improvement.^{8,34} Of note, timothy grass–specific serum IgE and IgG₄ remained less than the limit of detection in the subgroup with no measurable timothy grass–specific serum IgE at baseline.

The favorable safety profile of 300IR 5-grass pollen sublingual tablet was consistent with that observed in previous trials in adults and children.^{14,15,19} The most commonly reported TEAEs were application site reactions. No anaphylaxis or treatment-related serious adverse events were reported.

In conclusion, in this US study, preseasonal and coseasonal treatment with 300IR 5-grass pollen sublingual tablet demonstrated clinically meaningful efficacy and was safe and well tolerated in adults with grass pollen–associated ARC. Measurable timothy grass–specific serum IgE were associated with greater seasonal symptoms, enabling assessment of treatment efficacy.

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Clinical implications: Preseasonal and coseasonal treatment with 300IR 5-grass pollen sublingual tablet is effective and well tolerated. A minimum level of allergen-specific serum IgE identifies a population sufficiently symptomatic to evaluate benefit.

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METHODS

Randomization

Eligible participants were randomized 1:1 to active treatment or placebo by using a computer-generated list (block size of 4). The randomization list was created by Quintiles South Africa with SAS System version 8.2 software (SAS Institute). Treatments were allocated to the study subjects chronologically with the next available treatment number in a consecutive and ascending way in the order of randomization. An electronic and paper copy of the complete randomization list was retained in a secure place with restricted access. Quintiles Pharmacovigilance and the investigational study centers were to receive study center-specific copies of the randomization code break envelopes.

Study treatment and rescue medication

Active treatment consisted of 300IR SLIT tablets containing a standardized 5-grass pollen allergen obtained by means of extraction of a mixture of 5 grass pollens in equal amounts (orchard grass, *Dactylis glomerata*; Kentucky bluegrass, *Poa pratensis*; perennial rye grass, *Lolium perenne*; sweet vernal grass, *Anthoxanthum odoratum*; and timothy grass, *Phleum pratense*).^{E1} The IR is a measure of biological potency (skin reactivity) used to describe the strength of an allergen extract. The IR is the biological unit used by Stallergenes (Antony, France). An allergen extract contains 100 IR/mL when, on an SPT using a Stallergene point, it induces a wheal diameter of 7 mm in 30 subjects sensitized to this allergen (geometric mean). The cutaneous reactivity of these subjects is simultaneously demonstrated by a positive SPT response to either 9% codeine

phosphate or 10 mg/mL histamine. Each 300IR tablet contains 20 to 25 µg of group 5 major grass pollen allergens.

Double blinding (participant and investigator) was established by use of a matching placebo tablet (identical in appearance and taste to the active tablet).

Treatment was initiated approximately 4 months before the expected start of the grass pollen period at each study center and continued for its duration. One 300IR or placebo tablet was to be taken sublingually at the same time every day from the randomization visit to the end of the treatment period. Participants were instructed to leave the tablet under the tongue until it had completely dissolved before swallowing. The first 3 doses were taken at the study site, and the participants were monitored for 30 minutes. The remainder of the treatment was taken at home. Self-injectable epinephrine was provided for use in the event of a severe systemic reaction, and study subjects were given instructions in its use. Rescue medications (oral and eye drop antihistamines and nasal corticosteroids) were supplied to participants, who were instructed to use them according to a stepwise regimen for the management of severe or intolerable ARC symptoms. Participants were to consult the investigator if they remained symptomatic despite these treatments. Investigators could then provide study subjects with oral corticosteroids.

Participants were considered treatment compliant if the number of tablets taken was between 80% and 120% (inclusive) of the expected value.

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