

Safety Review of 5-Grass Pollen Tablet from Pooled Data of Clinical Trials



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What is already known about this topic? The 300 Index of Reactivity 5-grass pollen sublingual tablet has been proven safe and well tolerated in patients with grass pollen–induced allergic rhinitis associated or not with intermittent asthma in several clinical trials.

What does this article add to our knowledge? Pooling of safety data collected over the clinical development program in 1514 actively treated subjects provides better knowledge of the safety profile of the 5-grass pollen sublingual tablet over time and in patients of special interest.

How does this study impact current management guidelines? The pooled safety results in the overall population and in subgroups such as patients with asthma will help health care professionals in improving their management and educating the patients receiving this treatment.

BACKGROUND: The 5-grass pollen sublingual tablet has been approved for the treatment of grass pollen–induced allergic rhinoconjunctivitis in subjects with or without intermittent asthma. **OBJECTIVE:** To provide a comprehensive analysis of the safety profile of the 5-grass tablet on the basis of pooled data from 8 clinical trials.

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Financial support for the development of this article was provided by Stallergenes. Stallergenes designed and provided funding for the studies described in this article.

Conflicts of interest: T. B. Casale has received consultancy fees from Stallergenes and has received research support from Stallergenes and Merck. L. S. Cox has received personal fees from MedImmune, Circassia, Stallergenes Greer, Novartis, Biotech, and Genentech. U. Wahn has received consultancy fees from Allergopharma, Stallergenes, ALK, Novartis, Danone, and Nutricia and has received lecture fees from Allergopharma, Stallergenes, ALK, Danone, and Nestle. D. B. K. Golden has received consultancy fees from Stallergenes; has provided expert testimony for Litvak & Trifolis PC; has received research support and lecture fees from Genentech and Stallergenes Greer; receives royalties from UpToDate; and has received payment for developing educational presentations from PeerView. B. Bons has received consultancy fees from Stallergenes Greer. A. Didier has received consultancy fees, travel support, and fees for participation in review activities from Stallergenes.

Received for publication February 20, 2017; revised March 29, 2017; accepted for publication April 12, 2017.

Available online July 19, 2017.

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2017.04.020>

METHODS: Subjects (5-65 years old) with medically confirmed grass pollen–induced allergic rhinoconjunctivitis were included in the double-blind studies. Those with intermittent asthma not requiring treatment other than inhaled beta-2 agonists could participate. Randomized subjects received a 5-grass or placebo tablet daily 2 or 4 months preseasonally and coseasonally (5 single-season studies, over 3 years in a long-term study) or outside the season (phase I studies). Adverse events were pooled and analyzed descriptively.

RESULTS: Among 2,512 subjects enrolled, 1,514 received the 5-grass tablet. A total of 1,038 adults and 154 pediatric (5-17 years old) subjects were treated with the 300 Index of Reactivity dose (vs 840 and 158 placebo recipients, respectively); 17% had intermittent asthma, and 62% were polysensitized. Adverse reactions (ADRs) reported in more than 10% of actively treated subjects were mild or moderate application-site reactions, for example, oral pruritus 25% (placebo 4%) and throat irritation 21% (placebo 3%). These generally occurred during the first week of treatment and decreased over time. They led to discontinuation in less than 2.5% of subjects. None of the 3 serious ADRs were reports of anaphylaxis. No notable differences were detected in terms of incidence, nature, and severity of ADRs between adult and pediatric populations, nor between subjects with or without asthma.

CONCLUSIONS: The pooled analysis in 1,514 subjects from 8 clinical studies demonstrates that the 5-grass pollen sublingual tablet has a similar good safety profile in adult and pediatric patients with or without mild, intermittent asthma. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1717-27)

Key words: 5-Grass pollen tablet; Grass pollen; Allergic rhinoconjunctivitis; Asthma; Sensitization; Allergy immunotherapy; Allergen-specific immunotherapy; Sublingual immunotherapy; Safety; Clinical trial

Abbreviations used

AE- Adverse event
 ARC- Allergic rhinoconjunctivitis
 AIT- Allergen-specific immunotherapy
 IR- Index of Reactivity
 SCIT- Subcutaneous immunotherapy
 SLIT- Sublingual immunotherapy
 TEAE- Treatment-emergent adverse event

Allergic rhinitis with or without conjunctivitis is a globally prevalent disease affecting between 10% and 30% of adults and up to 40% of children, totaling more than 500 million people worldwide.^{1,2} Grass pollens specifically are among the most prevalent and clinically relevant sources of aeroallergens that trigger this disease.^{3,4} Depending on the severity of allergic rhinoconjunctivitis (ARC) symptoms, the patient's physical or psychological conditions, quality of life, family and social interactions, and work/school performances may be considerably affected.² Moreover, patients affected by ARC are at increased risk for the development of asthma and other comorbidities.¹

Current recommendations to clinicians for the management of ARC now include a combination of patient education, allergen avoidance, symptomatic pharmacotherapy, and allergen-specific immunotherapy (AIT) through a stepwise therapeutic approach.^{2,5,6} AIT is a therapeutic option for patients whose symptoms are not adequately controlled by avoidance measures or standard medications, those experiencing unacceptable adverse effects with standard medications, or those who wish to reduce the long-term use of medications.⁷ AIT is the only therapy that has been shown to be disease modifying, with benefits persisting for several years after treatment discontinuation in most patients.⁸

In the United States, subcutaneous immunotherapy (SCIT) serves as the primary delivery method for AIT and has a demonstrated therapeutic benefit in both short-term symptom management and longer-term disease modification.⁹ Potential risks and use limitations associated with SCIT are the potential of near-fatal or fatal anaphylaxis and while not as serious, the discomfort and inconvenience of frequent injections. Recent availability of sublingual immunotherapy (SLIT) tablets represents a viable alternative with similar efficacy and a favorable safety profile.^{2,9} Importantly, SLIT may be proposed as an early treatment in the therapeutic strategy for respiratory allergy according to scientific societies.⁸

The 5-grass pollen sublingual tablet has been developed during the last decade for the treatment of patients with grass pollen-induced ARC confirmed by positive skin test result or *in vitro* testing for pollen-specific IgE to any of the 5 grass species included in the product. Randomized, double-blind, placebo-controlled trials have been conducted showing the product efficacy.¹⁰⁻¹⁶ The purpose of the present article was to provide a comprehensive and thorough review of the safety profile of the 5-grass pollen tablet from the clinical development program.

METHODS**Design overview**

The overall clinical safety experience with 5-grass pollen sublingual tablet (Stallergenes, Antony, France) is based on pooled data from all subjects enrolled in 8 studies regardless of the dose or

treatment regimen, treatment duration, subject age, or study duration. A tabulated summary of the studies is presented in Table E1 in this article's Online Repository at www.jaci-inpractice.org. The studies included in the development program were VO33.04DK (Safety and tolerability study), VO34.04 (European study; NCT00367640), VO40.05 (Extension of European study), VO52.06 (Pediatric study; NCT00409409), VO53.06 (Long-term study; NCT00418379), VO56.07A (Allergen exposure chamber study; NCT00619827), VO60.08 (2-month preseasonal regimen study; NCT00803244), and VO61.08USA (US study; NCT00955825).¹⁰⁻¹⁶ All studies were randomized, double-blind, placebo-controlled and were conducted globally between 2004 and 2011. Ethics committees or institutional review boards approved all study protocols and all subjects signed informed consent before any study procedure was performed.

Settings and participants

All subjects (5-65 years old) enrolled in the development program had a clinical history of grass pollen-associated ARC for at least 2 years, confirmed by positive skin prick test to 5-grass pollen mix (ex-US) or timothy grass (US) and timothy grass-specific serum IgE level of 0.7 kU/L or more (except in the US study). Their Retro-spective Rhinoconjunctivitis Total Symptom Score evaluated on the most severe days of the pollen season preceding enrolment was at least 12 out of 18. Polysensitized subjects, that is, demonstration of antigen-specific IgE to 2 or more allergens by skin prick testing or *in vitro* testing,¹⁷ could be enrolled as long as they did not have significant clinical symptoms of ARC due to allergens other than grass pollen during the season. Subjects with asthma requiring treatment other than with inhaled beta-2 agonists and those receiving continuous therapy with corticosteroids or beta-blocker therapy were excluded.

Randomization and interventions

Active treatment consisted of sublingual tablets containing an allergen mixture obtained by concurrent extraction from 5 different grass pollens in equal amounts (sweet vernal grass, *Anthoxanthum odoratum* L.; cockfoot/orchard, *Dactylis glomerata* L.; perennial rye grass, *Lolium perenne* L.; timothy, *Phleum pratense* L.; and meadow/Kentucky blue grass, *Poa pratensis* L.) at doses of 100IR, 300IR, and 500IR. The Index of Reactivity or "IR" is the potency unit used by Stallergenes to quantify the allergenic activity of the 5-grass pollen extract. An in-house reference standard for potency measurement was established on the basis of titrated skin prick testing of allergic subjects.^{16,18} The mean dosage of 300IR/mL corresponds to 20 to 25 µg/mL of the group 5 major allergens^{12,16} and is equivalent to approximately 9000 bioequivalent allergy units.¹⁹ Active and corresponding placebo tablets were matched in packaging, shape, taste, color, and appearance to ensure blinding. In all studies, subjects were randomized to receive either active treatment or placebo through a computer-generated scheme. The European study (VO34.04) tested different doses of active treatment ranging from 100IR to 500IR. The selected dose, 300IR, was further investigated in subsequent studies.

Various administration schedules were used in the clinical studies. In the Safety and tolerability study and the Allergen exposure chamber study, subjects were treated for 10 days and 4 months, respectively, outside the pollen season. The other 6 clinical trials were natural field studies in which treatment was administered beginning either 4 months or 2 months before the grass pollen season and continued throughout the season. In addition,

2 treatment-initiation schemes were used (ie, a 3-day dose escalation: day 1—100IR, day 2—200IR, and day 3—300IR for the European and Pediatric studies, and direct administration of the maintenance dose without escalation for subsequent studies). The natural field studies spanned a single allergy season except for the Long-term study (VO53.06) in which subjects received treatment discontinuously for 3 consecutive periods over 3 years and were followed for 2 years posttreatment.

Rescue medications (oral and eye drop antihistamines and nasal corticosteroids) were provided to participants in the natural field studies. Subjects were instructed to use them according to a stepwise regimen for the management of severe or intolerable ARC symptoms. If subjects remained symptomatic despite these treatments, they could be provided with oral corticosteroids upon prescription by the investigator. In addition, self-injectable epinephrine was provided to US study participants for use in the event of a severe systemic allergic reaction.

Outcomes and follow-up

In all studies of the clinical development program, safety was documented by adverse event (AE) reporting, laboratory data, and physical examination findings (including vital signs). Participants spontaneously reported AEs and concomitant medications on daily record cards and AEs were continually monitored and recorded by the investigators at visits. The characteristics of AEs that were collected throughout the studies included the onset and resolution dates, severity, seriousness, action taken (none, medication given, interruption or discontinuation of investigational product), outcome, and investigator's causality assessment. Serious AEs were those that were immediately life-threatening or resulted in hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, congenital anomalies/birth defects, or death.

When medical complications or reactions due to drug intolerance occurred, subject discontinuation in the study was left to the investigator's discretion. The follow-up period for serious AE collection extended to 30 days after the subject had taken the last dose of the investigational product. Serious AEs or AEs leading to study discontinuation were followed up until resolution. For the purpose of *post hoc* analyses, asthma-related AEs were defined as any symptom suggestive of asthma (eg, dyspnea, wheezing, cough, and chest discomfort). In addition, to ensure that no cases of anaphylaxis not specifically reported were missed, the safety database was reviewed by an independent blinded panel of 3 experts on the basis of the Clinical Criteria for Diagnosing Anaphylaxis²⁰ adapted to the context of SLIT. Any cases with sudden onset of an AE that by itself could meet the criteria for anaphylaxis or at least 2 concomitant AEs evocative of anaphylaxis involving 2 or more of the following body organ systems—respiratory, gastrointestinal, cardiovascular, and skin—were adjudicated.

Statistical analysis

All randomized subjects who received any dose of the study treatment or placebo (at least once) comprised the Safety Analysis Set. Safety data from all 8 studies were included in the safety database. Because of the heterogeneity in the Medical Dictionary for Regulatory Activities versions used across the development program, the coding of all AEs was updated and harmonized using Medical Dictionary for Regulatory Activities version 14.1.

For pooled safety analyses, treatment-emergent adverse events (TEAEs) were defined as any AE that started on or after the day of

the first dose of the study treatment and up to and including the 30th day after the last administration of the study treatment. All other AEs were classified as non-TEAEs.

TEAEs were analyzed descriptively. The rules for imputation of missing data and to calculate all derived variables (eg, the onset or duration of TEAEs, treatment duration...) were homogenized for all studies. Results were expressed in numbers and/or percentages of subjects reporting TEAEs. When a subject had experienced multiple episodes of any AE, the AE was counted once, or once by severity grade (if different severity grades were assigned).

The overall pooled analysis, referred to as "Overall pool," included all subjects who received the 5-grass pollen tablet or placebo in all studies regardless of the dose or treatment regimen, treatment duration, subject age, or study duration. Additional pooled analyses were performed: (1) all adults (≥ 18 years old at entry) who received the 300IR 5-grass pollen tablet or placebo from studies VO33.04DK, VO34.04, VO53.06 Year 1, VO60.08, and VO61.08USA referred to as "Adult pool," (2) all children and adolescents (age 5-17 years at entry) who received the 300IR 5-grass pollen tablet or placebo from studies VO52.06 and VO60.08 referred to as "Pediatric pool," and (3) population subsets according to sex, age, asthma and sensitization status at baseline.

RESULTS

Safety population

Overall, 2,512 subjects were enrolled in the clinical development program and 1,514 subjects were treated with 5-grass pollen sublingual tablets at doses of 100IR, 300IR, or 500IR (Figure 1). A total of 1,038 adults and 154 children and adolescents who received the 5-grass pollen tablet as indicated (ie, treatment with 300IR initiated 4 months before the pollen season and continued for its duration) comprised the adult pool (plus 840 placebo recipients) and the pediatric pool (plus 158 placebo recipients), respectively. The main reason for discontinuation was withdrawal of consent (6.7% of subjects in the active group and 5.4% in the placebo group). Ninety-three subjects were discontinued for AEs including 81 of the 1,514 (5.4%) who received active treatment. All randomized subjects were included in the safety analyses.

Demographic and baseline characteristics

Demographic and disease characteristics were similar in the active and placebo groups (Table I). At baseline, fewer than 20% of subjects had intermittent asthma (ie, not requiring treatment other than inhaled beta-2 agonists): 17% to 18% in adults and 21% to 22% in pediatrics. Most were polysensitized (ie, positive skin prick test to grass pollen and at least 1 other allergen): about 64% in adults and 60% in pediatrics.

Duration of exposure

In the natural field studies, 2 schedules of preseasonal (ie, 2-month or 4-month) treatment were evaluated depending on the studies. Both were tested with discontinuous treatment for 3 consecutive grass pollen seasons in the long-term study. Considering the geographic and yearly variations (duration of the pollen season and year-to-year variability), most subjects, whether adult or pediatric, were treated for a minimum of 3 months on average (taking into account discontinuations). More than 40% of subjects were treated for more than 6 months (Table II).

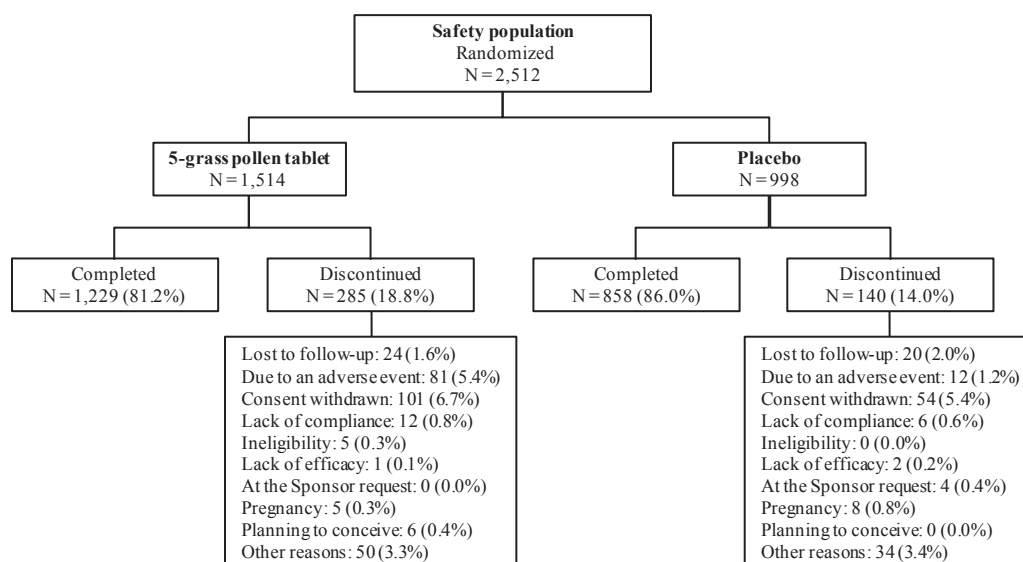


FIGURE 1. Subject disposition. Across the development program, subjects were randomized to receive once daily either placebo or active treatment (ie, 100IR, 300IR, or 500IR 5-grass pollen extract sublingual tablet). Reasons for discontinuations were monitored.

TABLE I. Demographic and baseline characteristics of the pooled populations—Safety Set

Characteristic	Overall pool		Adult pool		Pediatric pool	
	5-grass pollen tablet (N = 1,514)	Placebo (N = 998)	300IR tablet (N = 1,038)	Placebo (N = 840)	300IR tablet (N = 154)	Placebo (N = 158)
Age (y), mean $\pm$ SD	29.0 $\pm$ 10.48	28.8 $\pm$ 11.89	31.5 $\pm$ 9.39	32.1 $\pm$ 9.99	10.9 $\pm$ 3.36	11.6 $\pm$ 3.13
5-11 y, n (%)	87 (5.7)	74 (7.4)	—	—	87 (56.5)	74 (46.8)
Sex: male, n (%)	870 (57.5)	551 (55.2)	583 (56.2)	451 (53.7)	102 (66.2)	100 (63.3)
ARC duration (y),* mean $\pm$ SD	13.6 $\pm$ 9.92	14.2 $\pm$ 11.03	15.5 $\pm$ 10.38	15.9 $\pm$ 11.18	4.7 $\pm$ 2.59	5.2 $\pm$ 2.86
RRTSS,† mean $\pm$ SD	14.2 $\pm$ 1.79	14.3 $\pm$ 1.79	14.3 $\pm$ 1.82	14.4 $\pm$ 1.82	14.1 $\pm$ 1.79	14.0 $\pm$ 1.61
Intermittent asthma,‡ n (%)	242 (16.0)	183 (18.3)	179 (17.3)	149 (17.7)	32 (20.8)	34 (21.5)
Polysensitized, n (%)	927 (61.2)	633 (63.5)	663 (63.9)	538 (64.1)	92 (59.7)	95 (60.1)

N, Number of subjects per treatment group; n, number of subjects for whom data were available; RRTSS, Retrospective Rhinoconjunctivitis Total Symptom Score.

*Data were not available for subjects in study VO33.04DK (23 actively treated and 7 placebo-treated subjects).

†RRTSS was not assessed in studies VO33.04DK and VO56.07A.

‡Data were not available for 2 actively treated subjects.

TABLE II. Extent of exposure to study treatment in the pooled populations—Safety Set

Exposure (d), n (%)	Overall pool		Adult pool		Pediatric pool	
	5-grass pollen tablet (N = 1,514)	Placebo (N = 998)	300IR tablet (N = 1,038)	Placebo (N = 840)	300IR tablet (N = 154)	Placebo (N = 158)
≤ 7	18 (1.2)	4 (0.4)	16 (1.5)	4 (0.5)	0 (0.0)	0 (0.0)
8-30	65 (4.3)	19 (1.9)	46 (4.4)	18 (2.1)	6 (3.9)	1 (0.6)
31-90	52 (3.4)	36 (3.6)	56 (5.4)	31 (3.7)	1 (0.6)	5 (3.2)
91-181*	633 (41.8)	524 (52.5)	920 (88.6)	787 (93.7)	147 (95.5)	152 (96.2)
182-364	566 (37.4)	248 (24.8)	—	—	—	—
≥ 365	180 (11.9)	167 (16.7)	—	—	—	—

N, Number of subjects per treatment group; n, number of subjects exposed to treatment.

* ≥ 91 for adult and pediatric pools.

Safety in overall population and by age group

In all considered pools (Overall, Adult, and Pediatric), actively and placebo-treated participants reported TEAEs with similar frequencies (Table III). Fewer than 11% of subjects receiving any

dose ($<12\%$ in the placebo groups) had at least 1 severe TEAE. Treatment-related AEs reported in more than 10% of actively treated subjects were mild or moderate application-site reactions such as oral pruritus, throat irritation, or mouth edema. The

TABLE III. TEAEs and most frequent* treatment-related AEs in the pooled populations—Safety Set

Subjects reporting at least 1 AE	Overall pool		Adult pool		Pediatric pool	
	5-grass pollen tablet (N = 1,514)	Placebo (N = 998)	300IR tablet (N = 1,038)	Placebo (N = 840)	300IR tablet (N = 154)	Placebo (N = 158)
TEAE, n (%)	1,164 (76.9)	697 (69.8)	805 (77.6)	558 (66.4)	130 (84.4)	125 (79.1)
→ Mild	982 (64.9)	512 (51.3)	670 (64.5)	391 (46.5)	111 (72.1)	101 (63.9)
→ Moderate	656 (43.3)	381 (38.2)	438 (42.2)	293 (34.9)	70 (45.5)	66 (41.8)
→ Severe	152 (10.0)	113 (11.3)	102 (9.8)	100 (11.9)	17 (11.0)	8 (5.1)
Drug-related TEAE	880 (58.1)	200 (20.0)	606 (58.4)	158 (18.8)	82 (53.2)	31 (19.6)
Gastrointestinal disorders	706 (46.6)	82 (8.2)	486 (46.8)	70 (8.3)	68 (44.2)	6 (3.8)
Oral pruritus	385 (25.4)	44 (4.4)	257 (24.8)	39 (4.6)	34 (22.1)	3 (1.9)
Edema mouth	131 (8.7)	5 (0.5)	85 (8.2)	5 (0.6)	19 (12.3)	0 (0.0)
Tongue pruritus	129 (8.5)	7 (0.7)	81 (7.8)	6 (0.7)	9 (5.8)	1 (0.6)
Respiratory, thoracic, and mediastinal disorders	443 (29.3)	79 (7.9)	301 (29.0)	60 (7.1)	31 (20.1)	14 (8.9)
Throat irritation	321 (21.2)	34 (3.4)	218 (21.0)	24 (2.9)	16 (10.4)	8 (5.1)
Ear and labyrinth disorders	124 (8.2)	8 (0.8)	86 (8.3)	4 (0.5)	6 (3.9)	2 (1.3)
Ear pruritus	116 (7.7)	7 (0.7)	85 (8.2)	4 (0.5)	4 (2.6)	1 (0.6)

N, Number of subjects per treatment group; n, number of subjects reporting an event.

An individual subject could have reported more than 1 episode of an AE, but contributed only once or once by severity grade (if different severity grades were assigned).

In Long-term study VO53.06, 207 subjects randomized in 1 of the 2 active groups received placebo for 2 mo before starting active treatment.

*Reported in at least 5% of subjects in any treatment group.

safety profile in terms of severity and nature of events in children and adolescents was generally consistent with that observed in adults. Serious TEAEs were reported in less than 2% of subjects in both treatment groups. Of the serious events experienced by 22 actively treated subjects, 3 considered drug-related by the investigator were reported in adults (none in children/adolescents): (1) 2 application-site reactions (severe laryngeal edema and severe local allergic reaction) occurred 5 minutes after the first intake and resolved with corticosteroids and/or antihistamines. (2) The third event, diarrhea, was concomitant with an infection and resolved with antibiotics. Seventy-seven (5.1%) subjects receiving any dose (4.7% of adults and 4.5% of children/adolescents receiving 300IR) and 12 (1.2%) in the placebo group prematurely discontinued a study because of TEAEs. Application-site reactions such as oral pruritus or pharyngeal edema were the main reasons for discontinuation regardless of the age category. No deaths, intensive care unit admissions, onset of autoimmune disorders, or eosinophilic esophagitis were reported in any of the clinical studies. There were no reports of anaphylaxis and no epinephrine was used in any actively treated subject. No case of anaphylaxis was further identified after review of the safety database by the 3 independent experts.

Time to onset of treatment-related AEs

The time course of TEAEs (time to first occurrence) most commonly associated with SLIT (ie, the application-site reactions) was explored. Most occurred on the first day or during the first week of treatment and decreased in subsequent weeks (Figure 2). In children and adolescents, oral pruritus and mouth edema generally occurred after 1 day of treatment (Figure 2, B). In the Long-term study, application-site reactions were mainly reported on the first day of each treatment period and decreased on subsequent days and weeks and from year to year (Figure 3). The onset of treatment-related AEs according to the treatment-initiation scheme was further investigated in adults during the first 3 days. Adverse reactions, and specifically application-site

reactions, mostly of mild severity, were reported with a higher incidence in 871 adults who received a direct administration of 300IR from day 1 compared with the 155 ones who had an escalation phase (Figure 4, A-C). All pediatric subjects received treatment with a 3-day titration scheme (100IR/day 1, 200IR/day 2, and 300IR for the duration of therapy).

Safety by asthma and sensitization status

In the Overall pool, the safety profile of subjects with intermittent asthma at baseline (Active = 242, Placebo = 183) was similar to that in subjects without asthma (Active = 1,270, Placebo = 815) (Table IV). No notable differences in terms of incidence, nature and severity (data not shown) of TEAEs, and drug-related TEAEs were observed in subjects with or without asthma in both adult and pediatric study populations. As observed in the overall population, application-site reactions were more frequently reported in subjects with asthma.

AEs leading to discontinuation were also reported with similar incidence in all subsets. Of the 425 subjects with asthma, 101 (Active 54 of 242 [22%], Placebo 47 of 183 [26%]) reported an AE of asthma or a related symptom during treatment. The causality of such events was assigned to the treatment in 13 of 37 adults and in 3 of 14 pediatric subjects who received 300IR. Three actively treated participants (including one 9-year-old child) and 10 who received placebo (including one 8-year-old child) were administered oral corticosteroids for an AE suggestive of asthma. There were no serious drug-related AEs nor worsening of asthma in any subject with intermittent asthma who received the 5-grass pollen tablet.

Similar incidence rates of TEAEs were reported in subjects receiving any active dose or placebo regardless of sensitization status (monosensitized: Active = 587, Placebo = 364; polysensitized: Active = 927, Placebo = 633; Table IV), drug or non-drug-related TEAE status, or serious versus nonserious TEAE status. Actively treated subjects showed no difference in withdrawal rates regardless of sensitization status

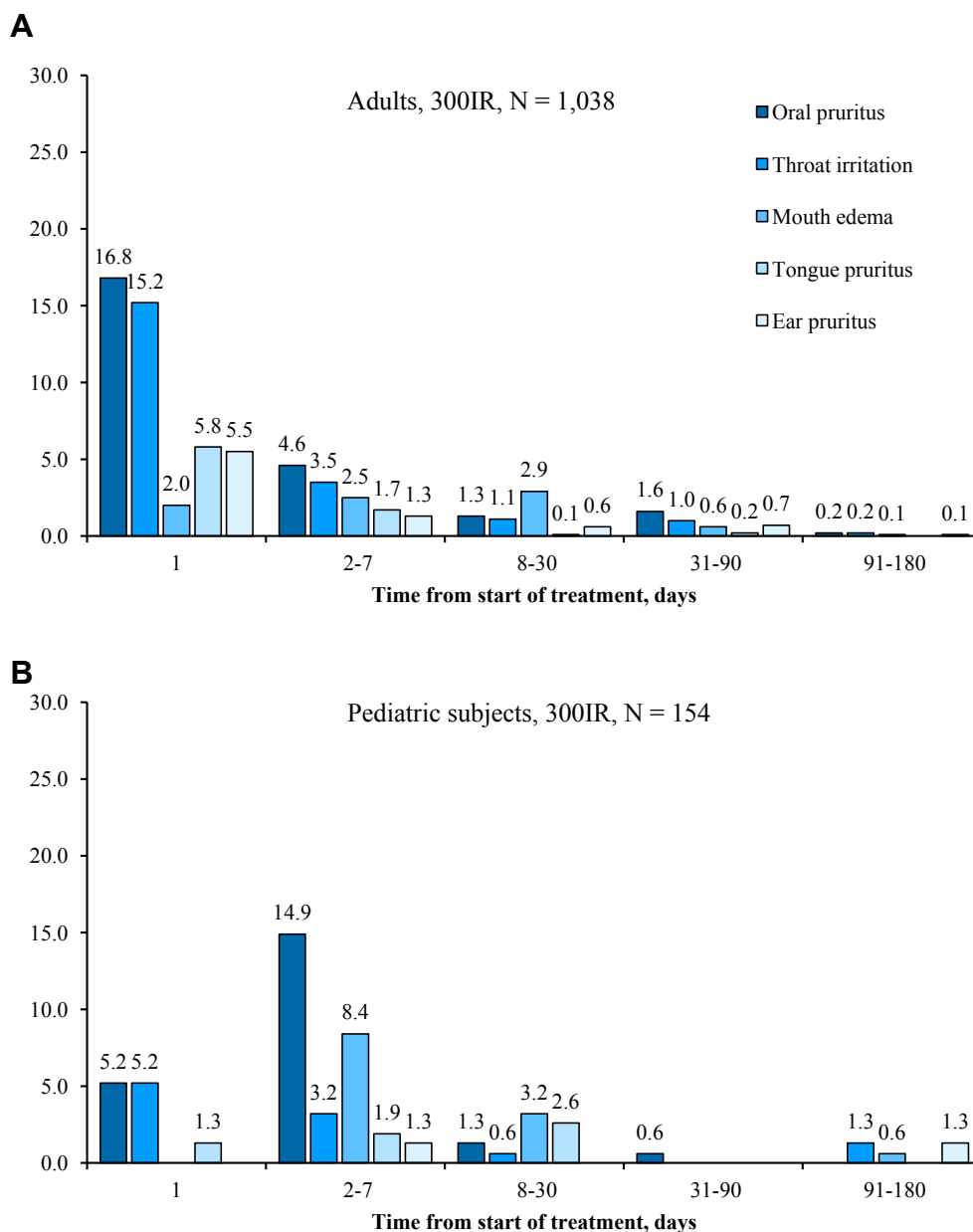


FIGURE 2. Incidence of most commonly reported treatment-related AEs by time to onset in adults treated with 300IR 5-grass pollen tablet (**A**) and children and adolescents treated with 300IR 5-grass pollen tablet (**B**). The y-axis refers to the percentage of subjects with first occurrence of events.

(monosensitized: 31 subjects [5.3%] or polysensitized: 46 subjects [5.0%]).

DISCUSSION

The safety experience with the 5-grass pollen sublingual tablet (more than 250,000 tablets administered to study participants) in this analysis will be discussed in the context of the safety profile of SCIT, which still represents the standard modality of immunotherapy,² specifically in the United States, for patients suffering from ARC in whom treatment with symptomatic medications is ineffective, poorly tolerated, or unwanted.⁷ Historically, SCIT has been associated with fatal and life-threatening reactions in exceptional

cases and recent data indicate a decrease in these events.^{21,22} With SLIT, pooled data analysis from the full development program demonstrated a favorable safety profile with the 5-grass pollen tablet in adult and pediatric subjects. As expected with this product, most adverse reactions in actively treated subjects were related to the route of administration, particularly oral pruritus and throat irritation. Application-site reactions were mostly mild or moderate, most often reported during the first week of treatment and decreased over time during the first preseasonal and coseasonal treatment period and over the subsequent preseasonal and coseasonal treatment periods. They rarely led to treatment discontinuation. Fewer than 2% of subjects reported serious AEs. Two serious reactions (laryngeal edema and local allergic reaction considered severe by the

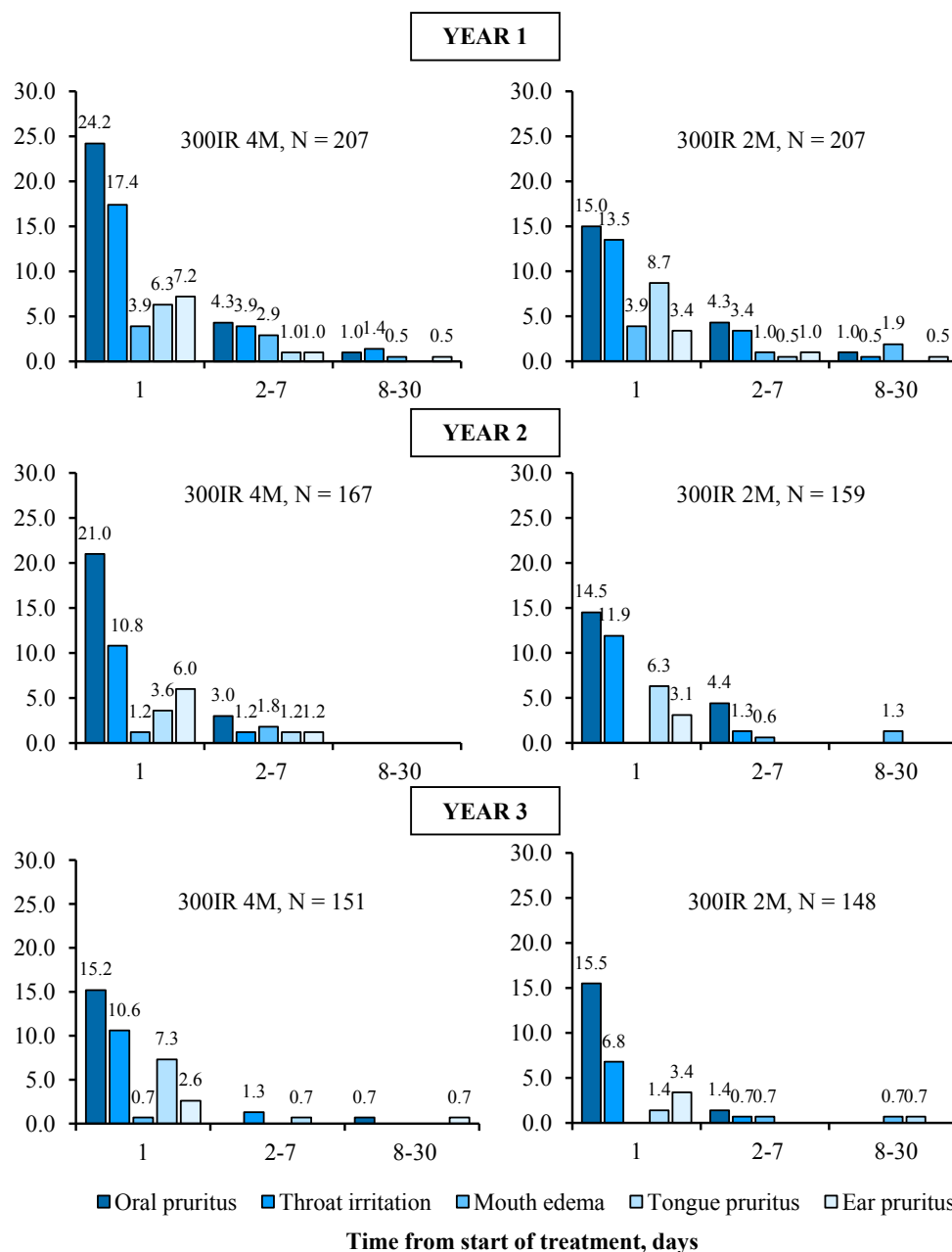


FIGURE 3. Incidence of most common treatment-related AEs reported over years by time to onset in subjects included in the Long-term study. The y-axis refers to the percentage of subjects with first occurrence of events. *4M*, 4-Month preseasonal treatment regimen; *2M*, 2-month preseasonal treatment regimen.

investigator) occurred soon after the first dose while the subject was under medical supervision. Importantly, none of the serious events were reports of anaphylaxis, and no epinephrine was used in any subject receiving active treatment. The safety profile was consistent between the subjects without and subjects with controlled asthma.

Overall, treatment with 5-grass pollen sublingual tablet was well tolerated in adults, adolescents, and children and in both monosensitized and polysensitized study subjects.

The favorable safety profile compared with SCIT may be partially explained by the nature of the immune response in the oral cavity: capture of the allergens by oral tolerogenic dendritic

cells within 15 to 30 minutes and without any significant exposure to blood immune cells.^{23,24} In addition, the oral and sublingual mucosa contain a limited number of proinflammatory cells such as mast cells that explains the lower and more localized allergen reactivity than that observed in the skin.²⁴

The safety profile of the 5-grass pollen sublingual tablet observed across the clinical development program supports the well-identified profile described in the scientific literature for SLIT in general, with any allergen. Based on relevant evidence-based information published since 2009, the World Allergy Organization Position Paper 2013 Update states that most AEs

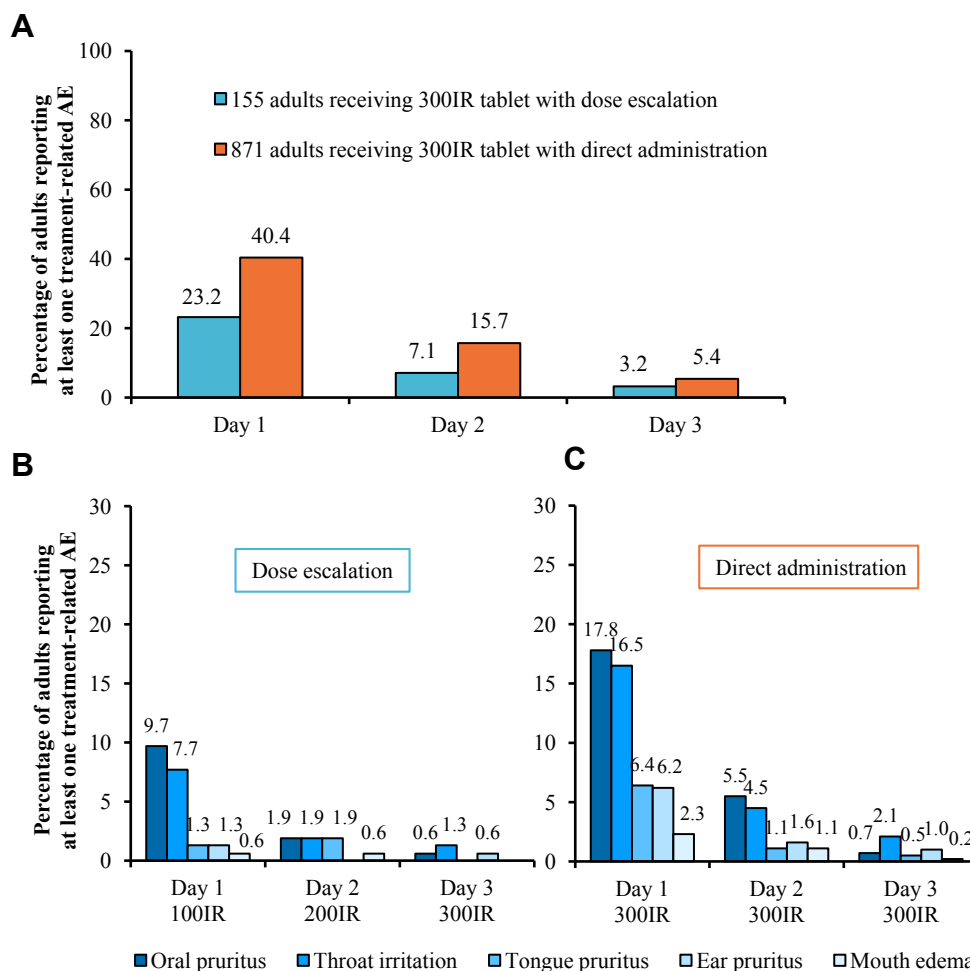


FIGURE 4. Percentages of adults reporting treatment-related AEs according to the treatment-initiation scheme. Overall TEAEs during the first 3 days of administration (A). Most frequent TEAEs during the first 3 days with the escalation phase (B) or with direct administration (C).

associated with SLIT are self-limited, local reactions (oral and gastrointestinal) most commonly occurring during the beginning of treatment and usually resolve within a few days or weeks without any medical intervention (eg, dose adjustment and medication).⁸ More specifically, the safety profile of the 5-grass pollen tablet is consistent with the profile of the timothy grass tablet, which mainly induces local allergic reactions early in treatment and generally of mild or moderate intensity.^{25,26} With both 5-grass and timothy SLIT tablets, adverse reactions decreased over the subsequent treatment periods of long-term studies.^{13,27}

No anaphylactic shock has been reported with either of the 2 tablets. In the published literature, only a few cases of anaphylaxis have been described with SLIT, and none with fatalities.^{8,23,28} Nine systemic allergic reactions were reported in clinical trials with the single grass tablet.^{25,26} Six of the cases were experienced with the first dose taken under medical supervision and none was considered serious or severe. No cases of anaphylaxis or systemic allergic reactions or fatalities were reported in the 1,514 subjects receiving the 5-grass tablet at any dose. In addition, none of them received epinephrine to treat severe allergic reactions in contrast to other studies conducted

with the timothy grass tablet.^{25,26,29} Nevertheless, to prevent and mitigate the potential risk for severe anaphylaxis or laryngopharyngeal reactions with the 5-grass tablet, a specific action plan was implemented including a surveillance system involving signal detection and data analysis, and safe use measures described in the labeling.

As for any SLIT products, the first dose of 5-grass tablet is administered under medical supervision and the patient monitored for at least 30 minutes.^{19,30,31} In the United States where SLIT is a novel route of AIT, prescription of epinephrine is required in the Prescribing Information.^{19,32} Also, in the United States, direct administration of 300IR on the first day of treatment for adults is recommended despite a slightly greater incidence of application-site reactions at treatment initiation compared with a dose-escalation scheme.

The safety profile of 5-grass tablet administered to 154 children and adolescents did not differ from that observed in adults. The safety and convenience of administration of this treatment as compared with SCIT might provide a better alternative for patients of this age category. Clinical trials with the timothy grass tablet led to similar conclusions.^{33,34} Two postauthorization safety studies performed in Germany including 5- to 17-year-old

TABLE IV. Overview of TEAEs in pooled subpopulations by asthma status or sensitization status

	Subjects with asthma (N = 425*)		Subjects without asthma (N = 2,085*)		Monosensitized subjects (N = 951†)		Polysensitized subjects (N = 1,560†)	
	5-grass pollen tablet (N = 242)	Placebo (N = 183)	5-grass pollen tablet (N = 1,270)	Placebo (N = 815)	5-grass pollen tablet (N = 587)	Placebo (N = 364)	5-grass pollen tablet (N = 927)	Placebo (N = 633)
Overall pool								
TEAE, n (%)	197 (81.4)	147 (80.3)	965 (76.0)	550 (67.5)	453 (77.2)	247 (67.9)	711 (76.7)	449 (70.9)
Drug-related TEAE	144 (59.5)	39 (21.3)	734 (57.8)	161 (19.8)	348 (59.3)	76 (20.9)	532 (57.4)	124 (19.6)
Serious TEAE	2 (0.8)	4 (2.2)	20 (1.6)	7 (0.9)	9 (1.5)	7 (1.9)	13 (1.4)	4 (0.6)
Serious drug-related TEAE	0	0	3 (0.2)	0	2 (0.3)	0	1 (0.1)	0
TEAE leading to premature withdrawal	14 (5.8)	2 (1.1)	63 (5.0)	10 (1.2)	31 (5.3)	8 (2.2)	46 (5.0)	4 (0.6)
	N = 328*		N = 1,548*		N = 676†		N = 1,201†	
	300IR tablet (N = 179)	Placebo (N = 149)	300IR tablet (N = 857)	Placebo (N = 691)	300IR tablet (N = 375)	Placebo (N = 301)	300IR tablet (N = 663)	Placebo (N = 538)
Adult pool								
TEAE, n (%)	145 (81.0)	118 (79.2)	658 (76.8)	440 (63.7)	298 (79.5)	192 (63.8)	507 (76.5)	365 (67.8)
Drug-related TEAE	106 (59.2)	32 (21.5)	498 (58.1)	126 (18.2)	225 (60.0)	60 (19.9)	381 (57.5)	98 (18.2)
Serious TEAE	0	2 (1.3)	13 (1.5)	3 (0.4)	6 (1.6)	3 (1.0)	7 (1.1)	2 (0.4)
Serious drug-related TEAE	0	0	3 (0.4)	0	2 (0.5)	0	1 (0.2)	0
TEAE leading to premature withdrawal	12 (6.7)	1 (0.7)	37 (4.3)	8 (1.2)	16 (4.3)	6 (2.0)	33 (5.0)	3 (0.6)
	N = 66		N = 246		N = 125		N = 187	
	300IR tablet (N = 32)	Placebo (N = 34)	300IR tablet (N = 122)	Placebo (N = 124)	300IR tablet (N = 62)	Placebo (N = 63)	300IR tablet (N = 92)	Placebo (N = 95)
Pediatric pool								
TEAE, n (%)	28 (87.5)	28 (82.4)	102 (83.6)	97 (78.2)	53 (85.5)	49 (77.8)	77 (83.7)	76 (80.0)
Drug-related TEAE	17 (53.1)	6 (17.6)	65 (53.3)	25 (20.2)	36 (58.1)	11 (17.5)	46 (50.0)	20 (21.1)
Serious TEAE	0	1 (2.9)	1 (0.8)	1 (0.8)	0	1 (1.6)	1 (1.1)	1 (1.1)
Serious drug-related TEAE	0	0	0	0	0	0	0	0
TEAE leading to premature withdrawal	1 (3.1)	1 (2.9)	6 (4.9)	1 (0.8)	2 (3.2)	2 (3.2)	5 (5.4)	0

n, Number of subjects reporting an event.

An individual subject could have reported more than 1 episode of an AE, but contributed only once or once by severity grade (if different severity grades were assigned). In Long-term study VO53.06, 207 subjects randomized in 1 of the 2 active groups received placebo for 2 mo before starting active treatment.

*Asthma status at study entry was missing for 2 subjects.

†Sensitization status at study entry was missing for 1 subject.

subjects (N = 920) confirmed the safety profile established in the clinical development program.^{35,36} Two ongoing observational studies, one conducted in 5- to 9-year-old children in Europe and one in 10- to 65-year-old subjects in the United States, will substantially contribute to the product knowledge.

Allergic asthma is often associated with rhinoconjunctivitis in grass pollen allergic patients. In the clinical program, 20% of subjects had intermittent asthma (Global Initiative for Asthma treatment step 1) at study entry. No difference in the 5-grass tablet safety profile was observed whether subjects had asthma or not. No worsening of asthma was observed in subjects with asthma. These findings are consistent with those of other published studies.³⁷ The data remain limited to subjects with asthma requiring treatment level step 1 (mild asthma) or those with controlled asthma. Accordingly and because patients with severe, unstable, or uncontrolled asthma were reported to be at increased risk for systemic reactions with SCIT,^{7,22} grass pollen SLIT tablets are contraindicated in these patients. Conversely, according to worldwide organization recommendations, AIT may actually reduce the risk for the development of asthma in patients with allergic rhinitis due to seasonal or perennial allergy.^{1,7,8} Because SLIT has been associated with a reduced risk of systemic allergic

reactions when compared with SCIT,²³ it might be considered as a safer treatment option in patients with allergic asthma. In a phase I study, a SLIT house dust mite tablet was found safe at doses up to 6-fold higher than 300IR in subjects with house dust mite associated asthma of higher severity requiring corticosteroid therapy.³⁸ Clinical studies in subjects with moderate or severe asthma requiring corticosteroid therapy may be warranted to support the indication of the 5-grass tablet in such patients. Interestingly, a recent subgroup analysis in grass pollen allergic children and adolescents with asthma from a postmarketing study with the 5-grass tablet has shown that symptoms of asthma were improving after 1 and 2 years of treatment.³⁹

Sensitization to multiple allergens is commonly identified in patients with ARC.^{40,41} Consistently, across the clinical development program of 5-grass tablet, more than 60% of subjects were polysensitized to nongrass species antigens. In the polysensitized study subjects, both adult and pediatric subjects demonstrated a similar safety profile to monosensitized subjects. This finding is consistent with other SLIT studies with grass or other allergens, suggesting that the 5-grass tablet may be administered safely in grass pollen allergic patients sensitive to other unrelated allergens.^{40,42-44}

The 300IR 5-grass pollen sublingual tablet is a safe immunotherapy alternative to SCIT and appears to confer benefit to grass pollen allergic adult and pediatric patients in terms of both therapeutic effectiveness and improved quality of life.^{11,25} This analysis demonstrates that 5-grass SLIT tablet is a safe immunotherapy product suitable for patients with intermittent asthma. No worsening of asthma or anaphylaxis was reported in any subject with asthma who received the 5-grass pollen tablet. The extensive global postmarketing experience since 2008 confirms the safety and tolerability profile observed in all subgroups of patients, including the patients with asthma.^{35,45}

Acknowledgments

Medical writing and editorial assistance was provided by Josiane Cognet-Sicé and Kathy Abiteboul and biostatistical assistance was provided by Armelle Montagut, all employees of Stallergenes Greer.

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TABLE E1. Summary of the 5-grass pollen tablet clinical trials included in the pooled safety analysis

Study	Location	Population	Treatment	Exposed patients (n)	Treatment duration
VO33.04DK ^{E1}	Denmark	Patients allergic to grass pollen	100-500IR	23	2 wk (omitting weekends for 10 treatment days in total)
Phase I			Placebo	7	
2006		Age 18-50 y	Total	30	
VO34.04 ^{E2}	10 EU countries: Austria, Bulgaria, Czech Republic, Denmark, France, Germany, Hungary, Italy, Slovakia, Spain	Patients with grass pollen –related ARC with or without mild asthma	500IR (4M)	160	~4 mo preseasonally and ≥1 mo coseasonally
VO40.05			300IR (4M)	155	
Phase IIb/III			100IR (4M)	157	
2005-2006		Age 18-45 y	Placebo	156	
			Total	628	
VO52.06 ^{E3}	5 EU countries: Denmark, France, Germany, Poland, Spain	Patients with grass pollen –related ARC with or without mild asthma	300IR (4M)	139	~4 mo preseasonally and ≥1 mo coseasonally
Phase III			Placebo	139	
2007		Age 5-17 y	Total	278	
VO53.06 ^{E4,E5}	10 countries: Austria, Canada, Czech Republic, Denmark, France, Germany, Italy, Poland, Russia, Slovakia	Patients with grass pollen –related ARC with or without mild asthma	300IR (4M)	207	5 y: ~4 mo preseasonally and ≥1 mo coseasonally over 3 y, followed by 2 y without study treatment
Phase III			300IR (2M)	207	
2007-2011		Age 18-50 y	Placebo	219	
			Total	633	
VO56.07A ^{E6}	Austria (allergen exposure chamber)	Patients with grass pollen –related ARC without asthma	300IR	45	~4 mo
Phase I			Placebo	44	
2007-2008		Age 18-50 y	Total	89	
VO60.08 ^{E7}	5 EU countries: Czech Republic, France, Italy, the Netherlands, Spain	Patients with grass pollen –related ARC	300IR (2M)	188	~2 mo preseasonally and ≥1 mo coseasonally
Phase III			Placebo	193	
2009		Age 12-65 y	Total	381	
VO61.08 ^{E8}	USA (51 sites)	Patients with grass pollen –related ARC with or without mild asthma	300IR (4M)	233	~4 mo preseasonally and ≥1 mo coseasonally
Phase III			Placebo	240	
2009		Age 18-65 y	Total	473	

2M or 4M, patients received active treatment starting 2 or 4 mo, respectively, before the pollen season; ARC, allergic rhinoconjunctivitis; IR, index of reactivity.

Subjects in the 300IR (Studies VO34.04 and VO52.06) and the 500IR (Study VO34.04) treatment groups underwent a dose-escalation phase wherein a 100IR dose was taken on the first day, then increased by 100IR/d until the final randomized dose was reached.

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