

Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis

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Background: The efficacy and safety of the 300-index of reactivity (IR) dose of 5-grass-pollen sublingual immunotherapy (SLIT) tablets (Stallergènes, Antony, France) have been demonstrated for the treatment of hay fever in adults.

Objective: We sought to assess the efficacy and safety of this tablet in children and adolescents with grass pollen-related allergic rhinitis.

Methods: In this multinational, randomized, double-blind, placebo-controlled study, 278 children (5–17 years of age) with grass pollen-related rhinoconjunctivitis (confirmed by means of a positive grass pollen skin prick test response and serum-specific IgE measurement) received once-daily SLIT tablets or placebo. Treatment was initiated 4 months before the estimated pollen season and continued throughout the season. The primary outcome was the rhinoconjunctivitis total symptom score (RTSS), a sum of 6 individual symptom scores: sneezing, runny nose, itchy nose, nasal congestion, watery eyes, and itchy eyes. Secondary end points included rescue medication intake, individual scores, and safety.

Results: The intent-to-treat population included 266 children (mean age, 10.9 ± 3.22 years). The RTSS for the 300-IR group was highly significantly different from that of the placebo group ($P = .001$). The 300-IR group showed a mean improvement for the RTSS of 28.0% over that seen with placebo and a median improvement of 39.3%. Significant differences between the 300-IR and placebo groups were also observed regarding rescue medication score and proportion of days using rescue medication during the pollen season ($P = .0064$ and $P = .0146$,

respectively). Adverse events were generally mild or moderate in intensity and expected. No serious side effects were reported. **Conclusion:** Five-grass-pollen SLIT tablets (300 IR) reduce both symptom scores and rescue medication use in children and adolescents with grass pollen-related rhinoconjunctivitis. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Allergic rhinoconjunctivitis, grass pollen allergy, optimal dose, sublingual tablet, sublingual immunotherapy, children, adolescents

The prevalence of rhinitis with itchy-watery eyes (rhinoconjunctivitis) is increasing, and its burden is substantial.¹ It can begin at any age, and there is wide variation in prevalence, from 0.8% to 14.9% in 6- to 7-year-olds and from 1.4% to 39.7% in 13- to 14-year-olds.² In the International Study on Allergy and Asthma in Childhood,² it was found that in the 6- to 7-year-old group there is a global increase in rhinitis prevalence across most countries. In a German prospective birth cohort, seasonal allergic rhinitis (symptoms and sensitization) developed at up to 7 years of age in 15% of the children, with an increased risk in individuals with a positive family history for allergies. Longitudinal results of this study further indicate that remission of seasonal allergic rhinitis symptoms does not seem to occur frequently.³

Poorly controlled symptoms of allergic rhinitis might contribute to sleep loss or disturbance.⁴ For children, learning problems occur during school hours either through direct interference or indirectly because of nocturnal sleep loss and secondary daytime fatigue.^{5,6}

At present, allergen-specific immunotherapy is the only treatment for allergic rhinitis and asthma that might modify the diseases and thus potentially prevent the progression from allergic rhinitis to asthma.^{7,8} Subcutaneous immunotherapy in children is hampered by the inconvenience of injection and the risk of serious adverse events.⁴ Alternative routes of administration have been developed to make immunotherapy more acceptable and safer, particularly for children. Sublingual immunotherapy (SLIT) appears to be associated with a lower incidence of systemic reactions than subcutaneous immunotherapy⁹ and has been assessed as safe enough to allow for home administration. Prescribing physicians should consider how adherence will be monitored and whether the child has the ability to comply with the SLIT regimens.¹⁰

A recent randomized, placebo-controlled, double-blind study has determined that in an adult population the 300-index of reactivity (IR) tablet is the optimal dose of a 5-grass-pollen SLIT tablet for treating grass pollen-related allergic rhinitis over the

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Supported by Stallergènes.

Disclosure of potential conflict of interest: A. Tabar has served as a consultant for Stallergènes and received research support from Stallergènes. S. Halken has received honoraria for lectures for ALK-Abelló and Stallergènes and received research support from Stallergènes. The rest of the authors have declared that they have no conflict of interest.

Received for publication June 28, 2008; revised October 2, 2008; accepted for publication October 6, 2008.

Available online ■■■■.

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doi:10.1016/j.jaci.2008.10.009

Abbreviations used

ANCOVA: Analysis of covariance

IR: Index of reactivity

ITT: Intent-to-treat

RRTSS: Retrospective rhinoconjunctivitis total symptom score

RTSS: Rhinoconjunctivitis total symptom score

SLIT: Sublingual immunotherapy

first pollen season.¹¹ The aim of the current study is to determine whether this 300-IR dose of 5-grass-pollen tablets is safe and effective in the pediatric population with a pre-seasonal regimen starting 4 months before the expected start of the pollen season and continued throughout the season.

METHODS

Patients

The study included 278 children and adolescents (both girls and boys 5-17 years of age) with seasonal grass pollen-related allergic rhinitis. All patients had grass pollen-related moderate-to-severe allergic rhinoconjunctivitis for at least 2 years confirmed by means of a positive skin prick test response (wheal diameter, >3 mm) and a timothy grass pollen-specific IgE level of at least class 2 (≥ 0.7 kU/L; Immulite 2000 3gAllergy; DPC, Los Angeles, Calif) assessed at the screening visit. Eligible patients also had a score of at least 12 of a possible 18 on the retrospective rhinoconjunctivitis total symptom score (RRTSS), determined on the basis of the most severe symptoms during the previous pollen season. The skin prick test included pollen from 5 grasses: allergens of orchard [*Dactylis glomerata*], meadow [*Poa pratensis*], perennial rye [*Lolium perenne*], sweet vernal [*Anthoxanthum odoratum*], and timothy [*Phleum pratense*] grasses).

Participants were investigated for sensitization to other allergens by testing a panel of the most common allergens in each country. Children with asthma requiring treatment only with β_2 -agonists could be included. The main exclusion criteria were patients with symptoms of rhinoconjunctivitis during the grass pollen season caused by sensitization to allergens other than grass pollen, including perennial allergens causing rhinitis symptoms, asthma requiring treatment other than β_2 inhaled agonists; participants who had received any desensitization therapy for grass pollen; and the usual contraindications for specific immunotherapy, such as concomitant β -blocker therapy, severe and/or stable asthma, severe immune deficiency or autoimmune disease, or malignancies. Written consent was obtained from patients/parents/legal guardians in accordance with local laws, requirements were completed in accordance with the International Conference on Harmonization guidelines on good clinical practice, and the study was approved by local ethics committees.

Immunotherapy

SLIT tablets containing freeze-dried allergen extract of 5 grass pollens (orchard, meadow, perennial rye, sweet vernal, and timothy grasses; Stallergenes SA, Antony, France) at a dose of 300 IR together with matching placebo were used for the study. The drug product was manufactured by Stallergenes SA as an aqueous extract made from the mixture of 5 grass pollens.¹² Excipients used in both active and placebo tablets include lactose, sodium stearate, and sodium croscarmellose. Such tablets dissolve completely in less than 2 minutes. Allergens are subsequently captured by oral dendritic cells within 30 to 60 minutes.¹³ A previous study in adults had showed that the 300-IR SLIT tablet containing 5 grass pollens was well tolerated and effective in reducing the symptoms of rhinitis and conjunctivitis caused by grass pollens. The highest dose (500 IR) was no more effective but induced more adverse events. The 100-IR dose was not effective; this dose was on the slope of the dose-response curve in contrast with the 300-IR and 500-IR doses, which were on the plateau of the curve. Thus the optimal dose of allergen (300 IR) for SLIT has been found in this adult study.¹¹

The IR is a measure of biologic potency (skin reactivity) used to describe the strength of an allergen extract; 100 IR is defined as the concentration eliciting, by means of skin prick testing with a Stallerpoint, a geometric mean wheal size of 7 mm in diameter in 30 patients sensitive to the corresponding allergen.¹⁴ Group 5 is a 27- to 33-kD major allergen with ribonuclease activity found in grass species from the Pooideae subfamily.¹⁵ A 300-IR tablet corresponded to approximately 20 μ g of the group 5 major allergens.

The placebo tablet matched the active treatment in size, shape, and color but contained no active ingredients. Excipients were identical to those in the active treatment tablets, with the addition of caramel and quinoline yellow. Allergen or placebo tablets were to be taken sublingually once daily at the same time. The patient was instructed to keep the tablet under the tongue until complete dissolution before swallowing.

Study design

This was a multicenter, multinational, double-blind, placebo-controlled, phase III study in children with grass pollen-related allergic rhinitis. It was conducted between December 16, 2006, and September 12, 2007, at 29 study centers in 5 European countries: France (n = 6), Spain (n = 6), Germany (n = 6), Poland (n = 9), and Denmark (n = 2).

Patients were screened, and those eligible were randomized 1:1 to 2 groups: one group received once-daily SLIT with 300 IR of allergen extract in a tablet formulation, and the other group received placebo. The randomization list was stratified by study center and organized in blocks. Treatment began 4 months before the expected start of the pollen season according to the data collected by the European Aeroallergen Network (available at <http://www.univie.ac.at/ean>; for details, see this article's Methods section in the Online Repository at www.jacionline.org) and continued throughout the season. The dose of SLIT was increased by 100 IR per day over 3 days; the placebo group received the same number of tablets as the active treatment group during this period. The first dose was administered under the investigator's supervision, and the children were observed for 30 minutes for evidence of local reactions, systemic reactions, or both. From the second day, treatment was taken at home.

The study consisted of 3 phases (screening, treatment, and follow-up) and 7 visits over a period of 7 to 8 months. The scheduled times of each visit were chosen with respect to the local pollen season, as outlined in the study design (Fig 1).

Efficacy and safety assessments

The primary outcome was the efficacy of the treatment on the rhinoconjunctivitis total symptom score (RTSS), which included the 6 most common symptoms of pollinosis (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes). A score ranging from 0 to 3 was used for each symptom: 0, no symptoms; 1, mild symptoms (symptoms clearly present but minimal awareness, easily tolerated); 2, moderate symptoms (definite awareness of bothersome but tolerable symptoms); and 3, severe symptoms (symptoms hard to tolerate and/or cause interference with activities of daily living, sleeping, or both).

From approximately a month before and during the pollen season, patients (under the supervision of the parent/guardian) or their parents/guardians completed a daily diary card to individually score nasal and ocular symptoms. The mean RTSS (mean of daily RTSS) was calculated over the entire pollen season.

In case of severe symptoms, patients could use rescue medication. Patients were instructed to start with an oral antihistamine, an ocular antihistamine, or both and, if the symptoms were not alleviated, to progress to an intranasal corticosteroid and at the ultimate stage return to the investigator site to be prescribed an oral corticosteroid. Thus the daily rescue medication score (0, no medication; 1, antihistamine; 2, intranasal corticosteroid; 3, oral corticosteroid), and the proportion of days with rescue medication could be calculated, and the mean over the season could be determined and compared between treatment groups. In addition, the effect of immunotherapy on the 6 individual symptom scores was analyzed as a secondary outcome.

Blood samples were taken before and at the end of the pollen season to measure serum immunologic markers (IgG4 and IgE specific for grass pollen

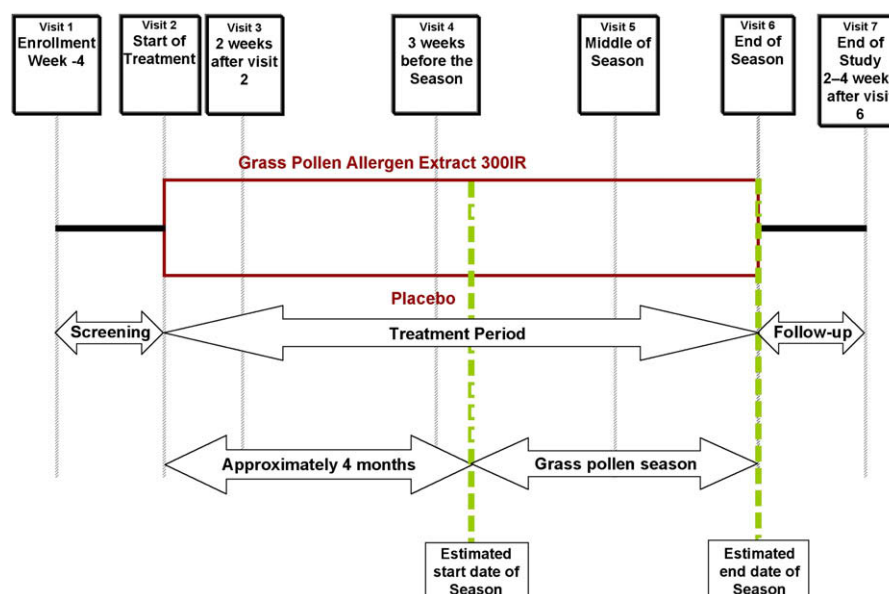


FIG 1. Study design. Treatment began approximately 4 months before the expected start of the grass pollen season and continued throughout a single pollen season.

allergens). Adverse events were monitored throughout the study (for details, see this article's Methods section in the Online Repository).

Population and statistical analysis

The safety population includes all patients who received at least 1 dose of the investigational product. The ITT population includes all patients who received at least 1 dose of the investigational product and had an RRTSS and at least 1 RTSS measured during the pollen period while receiving treatment. The ITT population will be regarded as primary for the efficacy analyses. The per-protocol population includes all patients who completed the study according to the protocol and had no major protocol violations. Patients should qualify for inclusion in the ITT population to be included in the per-protocol population. Patients who are withdrawn from the study because of a lack of efficacy or an adverse event related to the investigational product will be included in the per-protocol population if they are otherwise valid.

The primary efficacy variable was analyzed with analysis of covariance (ANCOVA), with treatment and pooled study center as main effects. Descriptive statistics were performed for all efficacy, safety, and immunologic data (for details, see this article's Methods section in the Online Repository).

RESULTS

A total of 320 children were screened, and 278 patients were randomized to one of 2 treatment groups, 300 IR ($n = 139$) and placebo ($n = 139$), at 29 study centers. The baseline demographic and clinical characteristics of each group are presented in Table I. All characteristics were well balanced at baseline between treatment groups. Fig 2 describes the overall participant flow for the study.

The proportion of compliant patients was almost equivalent in the study groups (95% in the placebo group and 94% in the active group). A compliant patient is one with a compliance rate between 80% and 120%.

The mean treatment duration before the pollen season was 112.6 ± 10.1 days, and the mean duration during the pollen season was 38.6 ± 16.2 days.

TABLE I. Demographic characteristics of children included in the study (ITT population)

	Placebo ($n = 135$)	300 IR ($n = 131$)	All ($n = 266$)
Sex (% female/% male)	37.0/63.0	34.4/65.6	35.7/64.3
Age (y)			
Mean $\pm$ SD	11.2 ± 3.07	10.5 ± 3.34	10.9 ± 3.22
Median (range)	11 (5-17)	10 (4-17)	11 (4-17)
Age group (% 5-11 y/% 12-17 y)	52.6/47.4	62.6/37.4	57.5/42.5
BMI (mean $\pm$ SD)	19.0 ± 3.91	18.4 ± 3.27	18.7 ± 3.62
Asthma (%)	21.5	21.4	21.4
Sensitization status (% monosensitized/% polysensitized)	40.7/59.3	41.2/58.8	41.0/59.0

BMI, Body mass index.

Primary efficacy measure

The mean RTSS $\pm$ SD during the pollen period in the 300-IR group (3.25 ± 2.860) was lower than that in the placebo group (4.51 ± 2.931). The ANCOVA of the mean RTSS showed that the difference between the 300-IR and placebo groups was highly statistically significant ($P = .0010$), with a least squares mean difference of -1.13 (95% CI, -1.80 to -0.46). Compared with the placebo group, the 300-IR group showed a mean improvement of 28.0% and a median improvement of 39.3% for the mean RTSS (Table II).

In addition, data for the per-protocol population were similar to those obtained for the ITT population. Daily mean RTSSs by treatment group, as well as daily pollen counts, are presented in Fig 3.

Secondary efficacy measures

The mean rescue medication score of the 300-IR group was highly statistically significantly different from that of the placebo group ($P = .0064$), with a least squares mean difference of -0.20 (95% CI, -0.34 to -0.06). Compared with the placebo group, the

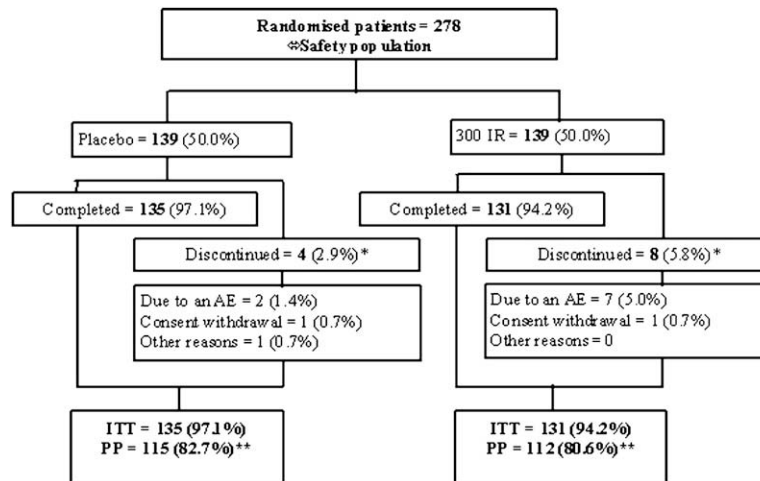


FIG 2. Patient disposition. AE, Adverse event; PP, per-protocol. *Twelve (4.3%) patients were excluded from the ITT population because they withdrew before the pollen season and therefore had no efficacy assessment. **Thirty-nine patients (18.3%) were excluded from the per protocol population for different protocol deviations, mainly poor compliance or use of prohibited medications.

TABLE II. RTSSs and rescue medication scores throughout the pollen season (ITT population)

	RTSS				RMS	
	ITT population		Per-protocol population		ITT population	
	Placebo group	300-IR group	Placebo group	300-IR group	Placebo group	300-IR group
No.	135	131	115	112	135	131
Mean $\pm$ SD	4.51 $\pm$ 2.931	3.25 $\pm$ 2.860	4.43 $\pm$ 2.805	3.28 $\pm$ 2.642	0.79 $\pm$ 0.647	0.60 $\pm$ 0.611
P value	.001		.0016		.0146	
Median (minimum–maximum)	4.08 (0.00–14.65)	2.48 (0.00–18.00)	4.00 (0.00–14.65)	2.49 (0.00–10.93)	0.76 (0.00–2.46)	0.39 (0.00–2.00)
Improvement (% mean/% median)	28.0/39.3		25.9/37.6		24.1/48.7	

RMS, Rescue medication score.

300-IR group showed a mean improvement of 24.1% and a median improvement of 48.7% for the mean rescue medication score (Table II).

The mean proportion of days patients in the 300-IR group were taking at least 1 rescue medication (35.4%) was statistically significantly less than in patients in the placebo group (46.5%, $P = .0146$).

The pattern of rescue medication use was similar between the 2 treatment groups, with the majority of patients using oral antihistamines (>63.4%) and only a small proportion of patients using oral corticosteroids (<5.2%).

Children taking the 300-IR dose had lower mean individual symptom scores compared with those taking placebo for all 6 individual symptom scores. There was a statistically significant difference between the 300-IR and placebo groups for 4 of the 6 individual mean symptom scores ($P \leq .0380$ for runny nose, nasal congestion, itchy eyes, and watery eyes). The highest improvement was observed for nasal congestion and ocular symptoms. Asthma and sensitization status have no effect on the efficacy results (for details, see this article's Results section in the Online Repository at www.jacionline.org).

Immunologic data

For children receiving the 300-IR dose (ITT population), the geometric mean level of grass-specific IgG4 (in micrograms per

liter) more than tripled from baseline (before treatment) to the end of treatment (ratio, 3.37), whereas children receiving placebo showed little change in IgG4 levels (ratio, 1.41).

By contrast, for timothy grass-specific IgE, the geometric mean level before treatment and at the end of treatment were similar for both those children who received active treatment (ratio, 1.35) and those who received placebo (ratio, 1.64). Immunologic markers (IgE and IgG4) are summarized descriptively in the Results section of the Online Repository (also see Table E1 in this article's Online Repository at www.jacionline.org).

Safety

Five patients reported serious adverse events. Two in the active and 3 in the placebo group had 1 exacerbation of asthma and 1 case of Burkitt lymphoma, but none of them was attributed by the investigator to the study treatment. This last patient presented with severe nasal congestion before the first study drug administration, which was considered by the investigator to be the first symptoms of the Burkitt lymphoma. In the placebo group 3 patients have experienced 1 episode of severe abdominal pain (considered related to the study drug), 1 episode of moderate gastroduodenitis (not attributed to the study drug), and 1 moderate multiple traumatism before the first dose.

A total of 902 treatment-emergent adverse events were reported by 232 (83.5%) patients (84.9% in the 300-IR group

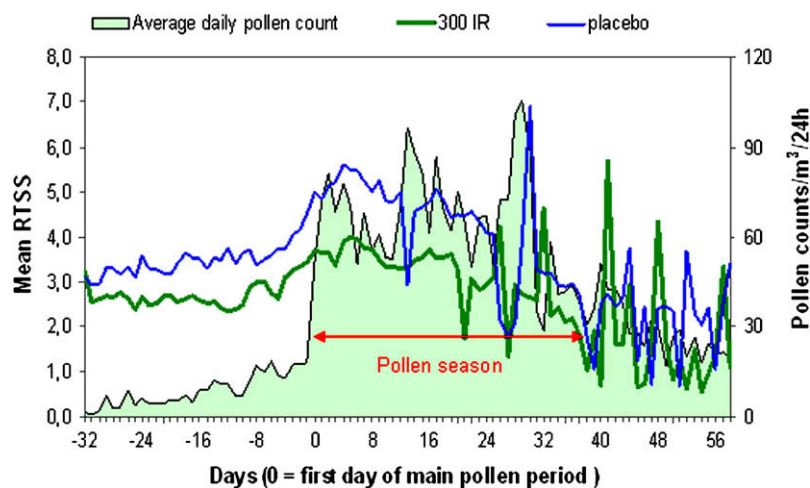


FIG 3. Daily mean RTSS and pollen counts (ITT population). Mean RTSSs of both the treatment and placebo groups throughout the pollen season are shown in relation to the daily pollen counts. The main pollen season is marked.

and 82.0% in the placebo group). Adverse events led to withdrawal from the study in 9 patients (7 in the 300-IR group and 2 in the placebo group). In the 300-IR group these adverse events comprised 1 episode of chest discomfort, 1 episode of oral mucosal blistering, 3 episodes of oral pruritus, 1 episode of edema of the mouth, and 1 episode of vomiting.

The majority of treatment-emergent adverse events were mild to moderate in severity for both treatment groups. Seventeen (12.2%) patients in the 300-IR group and 8 (5.8%) patients in the placebo group experienced severe treatment-emergent adverse events, whatever the relationship to the treatment. Frequencies of treatment-emergent adverse events are provided in Table E2 (available in this article's Online Repository at www.jacionline.org).

DISCUSSION

In this study a pediatric population with grass pollen-related allergic rhinoconjunctivitis was treated with the 300-IR dose of the 5-grass-pollen SLIT tablet. A highly statistically significant reduction in total rhinoconjunctivitis symptoms (as measured by the RTSS) in children receiving the 300-IR dose was observed compared with those receiving placebo (least squares mean difference, -1.13 ; 95% CI, -1.80 to -0.46 ; $P = .0010$), as well as a lower use of rescue medication ($P = .0064$).

Few studies have assessed the efficacy of SLIT in children with allergies to grass pollen.¹⁶⁻²⁰ Although 1 meta-analysis suggested that SLIT is not of particular benefit for allergic rhinitis in children,²¹ 2 other more recent meta-analyses concluded SLIT to be safe and effective in children.^{22,23} In the latter analysis 484 patients were included, 245 of whom received SLIT and 239 of whom received placebo. SLIT induced a significant reduction in nasal symptoms compared with placebo (least squares mean difference, 0.56 ; 95% CI, 1.01 - 0.10 ; $P = .02$).²³ However, significant interstudy heterogeneity was found ($P < .001$). A recent published review on immunotherapy in youngsters stated that the heterogeneity among these SLIT trials can be explained by the clinical diversity (variability in participants, intervention, and outcomes) and methodological differences (variability in trial design and

quality) and recommended that more adequately designed studies were conducted.²⁴ Meanwhile, a SLIT task force comprehensive review concluded that “a consistent relationship between allergen dose, treatment duration and clinical efficacy has not been established and further research is clearly needed.”^{10,25}

More recently, guidance to evaluate the effect of SLIT in allergic rhinitis and well-designed studies to determine the optimal dosage of SLIT tablets have become available.^{10,11,26} It has previously been demonstrated that the 300-IR dose of this 5-grass-pollen SLIT tablet was the optimal dose in adult patients.¹¹ Our results have demonstrated that in a pediatric population from 5 to 17 years of age, the 300-IR dose results in significant improvement in symptom scores compared with placebo. In the first treatment season there was a reduction of 28% for mean symptom score and 39% for median symptom score. For example, the level of improvement of mean RTSS compared with placebo exceeded the 20% threshold, which is suggested as the threshold for clinically relevant efficacy.²⁷ This magnitude of effect is similar to that found in recent studies using SLIT tablets in adult populations^{11,28,29} and occurred despite use of rescue medication. These studies have used either a very brief¹⁶ or no-treatment phase.²⁸ Nevertheless, both short- and long-term immunotherapy studies are needed to determine the optimal duration of treatment regimens and at what stage before the onset of the pollen season it is optimal to begin treatment.¹⁰ In this study efficacy was obtained after a preseasonal (4 months before the season) allergen administration, and clinical efficacy was observed throughout the pollen season.

The rescue medication use (percentage of days with rescue medication) was significantly lower in the 300-IR group compared with that seen in the placebo group ($P = .0004$). An assessment of rescue medication score showed a significantly reduced score for the 300-IR group compared with the placebo group ($P = .0064$), with a median reduction of 48.7% during the pollen season.

For children taking the 300-IR dose, an improvement was seen for all 6 individual symptom scores, particularly nasal congestion and ocular symptoms. In the placebo group using rescue medication (essentially antihistamines, nasal steroids, or both), nasal

congestion and ocular symptoms were poorly controlled, which agrees with the known effects of each of these medications on the specific symptoms of either allergic rhinitis or allergic conjunctivitis.³⁰

Both children allergic only to grass pollens (monosensitized) and those sensitive to grass pollen plus other allergens (poly-sensitized) were studied, and both groups showed evidence of comparable improvement. This is of importance in clinical practice because the majority of patients with allergy are polysensitized. These data extend the possibility of the use of specific immunotherapy to a wider population of patients with allergies in countries in which its use is currently restricted to monosensitized patients.¹¹

The rate and severity of side effects observed in this study were similar to those reported in other tablet-based SLIT studies. There were no serious side effects related to the medication. These data are in agreement with the safety profile of SLIT according to systematic reviews, meta-analyses, clinical trials,^{22,31,32} and post-marketing surveillance.⁹ In general, SLIT appears to be associated with fewer serious adverse effects and might be tolerated in children as young as 2 years; however, local reactions are relatively common (up to 75% of patients), and severe reactions have been reported. Currently, there have been no fatalities associated with the use of sublingual therapy. There have been 4 anaphylactic reactions reported in the literature.¹⁰ As noted previously, a recent study including 60 children (5-12 years) with grass pollen-related rhinoconjunctivitis with or without asthma found that SLIT grass pollen tablets were well tolerated in this age group at the same dose used by adults.³³ Of these children, 45 received a 28-day treatment with a grass pollen tablet outside the grass pollen season, and 15 received placebo tablets. In the active treatment group 78% of children reported 1 or more adverse events (essentially mild-to-moderate oropharyngeal local reactions) compared with 33% of children in the placebo group who reported adverse events. Only 2 patients discontinued treatment because of adverse events. These data, together with the safety data in the current study, suggest that the SLIT grass pollen tablets are well tolerated by children older than 5 years at the same dose used by adults.

The current study shows that the 300-IR SLIT tablet containing 5 grass pollens was well tolerated and effective in reducing the symptoms of rhinitis and conjunctivitis caused by grass pollen in a pediatric population. This study demonstrates first-season efficacy in children and adolescents given preseasonal and coseasonal specific immunotherapy, but this needs to be assessed in a long-term, placebo-controlled trial over several years. Further studies are also needed to identify the optimal maintenance dose, and longer-term data are required to confirm whether SLIT will prevent progression from allergic rhinitis to asthma.

This study confirms that the 300-IR dose of a 5-grass-pollen SLIT tablet is effective and well tolerated in the treatment of allergic rhinitis in children aged 5 to 17 years and is effective from the first pollen season.

We thank the investigators, nurses, and participants who made this study possible: Dr Lars G. Hansen, Dr Kirsten Skamstrup Hansen, Dr François Payot, Dr François Bremont, Dr Joel Levy, Dr Roger Alt, Dr Mireille Ruer Mullard, Dr Jean-Marc Houssel, Prof Jurgen Seidenberg, Dr K. Nemat, Dr W. Rebiën, Dr Folster-Hoelst, Prof Dr Carl-Peter Bauer, Dr Teresa Malaczynska, Dr Dorota Kardas-Sobantka, Prof Jerzy Hofman, Dr Renata Baranowska, Dr Iwona Stelmach, Dr Ewa Springer, Dr Andrzej Emeryk, Prof Krzysztof

Buczyłko, Dr Elena Alonso Lebrero, Dr Montserrat Bosque Garcia, Dr Felix Lorente Toledano, Dr Maria-Flora Martin Munoz, and Dr Maria-Teresa Giner Munoz.

Clinical implications: When treating hay fever with 5-grass-pollen SLIT tablets, the optimal dose of 300 IR in adults was also effective and well tolerated in children and adolescents from the first pollen season.

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METHODS

Pollen counts

For each center, the beginning and end of the pollen season were based on the estimated average pollen season over the past 5 to 10 years according to the data collected by the European Aeroallergen Network (available at <http://www.univie.ac.at/ean>). The pollen season was defined as the first day of the first 3 consecutive days with a grass pollen count of greater than 30 grass pollen grains/m³ of air to the last day of the last 3 consecutive days with a pollen count of greater than 30 grains/m³.

Safety assessments

Safety assessments included monitoring of adverse events, physical examinations, and conventional laboratory tests. Adverse events were reported, focusing on the date of onset, occurrence, duration, intensity, action taken, outcome, and relationship to study drug. Adverse events were monitored throughout the study and graded according to the MedDRA dictionary (version 9.1; available at <http://meddramsso.com>). The safety population included all patients who were randomized and had received at least 1 dose of investigational product.

Statistical analysis

The primary analyses were performed for the ITT and per-protocol populations. The secondary analyses were performed for the ITT population alone.

Previous studies^{E1,E2} indicated that a sample size of 117 patients per group would have an 80% power to detect a difference between placebo and the 300-IR dose in the mean RTSS, assuming an overall α value of .05 and a common SD of 3.3. Assuming a 15% dropout rate, target recruitment was for 140 patients in each treatment arm.

The primary efficacy variable was analyzed by using an ANCOVA with treatment and pooled study center as main effects, and the RRTSS, age, sex, asthma status (presence or absence of asthma), and sensitization status (monosensitized vs polysensitized) of the patient as covariates. A point estimate and 95% CI for the difference in the adjusted means between the 300-IR dose and placebo was calculated from the ANCOVA. The percentage improvement of the mean and median RTSSs for the 300-IR dose over placebo is provided.

Immunologic parameters

Blood samples were taken before and at the end of the pollen season to measure serum immunologic markers (IgG4 and IgE specific for grass pollen allergens). Complementary results and analyses that included levels of immunologic marker (IgE and IgG4) levels were summarized descriptively (geometric mean and 95% CI) by treatment group over visits and for the ratio of end point/baseline.

RESULTS

Secondary efficacy measures

Pooled sites, asthma, and cosensitization status.

Analyses of covariates for the mean RTSS showed that although pooled study center was a statistically significant covariate, the treatment by pooled study center interaction was not statistically significant, suggesting that any differences between treatment groups were consistent over pooled study centers. Sex was a statistically significant covariate in the models. However, the treatment by sex interaction was not statistically significant, and thus any differences between treatment groups were consistent over sexes. Furthermore, asthma and sensitization status have no effect on the efficacy results.

Efficacy assessed by RTSS by age of children. Patients aged 12 to 17 years had higher mean RTSSs and individual mean symptom scores than those in the 5- to 11-year age category for both treatment groups. However, whatever the age range (5-11 or 12-17 years), the mean RTSS was observed to be lower in those receiving the 300-IR dose than in those receiving placebo. A similar pattern was seen for all 6 of the individual symptom scores when analyzed by the age of the treatment group.

Immunologic data. For children receiving the 300-IR dose (ITT population), the geometric mean level of timothy grass-specific IgG4 (in micrograms per liter) more than tripled from baseline (before treatment) to the end of treatment (ratio, 3.37), whereas children receiving placebo showed little change in IgG4 levels (ratio, 1.41).

By contrast, for timothy grass-specific IgE levels, the geometric mean level before treatment and at the end of treatment were similar for both those children who received active treatment (ratio, 1.35) and those who received placebo (ratio, 1.64; [Table E1](#)).

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TABLE E1. Exploratory efficacy: immunologic markers and summary statistics (ITT population)

Test (U)	Treatment	Visit	No.	Geometric mean	Geometric 95% CI
IgG4 (μg/L)	300 IR	Visit 1 (screening)	131	335.62	(280.74-401.24)
		End point*	131	1130.0	(900.59-1417.7)
		Ratio†	131	3.37	(2.88-3.94)
	Placebo	Visit 1 (screening)	135	288.46	(247.15-336.66)
		End point*	135	407.24	(342.99-483.53)
		Ratio†	135	1.41	(1.28-1.55)
IgE (kU/L)	300 IR	Visit 1 (screening)	131	32.25	(25.47-40.84)
		End point*	130	43.08	(34.20-54.26)
		Ratio†	130	1.35	(1.18-1.54)
	Placebo	Visit 1 (screening)	135	29.69	(23.56-37.42)
		End point*	135	48.59	(39.14-60.32)
		Ratio†	135	1.64	(1.37-1.95)

*End of treatment, including early discontinuation patients.

†End point/visit 1.

TABLE E2. Most frequent related treatment-emergent adverse events (TEAEs): incidence of 5% or greater in the safety population

	Placebo (n = 139)			300 IR (n = 139)		
	No. of patients	Percentage of patients	No. of events	No. of patients	Percentage of patients	No. of events
Patients with related TEAEs	28	20.1	45	75	54.0	187
Oral pruritus	2	1.4	2	45	32.4	59
Edema of the mouth	0	0.0	0	18	12.9	19
Throat irritation	7	5.0	10	11	7.9	11