

Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis

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Summary

Background Sustained efficacy over three pollen seasons of pre- and co-seasonal treatment with 300IR 5-grass pollen sublingual tablet has been demonstrated in adults with moderate-severe grass pollen-associated allergic rhinoconjunctivitis.

Objective To assess the efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet during the post-treatment pollen season of this long-term study.

Methods Adults aged 18–50, sensitized to grass pollen, with a history of allergic rhinoconjunctivitis for more than two pollen seasons, and a retrospective rhinoconjunctivitis total symptom score ≥ 12 (0–18 scale), were randomized to receive Placebo or a 300IR tablet daily beginning either 4 months (4M) or 2 months (2M) prior to each pollen season and continuing for its duration for three consecutive years. They were followed over the subsequent immunotherapy-free pollen season. Post-treatment efficacy was evaluated using the Average Adjusted Symptom Score (AAdSS, adjusting the Rhinoconjunctivitis Total Symptom Score for rescue medication usage) during the post-treatment pollen period. Secondary endpoints included Average Rhinoconjunctivitis Total Symptom Score (ARTSS), Average Rescue Medication Score (ARMS), overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score and safety evaluation. Efficacy variables were analysed using ANCOVA.

Results Overall, 435 patients contributed to the Year 4 efficacy analyses. The Least-Squares (LS) mean differences (95% confidence interval) in AAdSS between active treatment and Placebo over the fourth pollen period were -1.14 (-2.03 ; -0.26) ($P = 0.0114$) and -1.43 (-2.32 ; -0.53) ($P = 0.0019$) in the (4M) and (2M) groups, corresponding to -22.9% and -28.5% relative LS mean differences (vs. Placebo) respectively. The active groups also showed statistically significant differences compared to Placebo in ARTSS, ARMS and overall RQLQ score. No safety risk was identified during the post-treatment period.

Conclusions and Clinical Relevance Pre- and co-seasonal treatment with 300IR 5-grass pollen sublingual tablet administered discontinuously for three consecutive years is efficacious post-treatment, safe and well tolerated. Benefits of treatment were meaningful to patients.

Keywords 5-grass pollen tablet, allergen, allergic rhinoconjunctivitis, discontinuous regimen, grass pollen, post-treatment efficacy, pre- and co-seasonal treatment, rhinoconjunctivitis, sublingual immunotherapy

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Introduction

Seasonal Allergic Rhinoconjunctivitis (ARC), characterized by sneezing, itchy nose, nasal congestion, rhinorrhea, itchy eyes and watery eyes associated with pollen exposure affects up to 30% of adults and as many as 40% of children [1, 2]. Its prevalence is increasing world-wide [2]. ARC represents a substantial burden for patients, whose quality of life is markedly impaired [3].

Antihistamines and intranasal corticosteroids are the principle therapeutic options. These treat the symptoms of ARC but are not effective in all patients and are not disease modifying. Allergen immunotherapy (AIT) is an alternative for patients in whom treatment with symptomatic medications is unwanted, ineffective or poorly tolerated [4]. Treatment with AIT results in a decrease in the sensitivity of the nasal mucosa and conjunctiva, and changes in the humoral and cellular responses to the administered allergens [4, 5]. In addition, the benefits of AIT have been shown to persist after discontinuation of the treatment [6–8].

The efficacy and safety of 4 months pre- and co-seasonal treatment with 300IR (Index of Reactivity) sublingual tablets containing a mixture of freeze-dried extracts of 5 grasses [cocksfoot (*Dactylis glomerata*), meadow (*Poa pratensis*), rye (*Lolium perenne*), sweet vernal (*Anthoxanthum odoratum*) and timothy (*Phleum pratense*)] have been demonstrated in adults and children with grass pollen-induced ARC [9, 10]. The sustained efficacy (i.e. after 3 treatment years) of discontinuous treatment with this sublingual tablet has also been demonstrated in a long-term study [11]. Here, we report the efficacy and safety of this treatment during the subsequent immunotherapy-free pollen season of this study.

Methods

Study design

The study design and detailed results of the three years of discontinuous treatment have been reported previously (clinicaltrial.gov identifier: NCT00418379) [11]. Briefly, this randomized, double-blind, placebo-controlled, parallel-group, multi-centre trial conducted at 48 sites in 8 European countries, Russia and Canada was designed as a four-year study, consisting of three pre- and co-seasonal treatment periods (2007 to 2009) and the subsequent immunotherapy-free grass pollen season (2010). Using a computer-generated list, eligible patients were randomized 1 : 1 : 1 to receive Placebo or active treatment initiated 4 months (4M) or 2 months (2M) before the expected start of the grass pollen season and continued throughout the season. Patients were

treated discontinuously for the first three pollen seasons and did not receive investigational product during the fourth year. Patients, investigators and all other trial personnel remained blinded for the entire study. Local Regulatory Authorities and Independent Ethics Committees approved the protocol (EudraCT number 2006-003258-98). The study complied with Good Clinical Practices guidelines and patients gave their written informed consents before any study-associated procedure was performed.

Patients

The study enrolled men and women aged 18 to 50 with documented grass pollen-related ARC for at least the two previous grass pollen seasons, a positive skin prick test (wheal diameter > 3 mm) to 5-grass pollen mix extract, timothy grass-specific serum IgE $\geq$ 0.7 KU/L, and a Retrospective Rhinoconjunctivitis Total Symptom Score (RRTSS) $\geq$ 12 (on a 0–18 scale) based on the most severe days in the grass pollen season preceding enrolment. Patients underwent skin testing to a panel of aeroallergens: *D. pteronyssinus*, *D. farinae*, *Alternaria*, *Cladosporium*, cat, dog, guinea pig, horse, ragweed, mugwort, birch, hazel, alder, ash, olive, *Parietaria*, Cupressaceae, plane and oak.

Study subjects were excluded from participation if they had clinically significant seasonal or perennial ARC symptoms during the grass pollen season due to sensitization to other allergens, or asthma requiring treatment other than beta-2 inhaled agonists.

Before each study year, participation in the study was reassessed to confirm that patients were willing to continue for the next year. It was also confirmed that they had not developed symptoms of ARC during the grass pollen season due to sensitization to other allergens, asthma requiring treatment other than inhaled beta-2 agonists or contracted any other disease that might affect their participation in or the outcome of this study.

Study treatment and rescue medication

During each of the first three years of the study, patients were to take a sublingual tablet of 300IR 5-grass pollen or Placebo daily beginning approximately 4 months before the expected start date of the pollen season and throughout the season. To maintain blinding, active and placebo tablets were identical in appearance and taste and the patients randomized to the 2-month (2M) group took placebo tablets during the first two months of treatment.

Rescue medications (oral antihistamines, antihistamine eye drops and nasal corticosteroids) were supplied to patients every year. Patients were instructed to use them according to a stepwise regimen for the management of

severe or intolerable ARC symptoms. If patients remained symptomatic despite these treatments, investigators could provide patients with oral corticosteroids.

Grass pollen season

During the grass pollen seasons, pollen counts were monitored and recorded daily in the area of each study centre. For each centre, the pollen period was defined as starting on the first of three consecutive days with a grass pollen count ≥ 30 grains/m³ and ending on the last of three consecutive days with a grass pollen count ≥ 30 grains/m³. Pollen period start and end dates were determined before unblinding the data. The daily grass pollen count was the average of pollen counts weighted by the number of patients within the catchment area of each pollen trap. Overall pollen exposure by season was assessed by the area under the curve (AUC), calculated using the daily grass pollen count and the duration of the pollen period.

Assessments

At the same time every evening, patients were to record six individual Rhinoconjunctivitis Symptom Scores (RSSs: sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes) and use of rescue medication, if any, during the previous 24 hours. Diaries were to be completed from approximately three weeks before each pollen season until its end, using a 4-point descriptor scale from 0 (Absent) to 3 (Severe) for each symptom. The sum of the six daily individual RSSs defines the daily Rhinoconjunctivitis Total Symptom Score (RTSS, range 0–18). The daily Rescue Medication Score (RMS, range 0–3) was derived as follows: 0 = no rescue medication taken; 1 = use of antihistamine (oral and/or eye drops); 2 = use of nasal corticosteroid; 3 = use of oral corticosteroid. If a patient took two or more rescue medications on the same day, the highest score was used for the RMS.

The Average Adjusted Symptom Score (AAdSS) while on treatment during the third pollen period was the primary efficacy end-point for the study. The AAdSS during the fourth pollen period was the end-point for the assessment of post-treatment efficacy. The AAdSS is subject-specific and calculated as the average of the daily Adjusted Symptom Scores (AdSSs) during the pollen periods. The daily AdSS (range 0–18) is a score adjusting the daily RTSS for rescue medication usage. The RTSS was adjusted as follows: if the patient took rescue medication on a given day, the AdSS equalled the RTSS of that day or the AdSS of the day before, whichever was higher. The AdSS of the following day equalled the RTSS of that day or the AdSS of the day before, whichever was higher [12].

Secondary efficacy outcomes included the Average RTSS (ARTSS), an average of the daily RTSS during the pollen periods, each of the six RSSs, the Average Rescue Medication Score (ARMS), an average of the daily RMS during the pollen periods, and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score [13]. Patients evaluated their quality of life, at the expected middle of each pollen season, using the self-administered RQLQ (range 0–6) consisting of 28 questions in seven domains (activities, sleep, non-nose/eyes symptoms, practical problems, nasal symptoms, eye symptoms and emotional); the lower the score, the better the quality of life.

Serum timothy-specific immunological markers

Timothy grass-specific serum IgE and IgG₄ were measured at study entry and at the end of each pollen season (immunoCAP, Phadia).

Safety

Safety was assessed through review of adverse events (AEs), physical examination and laboratory test findings. AEs were monitored throughout the study and categorized according to the MedDRA dictionary (version 9.1). The Year 4 Safety Set included all patients who completed the first visit in Year 4.

Statistical analyses

In the initial study protocol, ARTSS during the third pollen period was specified as the primary efficacy end-point. Subsequently, an EMA guideline recommended the use of a score taking into account symptom score and rescue medication use [14]. Therefore, during the second year of the study, while all data remained blinded, the protocol was amended to specify the AAdSS during the third pollen period as the primary efficacy end-point. ARTSS was retained as a secondary end-point. The sample size of 144 evaluable patients per group provided 80% power to detect a difference of 20% between each of the 300IR groups and the placebo group in AAdSS during the third pollen period while on treatment.

Statistical analyses were performed using SAS[®] software (version 9.1.3, SAS Institute Inc., Cary, NC, USA). The Year 4 full analysis set (FAS) included all patients who started the post-treatment year and had at least one AdSS recorded during the pollen period of that year. The per-protocol set (PPS) included all FAS patients with at least 14 valid AdSS days during the pollen period or valid AdSS days for at least 50% of the pollen period and who completed the study without any major protocol deviations.

As per the Year 3 data, differences in AAdSS, ARTSS, ARMS and the six RSS vs. Placebo were analysed using

an analysis of covariance (ANCOVA) with treatment group and pooled centres as main effects, and age, sex, sensitization and asthma status as covariates. For the analysis of overall RQLQ at the middle of the pollen period, the overall RQLQ score at randomization was also added as a covariate. Unless otherwise specified, results are presented as the mean $\pm$ standard deviation. The threshold for statistical significance was set at $P < 0.05$ and all inferential tests were two sided.

Results

Study population

A total of 633 patients were included in the study and were randomized to receive Placebo ($n = 219$) or 300IR active treatment beginning 4 months [300IR (4M), $n = 207$] or 2 months [300IR (2M), $n = 207$] before the pollen season for three consecutive years. Of the 457 patients who completed study Year 3, 15 withdrew prior to Year 4 and 442 comprised the Year 4 Safety Set. The

Year 4 Full Analysis Set (FAS_{Year4}) consisted of 435 patients [143 in the 300IR (4M) group, 137 in the 300IR (2M) group and 155 in the placebo group]. In this study, 433 patients completed Year 4 (Fig. 1).

Demographic and baseline characteristics were similar across the treatment groups (Table 1). On average, patients had been affected by grass pollen-associated ARC for 12.9 years (SD, 8.98). The mean RRTSS (scale 0–18) was 14.1 (SD, 1.75), consistent with moderate-severe ARC symptoms. GINA step I asthma was reported in 13% of patients and 59% of patients were polysensitized (i.e. sensitized to 5-grass allergens and at least one of the other allergens tested).

Mean AUC of pollen counts during the Year 4 pollen period was similar to that recorded during the Year 1–3 pollen periods.

Efficacy

For the Year 4 pollen period, statistically significant differences compared to Placebo in the AAdSS LS

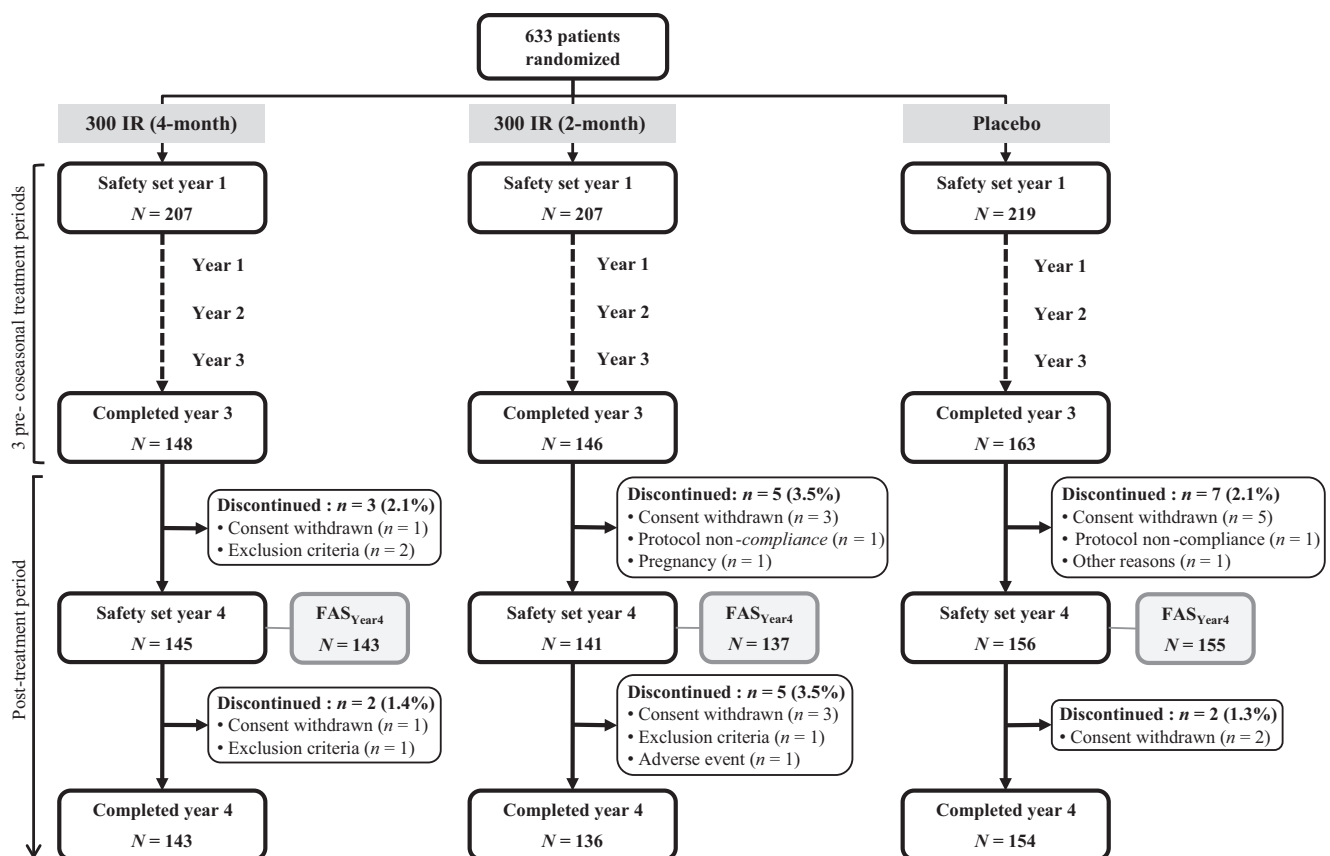


Fig 1. Patient disposition. Patients were randomized to receive placebo or active treatment initiated 4 months (4M) or 2 months (2M) before the grass pollen season and continued throughout the season. Patients were treated discontinuously for three consecutive years. The fourth year was immunotherapy free. Safety Set Year 1 included all patients who received at least one dose of treatment. Safety Set Year 4 included all patients who completed the first visit of Year 4. Full Analysis Set Year 4 (FAS_{Year4}) included all patients who started the post-treatment year and had at least one AdSS recorded during the pollen period of that year. IR = index of reactivity.

Table 1. Demographic and baseline disease characteristics (FAS_{Year4})

Description Category/Statistic	Treatment group			Total <i>N</i> = 435
	300IR (4M) <i>N</i> = 143	300IR (2M) <i>N</i> = 137	Placebo <i>N</i> = 155	
Gender, <i>n</i> (%)				
Male	92 (64.3)	84 (61.3)	94 (60.6)	270 (62.1)
Female	51 (35.7)	53 (38.7)	61 (39.4)	165 (37.9)
Age (years)				
<i>n</i>	143	137	155	435
Mean (SD)	30.7 (8.38)	31.0 (7.93)	30.0 (8.60)	30.6 (8.31)
Min–Max	18–49	18–51	18–49	18–51
BMI (kg/m ²)				
<i>n</i>	143	137	154	434
Mean (SD)	24.19 (3.637)	24.37 (3.736)	24.04 (4.217)	24.20 (3.876)
Min – Max	17.2–35.1	17.3–35.1	15.6–42.4	15.6–42.4
Duration of allergic rhinoconjunctivitis (years)				
<i>n</i>	143	137	155	435
Mean (SD)	13.26 (9.181)	12.78 (8.662)	12.69 (9.107)	12.90 (8.977)
Min–Max	1.5–42.1	1.5–39.0	1.6–44.0	1.5–44.0
RRTSS				
<i>n</i>	143	137	155	435
Mean (SD)	14.2 (1.73)	13.9 (1.73)	14.1 (1.78)	14.1 (1.75)
Min – Max	12–18	12–18	12–18	12–18
5-grass SPT weal diameter (mm)				
<i>n</i>	134	126	149	Not calculated
Mean (SD)	7.79 (2.392)	8.09 (2.745)	8.03 (2.601)	Not calculated
Min–Max	2.7*–17.1	3.8–17.9	3.0–16.4	Not calculated
Asthma status, <i>n</i> (%)				
Yes	18 (12.6)	17 (12.4)	21 (13.5)	56 (12.9)
No	125 (87.4)	120 (87.6)	134 (86.5)	379 (87.1)
Sensitization status, <i>n</i> (%)				
Mono-sensitized	59 (41.3)	57 (41.6)	62 (40.0)	178 (40.9)
Poly-sensitized	84 (58.7)	80 (58.4)	93 (60.0)	257 (59.1)

*One patient was included with SPT below 3 mm; this patient had timothy-specific serum IgE of 9.00 kU/L (RAST 3).

BMI, body mass index; FAS, Full Analysis Set; IR, index of reactivity; Max, maximum; Min, minimum; *N*, number of patients per treatment group; *n*, number of patients with data; SD, standard deviation; RRTSS, Retrospective Rhinoconjunctivitis Total Symptom Score; SPT, skin prick test.

means were observed in FAS_{Year4} for both 300IR (4M) and 300IR (2M) groups. The treatment effect for 300IR (4M) was estimated as the difference in LS means of -1.14 (95% CI: -2.03 ; -0.26 , $P = 0.0114$), corresponding to a relative LS mean difference from Placebo of -22.9% , while the treatment effect for 300IR (2M) was estimated as the difference in LS means of -1.43 (95% CI: -2.32 ; -0.53 , $P = 0.0019$), corresponding to a relative LS mean difference from Placebo of -28.5% . There was no significant difference between the two active treatment groups, and no impact of asthma or sensitization status on the efficacy results. The PPS results for Year 4 (PPS_{Year4}) were consistent with those of the FAS_{Year4}.

Throughout the Year 4 pollen period, the mean daily AdSSs were consistently lower in the active groups than in the placebo group (Fig. 2). The two components of the AAdSS (i.e. rhinoconjunctivitis total symptom

scores and rescue medication use) each showed statistically significant differences between active groups and placebo group during the Year 4 pollen period, with relative LS means differences vs. Placebo in ARTSS of -21.0% and -27.9% and relative LS means differences vs. Placebo in ARMS of -24.6% and -27.9% in the (4M) and (2M) groups respectively (Fig. 3). Also, each of the six rhinoconjunctivitis symptom scores was lower in the active treatment groups than in the placebo group with no significant difference between the active groups (Table 2). During the Year 4 pollen period, the overall RQLQ score differed significantly from Placebo for both 300IR (4M) ($P = 0.0001$) and 300IR (2M) ($P < 0.0001$). The treatment effect, estimated as the difference in LS mean, was -0.46 (95% CI: -0.70 ; -0.23) for 300IR (4M), corresponding to a relative LS mean difference from placebo group of -32.8% , and -0.53 (95% CI: -0.77 ; -0.29) for 300IR (2M),

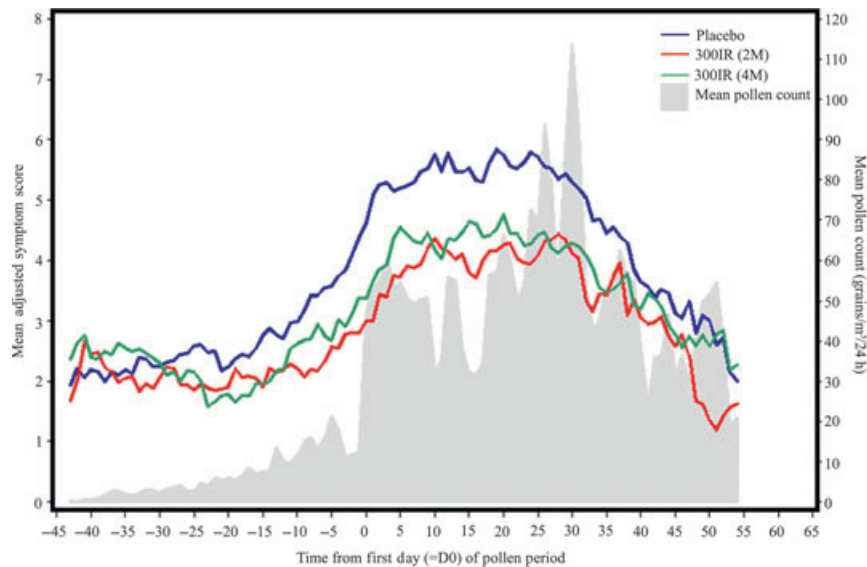


Fig 2. Daily mean Adjusted Symptom Scores and grass pollen counts for the Year 4 pollen period. The daily mean grass pollen count (grains/m³) was the average of pollen counts weighted by the number of patients within the catchment area of each pollen trap. $n \geq 30$ patients per treatment group with an adjusted symptom score. IR = index of reactivity.

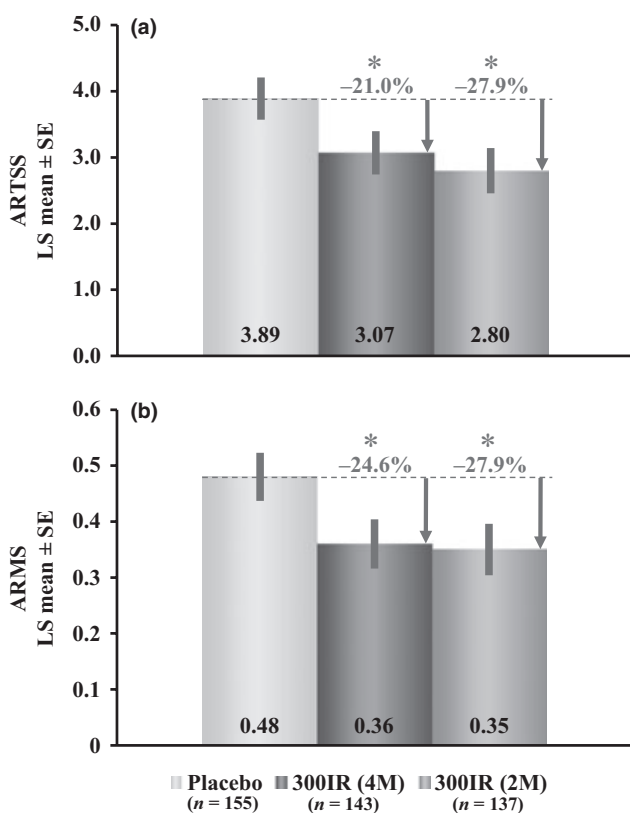


Fig 3. Least-square mean Average Rhinoconjunctivitis Total Symptom Score (a) and Average Rescue Medication Score (b) during the Year 4 pollen period (FAS_{Year4}) with relative differences vs. placebo. *Differences vs. placebo were statistically significant (ANCOVA, $P < 0.05$). Error bars represent the standard error of the LS means. ANCOVA = analysis of covariance, FAS = Full Analysis Set, IR = index of reactivity, LS = Least square, SE = standard error.

corresponding to a relative LS mean difference from placebo group of -37.6% . The relative mean reduction in the seven RQLQ domains in the active groups compared to placebo group observed during Year 4 ranged from -24.9% to -47.1% (Table 3).

Allergen-specific humoral immunological parameters

At baseline, timothy-specific serum IgE and IgG₄ were similar in the three treatment groups. In Year 1, after the first treatment period, the serum IgE end-point: baseline ratio was higher in both 300IR (4M) and 300IR (2M) groups compared to Placebo (2.05, 1.86 and 1.29 respectively). In subsequent study years, there was no marked difference between active treatment groups and Placebo with respect to these measures. At the end of the Year 4 pollen period, the timothy-specific serum IgG₄ end-point:baseline ratio in the active treatment groups was greater than 2 but it remained near 1 in the placebo group.

Safety

During Year 4, similar percentages of patients in the three treatment groups [31.7% in 300IR (4M), 34.8% in 300IR (2M), and 35.9% in Placebo] reported post-treatment AEs (PTAEs), the most frequent being nasopharyngitis. None of the four serious PTAEs reported during Year 4 (i.e. ligament injury, lumbar vertebral fracture, inguinal hernia and infectious mononucleosis) was considered drug-related by the investigators.

Asthma status and severity remained constant over the study four years and were similar across the three

Table 2. Individual Average Rhinoconjunctivitis Symptom Score during the pollen period (FAS_{Year4})

Treatment	LS mean	Difference in LS means vs. Placebo			Relative LS mean difference (%)
		Point estimate	(95% CI)	P-value	
Average rhinoconjunctivitis total symptom score					
300IR (4M)	3.07	−0.82	(−1.55, −0.09)	0.0282	−21.0
300IR (2M)	2.80	−1.09	(−1.83, −0.35)	0.0040	−27.9
Placebo	3.89				
Sneezing					
300IR (4M)	0.68	−0.10	(−0.26, 0.05)	0.1888	−13.3
300IR (2M)	0.61	−0.17	(−0.33, −0.02)	0.0312	−22.1
Placebo	0.78				
Rhinorrhea					
300IR (4M)	0.57	−0.16	(−0.31, −0.01)	0.0354	−22.1
300IR (2M)	0.50	−0.23	(−0.38, −0.08)	0.0031	−31.6
Placebo	0.73				
Nasal pruritus					
300IR (4M)	0.47	−0.20	(−0.34, −0.05)	0.0071	−29.5
300IR (2M)	0.49	−0.17	(−0.31, −0.02)	0.0217	−25.4
Placebo	0.66				
Nasal congestion					
300IR (4M)	0.55	−0.13	(−0.29, 0.03)	0.1040	−19.4
300IR (2M)	0.47	−0.21	(−0.37, −0.05)	0.0117	−30.5
Placebo	0.68				
Ocular pruritus					
300IR (4M)	0.53	−0.16	(−0.30, −0.01)	0.0322	−23.1
300IR (2M)	0.48	−0.20	(−0.35, −0.05)	0.0073	−29.3
Placebo	0.68				
Watery eyes					
300IR (4M)	0.29	−0.07	(−0.19, 0.05)	0.2727	−18.8
300IR (2M)	0.25	−0.11	(−0.23, 0.01)	0.0806	−30.4
Placebo	0.36				

Patients with data: 300IR (4M): *n* = 143; 300IR (2M): *n* = 137; placebo: *n* = 155.

Statistical analysis: ANCOVA.

ARTSS is the average of daily RTSSs during the pollen period. Daily RTSSs are the sum of the six individual rhinoconjunctivitis symptom scores.

ANCOVA, analysis of covariance; CI, confidence interval; FAS, Full Analysis Set; IR, index of reactivity; LS, least squares.

treatment groups. There were three occurrences of worsening asthma, one in the 300IR (4M) group and two in the placebo group; none was considered drug related by the investigator. No safety risk was identified post-treatment, all reported events being consistent with the considered population and pathology.

Discussion

The post-treatment efficacy of 300IR 5-grass pollen sublingual tablet in adults who completed three years of discontinuous pre- and co-seasonal treatment initiated 4 or 2 months before each grass pollen season and continued throughout the season was demonstrated over the subsequent, immunotherapy-free pollen season in this international, multi-centre study. There was no impact of asthma status or sensitization status on the efficacy results. The robustness of the post-treatment efficacy was supported by the consistently positive results on all secondary end-points.

In this study, both treatment regimens were associated with efficacy, suggesting that either could be used. Of note, in all studies investigating the 4-month pre-seasonal and co-seasonal regimen, treatment with 300IR 5-grass pollen sublingual tablet was efficacious and the benefit to patients was demonstrated [9–11, 15]. In contrast, in a study evaluating a 2-month pre-seasonal and co-seasonal regimen, the treatment was not efficacious [16]. The 5-grass pollen tablet was granted Marketing Authorization based on a 4-month pre- and co-seasonal regimen and it is this regimen that is to be followed in clinical practice.

Clinically, it is important to note that the patient-reported improvement in quality of life with active treatment was sustained over the fourth pollen period as well. Of note, in contrast to the studies investigating the clinical effect of symptomatic treatments for allergic rhinoconjunctivitis, rescue medication use was permitted in this study and was higher in Placebo-treated patients. This likely reduced the degree of impairment in the

Table 3. Rhinoconjunctivitis Quality of Life Questionnaire Score at the middle of pollen season (FAS_{Year4}): Overall and by domain

Score	Description Category/statistic	Treatment group		
		300IR (4M) N = 143	300IR (2M) N = 137	Placebo N = 155
Overall RQLQ	<i>n</i> (missing)	141 (2)	132 (5)	150 (5)
	Mean (SD)	0.95 (0.964)	0.86 (0.862)	1.41 (1.141)
	95% CI	(0.79, 1.11)	(0.72, 1.01)	(1.23;1.60)
	Min–Max	0.0–5.4	0.0–4.1	0.0–4.7
Relative difference vs. placebo		–32.7%	–38.9%	–
Activities	<i>n</i> (missing)	143 (0)	136 (1)	154 (1)
	Mean (SD)	1.36 (1.398)	1.13 (1.147)	1.89 (1.543)
	95% CI	(1.13, 1.59)	(0.94, 1.33)	(1.64, 2.13)
	Min–Max	0.0–5.7	0.0–5.0	0.0–5.7
Relative difference vs. placebo		–27.8%	–39.8%	–
Sleep	<i>n</i> (missing)	143 (0)	136 (1)	153 (2)
	Mean (SD)	0.57 (1.098)	0.62 (1.046)	0.87 (1.187)
	95% CI	(0.38, 0.75)	(0.44, 0.79)	(0.68, 1.06)
	Min–Max	0.0–5.7	0.0–4.7	0.0–4.7
Relative difference vs. placebo		–35.0%	–29.4%	–
Non-nose/-eye symptoms	<i>n</i> (missing)	142 (1)	135 (2)	153 (2)
	Mean (SD)	0.69 (0.966)	0.66 (0.866)	1.13 (1.203)
	95% CI	(0.53, 0.85)	(0.51, 0.81)	(0.93, 1.32)
	Min–Max	0.0–5.3	0.0–4.6	0.0–4.9
Relative difference vs. placebo		–38.4%	–41.3%	–
Practical problems	<i>n</i> (missing)	143 (0)	134 (3)	153 (2)
	Mean (SD)	1.57 (1.498)	1.22 (1.231)	2.10 (1.645)
	95% CI	(1.33, 1.82)	(1.01, 1.43)	(1.83, 2.36)
	Min–Max	0.0–6.0	0.0–5.0	0.0–6.0
Relative difference vs. placebo		–24.9%	–41.8%	–
Nasal symptoms	<i>n</i> (missing)	142 (1)	135 (2)	154 (1)
	Mean (SD)	1.29 (1.218)	1.22 (1.097)	1.89 (1.505)
	95% CI	(1.08, 1.49)	(1.03, 1.41)	(1.65, 2.13)
	Min–Max	0.0–5.5	0.0–5.0	0.0–6.0
Relative difference vs. placebo		–32.0%	–35.5%	–
Eye symptoms	<i>n</i> (missing)	143 (0)	136 (1)	154 (1)
	Mean (SD)	0.93 (1.082)	0.82 (0.965)	1.46 (1.456)
	95% CI	(0.75, 1.11)	(0.65, 0.98)	(1.23, 1.70)
	Min–Max	0.0–5.0	0.0–5.0	0.0–5.3
Relative difference vs. placebo		–36.2%	–44.3%	–
Emotional	<i>n</i> (missing)	143 (0)	136 (1)	153 (2)
	Mean (SD)	0.56 (0.907)	0.50 (0.837)	0.95 (1.140)
	95% CI	(0.41, 0.71)	(0.36, 0.65)	(0.77, 1.13)
	Min–Max	0.0–5.5	0.0–4.3	0.0–4.3
Relative difference vs. placebo		–41.6%	–47.1%	–

CI, confidence interval; FAS, Full Analysis Set; IR, index of reactivity; *n*, number of patients with data; SD, standard deviation.

placebo group compared to the 300IR groups, resulting in the potential underestimation of the treatment effect on quality of life. Therefore, the significant differences observed should be interpreted as the additive benefit of 300IR 5-grass pollen sublingual tablet on quality of life in patients who had access to symptomatic treatment.

A comparison of these study findings with those of studies of the post-treatment effects of subcutaneous immunotherapy (SCIT) for grass pollen-associated ARC would be of interest. However, few such studies have

been published and these have had methodological limitations. A small-scale study evaluating 32 adults who received timothy grass pollen SCIT for either 3–4 years or 6–7 years suggested persistent efficacy for three years post-treatment [17]. In a group of 28 children who had chosen a 3-year course of grass pollen SCIT or pharmacotherapy, symptoms and rescue medication use was significantly lower 12 years after treatment cessation in the SCIT patients compared to those who chose pharmacotherapy [18, 19]. In a randomized,

open-label study, 205 children received three years of grass pollen and/or birch-pollen SCIT or no SCIT, and were followed up for seven years after treatment discontinuation. The clinical effect, evaluated using a visual analogue scale, persisted seven years after termination of treatment [20]. Based on these data, the current 'Allergen immunotherapy: A practice parameter third update' states that immunotherapy might have a persistent clinical benefit [4]. Overall, the efficacy demonstrated in our double-blind, placebo-controlled study compares favourably to that suggested for grass pollen SCIT.

A recent study with timothy grass pollen sublingual immunotherapy administered over three years has also shown clinical benefit post-treatment [21–24]. Initially planned as a single-season study, it was later extended, resulting in a participation rate of approximately 55% before the second pollen season and 45% before the fourth pollen season. In contrast, in our study, patients were aware of the long-term design from the beginning and 70% remained in the study for the Year 4 pollen season.

Compared to pre-treatment levels, timothy grass-specific serum IgG₄ was significantly elevated in both active groups at the end of Year 4. This suggests the 300IR tablet is systemically immunoactive with changes in the humoral immune response even after cessation of the treatment.

One challenge of long-term studies is that the most symptomatic patients, especially those randomized to the placebo group, withdraw prematurely. Despite this intrinsic limitation of our study, we observed a post-treatment efficacy with active treatment.

The post-treatment safety profile reinforces the favourable safety and tolerability of 300IR 5-grass pollen sublingual tablet observed during the treatment periods of this study and in previous trials [9–11].

Conclusions

Discontinuous treatment with 300IR 5-grass pollen sublingual tablet is efficacious post-treatment, safe, and well tolerated in adults with moderate-severe grass pollen-associated allergic rhinoconjunctivitis. Benefits of treatment were meaningful to patients.

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Declaration of competing interest

A. Didier has received honoraria for lectures and for serving on advisory boards for Stallergenes, ALK-Abelló, AstraZeneca, Chiesi, GSK, MSD and Novartis. H.J. Malling has received research grants, been a speaker and served on advisory boards for Stallergenes, Allergopharma, ALK-Abelló, Biomar and Novartis. M. Worm has served on advisory boards for Stallergenes and has received honoraria for lectures for Stallergenes. F. Horak has declared no conflict of interest. G. Sussman has received research support from Stallergenes, Mast Cell Pharmaceuticals, Merck, Novartis and Schering-Plough, and is a medical advisor and/or has received honoraria for lectures for Anaphylaxis Canada, the Allergy Asthma and Immunology Society of Ontario, the Canadian Hereditary Angioedema Network, CSL Behring, Merck, Novartis and Pfizer. M. Melac, S. Soulié and R.K. Zeldin are employees of Stallergenes.

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