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## Persistence of treatment with 5-grass pollen tablets in patients with allergic rhinitis: a real-life study

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### ABSTRACT

**Background:** In patients with allergic rhinitis, treatment adherence to allergen immunotherapy varies greatly in randomized and real-life studies.

**Objective:** To evaluate the use of a 5-grass pollen tablet as sublingual immunotherapy, its treatment persistence, and the reasons for discontinuation in a real-life clinical setting.

**Methods:** This multicenter, prospective, open-label, noncontrolled observational study evaluated the use of sublingual immunotherapy with a 5-grass pollen tablet in a cross-sectional population of patients ( $\geq 5$  years old) with grass pollen-induced allergic rhinitis with or without asthma. The primary objective was to determine the percentage of patients persisting with treatment across 1 season in a pre-co-seasonal scheme. Secondary objectives included evaluation of reasons for treatment discontinuation, safety and adverse events; effectiveness (based on physician and patient assessments), and treatment compliance.

**Results:** The study included 196 patients (49.2% male, mean age 27.5 years, range 5.3–65.7 years), with treatment provided by 47 participating physicians. Sixty-seven percent of patients had polysensitivity and 32% had coexistent asthma. On average, patients were treated for 7 months with the 5-grass pollen tablet. After 1 month, 85% of all patients persisted with treatment, and 70% persisted after 7 months. Treatment discontinuation was due chiefly to known side effects (mild to moderate local allergic reactions). Most patients reported symptom improvement; 80% of all patients intended to continue treatment next season. **Conclusion:** Most patients with allergic rhinitis treated pre-co-seasonally with a 5-grass pollen tablet persisted with treatment after the first pollen season. Patients were willing to continue their treatment in the following season owing to improvement of symptoms.

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### Introduction

The prevalence of respiratory allergies has increased in recent decades. In Europe and North America, 1 in 4 of the population is affected by respiratory allergies (allergic rhinitis [AR] and allergic asthma), and the prevalence is increasing in most developing countries.<sup>1</sup> It is reported that more than 40% of patients with AR have asthma and 80% of patients with asthma have AR.<sup>2</sup> Furthermore, AR must be considered a risk factor for asthma because patients with AR have been found to be 3.5 times more likely to have asthma than the ordinary population.<sup>3–6</sup>

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Although allergen avoidance is recommended when possible, many patients with AR require medical treatment, primarily symptomatic relief, and increasingly the use of allergen immunotherapy (AIT) to modulate allergen responses.<sup>7,8</sup> AIT given by subcutaneous injection (subcutaneous immunotherapy) or by sublingual administration (sublingual immunotherapy; SLIT) has proven efficacy in decreasing symptoms and medication use in patients with AR<sup>9–14</sup> and are recommended in European Union, US, and international guidelines.<sup>7,8,11</sup>

Although Di Bona et al<sup>15</sup> recently asserted that grass pollen SLIT tablets had little benefit in alleviating symptoms, Devillier et al<sup>16</sup> in 2014 concluded that grass pollen SLIT tablets had a greater mean relative clinical impact than second-generation antihistamines and montelukast and a mean relative clinical impact similar to nasal corticosteroids.

As described by Cramer et al,<sup>17</sup> medication compliance can be defined as “the extent to which a patient acts in accordance with

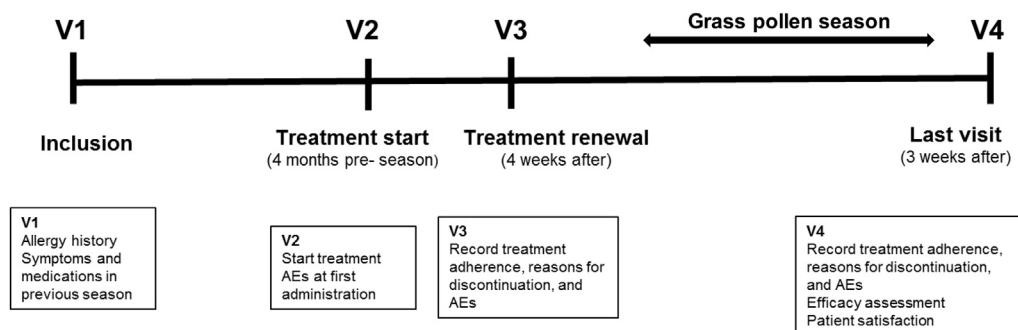


**Figure 1.** Study design. AEs, adverse events; V1, visit 1; V2, visit 2; V3, visit 3; V4, visit 4.

the prescribed interval, and dose of a dosing regimen,” whereas medication persistence (ie, continuing treatment for the prescribed duration) can be defined as “the duration of time from initiation to discontinuation of therapy.” For AIT, although compliance is usually high in clinical studies, data suggest that compliance and persistence are poorer in routine clinical practice.<sup>18–30</sup> Because AIT involves treatment for successive seasons, usually at least 3 years, some decreased compliance and loss of persistence can be expected, but this clearly compromises treatment effectiveness. Decreased compliance can occur for many reasons, including misunderstanding, patient dissatisfaction, and poor tolerability.<sup>24,26,28,29</sup>

There are limited data on treatment persistence of AIT in real-life settings from prospective studies. The purpose of this observational study was to evaluate in a real-life setting treatment persistence using a 5-grass pollen tablet containing freeze-dried allergen extracts of 5 grasses: cocksfoot (*Dactylis glomerata*), meadow grass (*Poa pratensis*), rye grass (*Lolium perenne*), sweet vernal grass (*Anthoxanthum odoratum*), and timothy grass (*Phleum pratense*). The efficacy and safety of this 5-grass pollen tablet has been reported previously in randomized controlled trials and post-authorization studies.<sup>31–38</sup>

## Methods

### Study Design

This was a multicenter, prospective, open-label, noncontrolled real-life observational study conducted in the Netherlands. The primary objective was to determine the percentage of subjects using 5-grass pollen tablets in a pre-co-seasonal scheme across the 2012 grass pollen season. This is a discontinuous pre-co-seasonal SLIT, in which a 5-grass pollen tablet with an index of reactivity (IR) of 300 is taken once daily, with treatment initiated approximately 4 months before the onset of the pollen season and continued until the end of the season. Secondary objectives were to determine reasons for treatment discontinuation, assess safety and adverse events (AEs), describe effectiveness of treatment based on physician and patient assessments, and describe treatment compliance by reporting how often the patient took the 5-grass pollen tablet as prescribed. Male and female subjects at least 5 years old with grass pollen-induced rhinitis (with or without conjunctivitis) were included. For inclusion, subjects were required to have symptoms of AR and confirmatory positive skin test and/or serum-specific IgE reactions to grass pollens and judged by the treating physician as showing an unsatisfactory response to previous symptomatic therapy. Exclusion criteria were those contraindications as stated in the Summary of Product Characteristics (SPC) for the 5-grass pollen tablet.<sup>39</sup>

The study protocol was reviewed and approved by local regulatory authorities and by the ethics board of the participating

centers, if required, and was conducted in accordance with the Declaration of Helsinki and guidelines on good clinical practice. Written informed consent was obtained from all patients before study enrolment and for minors was obtained from next of kin, caregivers, or guardians.

### Treatment, Assessments, and Analyses

At screening (visit 1; V1), subjects who had visited their physician during the grass pollen season of 2011 were assessed for study inclusion, and baseline data were collected. Data included allergy history and clinical symptoms, confirmatory allergologic examination, previous AIT treatments, and symptoms and medication use in the previous grass pollen season. Asthma diagnosis was based on the physician's clinical judgment. Symptoms were graded as mild, moderate, or severe in accordance with Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations.<sup>4,7</sup> After inclusion, SLIT with 5-grass pollen tablets was initiated at a second visit (V2), 4 months before the expected start of the grass pollen season of 2012. Grass pollen generally flower from May to August in the Netherlands. At this first treatment visit, after administration of the first 5-grass tablet of 100 IR under medical supervision, patients were monitored for 30 minutes, in accordance with the SPC.<sup>39</sup> If AEs occurred, they were described in detail (date of occurrence, description, and seriousness) in the visit questionnaire of V2, the intensity was graded by the patient (mild, moderate, or severe), and the causal relation was assessed by the investigator. AEs were classified a posteriori using Medical Dictionary for Regulatory Activities coding (MedDRA, Version 17.0, March 2014). Then, subjects self-administered the 5-grass pollen tablets once daily before and then during the pollen season, according to the SPC.

Subjects were reviewed after 1 month (visit 3; V3) and then after the end of the pollen season (visit 4; V4; ie, after 7 months of treatment). The study design is shown in Figure 1. At V3 and V4, subjects were questioned about treatment persistence, and any AEs and reasons for discontinuation were recorded from the questionnaire, which included questions regarding specific reasons for discontinuation (side effects, insufficient symptom improvement, patient has not returned or was lost to follow-up, patient wants no further treatment). At V4, physician and patient assessments of effectiveness were performed based on whether they believed the condition was improved, unchanged, or deteriorated; symptom rating at the end of the current pollen season (compared with previous seasons); and indication of intention to continue with treatment for the following season.

Persistence, safety, and effectiveness analyses included all subjects in the full analysis set (FAS) who received at least one 5-grass pollen tablet (at V2). The FAS persistent population (FAS-P) consisted of subjects who completed the treatment period and did not declare treatment discontinuation at V4; and the FAS discontinued

**Table 1**  
Subject demographics<sup>a</sup>

| Variable                            | FAS (n = 196) | FAS-P (n = 137) | FAS-D (n = 59) |
|-------------------------------------|---------------|-----------------|----------------|
| Sex                                 |               |                 |                |
| Male                                | 95 (49.2%)    | 72 (52.9%)      | 23 (40.4%)     |
| Female                              | 98 (50.8%)    | 64 (47.1%)      | 34 (59.6%)     |
| Age (y)                             |               |                 |                |
| Mean ± SD                           | 27.5 ± 14.3   | 27.7 ± 14.6     | 27.0 ± 13.6    |
| Range                               | 5.3–65.7      | 5.3–65.7        | 5.4–65.3       |
| BMI (kg/m <sup>2</sup> ), mean ± SD | 23.1 ± 4.8    | 23.0 ± 4.9      | 23.1 ± 4.4     |
| Asthma, %                           | 31.8          | 32.4            | 30.5           |
| Polysensitivity, %                  | 67.3          | 64.2            | 74.6           |
| Concomitant AIT, %                  | 14.3          | 10.9            | 22.0           |

Abbreviations: AIT, allergen immunotherapy; BMI, body mass index; FAS, full analysis set; FAS-D, discontinued-treatment population; FAS-P, persistent-treatment population.

<sup>a</sup>For 3 patients, age and sex data are unknown.

population (FAS-D) was comprised of subjects who were lost to follow-up, withdrew during the study, or declared having discontinued treatment at V3 or V4.

For each subject, the questionnaires were returned to the clinical research organization (Delta Consultants, Eybens, France) for analysis. In this observational study, no formal statistical analysis was planned, and only descriptive analyses were performed using SAS 9.2 (SAS Institute, Cary, North Carolina). Quantitative variables are described as mean, SD, median, range, and 95% confidence intervals, and qualitative variables are described as absolute frequency and percentage.

## Results

### Patient Disposition

Two hundred six patients were screened and prescribed the 5-grass pollen tablet at V1. Subjects who took at least the first 5-grass pollen tablets (at V2) constituted the FAS. Ten patients did not return for administration of the first dose given under physician supervision. Therefore, the study enrolled 196 patients for the FAS (FAS-P, n = 137; FAS-D, n = 59); 49.2% were male, with a mean age of 27.5 years (range 5.3–65.7 years). Most subjects (71.4%) were older than 17 years and 30 were children younger than 12 years. Treatment was provided by 47 participating physicians, most of whom were ear, nose, and throat specialists (63.8%), and 21.3% were allergists, 8.5% were primary care physicians, and 6.4% were pediatricians. The median number of subjects enrolled was 4 per physician (range 1–13). The distribution of physician specialty was similar between the FAS-D and FAS-P.

Asthma was reported in 31.8% of subjects and was graded as mild (72.6%), moderate (24.2%), or severe (3.2%). Most subjects (67.3%) had polysensitivity, most commonly to birch pollen (34.7%) and house dust mites (33.2%). Most subjects (98%) were prescribed the 5-grass pollen tablet for the first time; another immunotherapy was used by 28 subjects (14.3%; 22.0% in the FAS-D and 10.9% in the FAS-P). An overview of the study population demographics is presented in Table 1.

Symptoms during the previous grass pollen season consisted of nasal, eye, and lung complaints. Nasal complaints were reported by 99% and were rated as moderate or severe for 94.4% of subjects. More than 90% reported eye complaints, with moderate or severe symptoms reported in 70.5%. Only 41.3% of subjects reported lung symptoms; 17.9% regarded them as moderate or severe. Distribution of nasal, lung, and eye symptoms was similar between the FAS-P and FAS-D, except for severe eye symptoms (29.9% and 39.0% respectively). Almost all subjects (190, 96.9%) had used symptomatic medication during the previous grass pollen season: oral antihistamines (84.2%), nasal corticosteroids (71.6%), eye drops

(32.1%), bronchial  $\beta_2$ -agonists (18.9%), corticosteroids (14.2%), and other medications (10.0%).

### Persistence

For the primary objective, from V2 to V4, of the overall FAS, 137 subjects persisted with therapy (FAS-P), whereas 59 subjects (FAS-D) were lost to follow-up (n = 15) or discontinued treatment (n = 44). Patient flow is presented in Figure 2. After 1 month (V3), 167 subjects (85.2%) were still using the 5-grass pollen tablet, whereas 29 subjects (14.8%) had discontinued treatment. After 7 months (V4), more than two thirds of subjects (137, 69.9%) reported treatment persistence (Table 2). Subjects in the FAS-D had a shorter treatment duration (median 22 days; range 1–187 days) than those in the FAS-P who completed the study (median, 273 days [8.97 months], range 127–431 days [4.2–14.2 months]).

Reasons for treatment discontinuation are presented in Table 3. The main reason for treatment discontinuation in the FAS-D was side effects, with 20 subjects stating this as the reason at V3 and 13 subjects at V4. A smaller number of subjects discontinued because they did not want any further treatment. Overall, 33 of 59 subjects (55.9%) in the FAS-D (accounting for 16.8% of the total study population) discontinued owing to an AE. Most subjects in this study (80.6% of the FAS and 96% of the FAS-P) chose to continue with treatment during the next grass pollen season.

### Treatment Effectiveness

At the end of the pollen season, 17.4% of subjects reported no nasal symptoms and 34.8% reported moderate or severe symptoms. Eye complaints were evaluated in 153 subjects overall. None were reported for 53 subjects (34.6%). Of the 148 subjects who evaluated their lung complaints, 73.6% reported none, whereas moderate or severe lung complaints were reported by 8.1% of subjects (Table 4). As might be expected, when present, symptoms rated as moderate or severe occurred more frequently for subjects in the FAS-D. Overall, the number of subjects without nasal, eye, or lung symptoms was larger in the season treated with the 5-grass pollen tablet compared with the previous grass pollen season, whereas the severity of the nasal, eye, and lung complaints was lower.

Symptomatic medication was used by 124 subjects (79.5%) during the grass pollen season (16 subjects in the FAS-D [84.2%] and 108 subjects in the FAS-P [78.8%]). Agents used were oral antihistamines (77.4% of subjects), nasal corticosteroids (53.2%), eye drops (20.2%), bronchial  $\beta$ -agonists (13.7%), and bronchial corticosteroids (8.9%). There was no major difference in symptomatic medication use between the FAS-D and FAS-P. Compared with the previous grass pollen season, fewer subjects used symptomatic medication (79.5% vs 96.9%).

### Other Assessments

At V4, physician assessment of subject status compared with the previous year was performed. Improvement was reported for 73.4% of subjects available for assessment, with a clinically meaningful improvement in the FAS-P (108 subjects, 79.4%) compared with the FAS-D (5 subjects, 27.8%). Surprisingly, worsening status was reported by physicians only for 4 subjects, who were in the FAS-P (2.9%). No change was reported in 72.2% of those subjects discontinuing treatment compared with 17.6% in those persisting with therapy. Subject status self-assessment was comparable with the physician assessment, with 72.9% of all subjects reporting improvement, 23.9% reporting no change, and 3.2% reporting worsening (5 subjects, in the FAS-P). The FAS-P reported a larger proportion of disease improvement, with 79.4% reporting improvement compared with 26.3% in the FAS-D.

Treatment compliance was high throughout the study; 74% of subjects reported “always” taking the 5-grass pollen tablet daily,

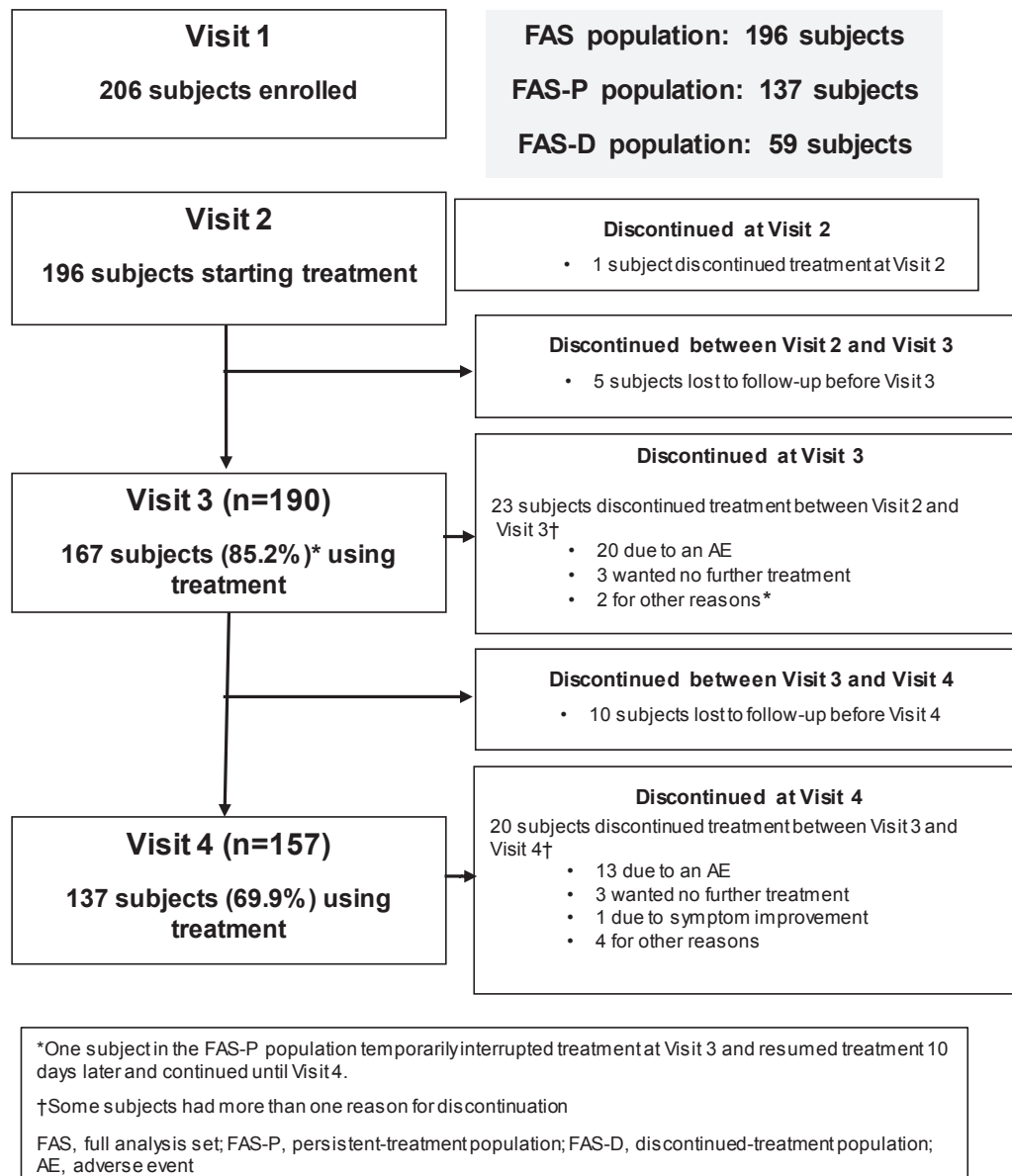


Figure 2. Study flow.

whereas 23% reported doing so “most of the time.” As expected, compliance was better in the FAS-P (100%, “always” or “most of the time”) than in the FAS-D (81%, “always” or “most of the time”). Most subjects chose to continue with treatment during the next grass pollen season, with the main reasons for continuing being a decrease in symptoms and/or symptomatic medication intake (61%) and the expectation of an increased effect the next year (55%).

**Table 2**  
Persistence with 5-grass pollen tablets throughout study<sup>a</sup>

| Variable          | FAS (n = 196) | FAS-D (n = 59) |
|-------------------|---------------|----------------|
| Visit 2 (day 1)   | 195 (99.5%)   | 58 (98.3%)     |
| Visit 3 (at 1 mo) | 167 (85.2%)   | 31 (52.5%)     |
| Visit 4 (at 7 mo) | 137 (69.9%)   | 0 (0%)         |

Abbreviations: FAS, full analysis set; FAS-D, discontinued-treatment population.

<sup>a</sup>Percentages are based on the number of patients in the corresponding FAS at the respective visit who discontinued treatment. One patient temporarily interrupted treatment at visit 3, resumed treatment 10 days later, and continued until visit 4.

Slightly more than half of all subjects (57.6%) unwilling to continue treatment gave the reason as too much discomfort from side effects.

#### Safety and Adverse Events

Almost half the subjects experienced an AE (47%) after the first administration, with slightly more in subjects discontinuing treatment (54%) compared with those persisting with therapy (43%). Across the study period, 471 AEs were recorded, occurring in 74% of subjects. More subjects in the FAS-D (86.4%) reported AEs than those in the FAS-P (68.6%). The intensity of the AEs was more often reported as severe in the FAS-D (28.2%) than in the FAS-P (10.1%).

All AEs were considered treatment-emergency AEs, with 87% of AEs considered by the physician to be certainly, probably, or possibly related to the 5-grass pollen tablet. One subject (in the FAS-D) experienced a serious AE with dyspnea, “palpitations,” and “nervousness.” All signs and symptoms were considered severe and related to treatment by the investigator. Overall, the most frequent

**Table 3**

Reasons for discontinuing treatment in discontinued-treatment population (n = 59)

| Reason for discontinuation          | Treatment stop at visit 3 (month 1; n = 23) <sup>a,b</sup> | Treatment stop at visit 4 (month 7; n = 20) <sup>a,b</sup> |
|-------------------------------------|------------------------------------------------------------|------------------------------------------------------------|
| Adverse events                      | 20 (87.0%)                                                 | 13 (65.0%)                                                 |
| Patient wanted no further treatment | 3 (13.0%)                                                  | 3 (15.0%)                                                  |
| Improvement of patient's symptoms   | —                                                          | 1 (5.0%)                                                   |
| Other                               | 2 (9.1%)                                                   | 4 (20.0%)                                                  |

<sup>a</sup>The number of subjects in this discontinued-treatment population is made up of subjects who stopped treatment and those lost to follow-up: 1 (visit 2) + 5 (visit 2 to 3) + 23 (discontinuing at visit 3) + 10 (visit 3 to 4) + 20 (discontinuing at visit 4) = 59.

<sup>b</sup>Percentages are based on the number of patients in the corresponding full analysis set at the respective visit who discontinued treatment; some patients might have discontinued for more than one reason.

treatment-emergency AEs were related to the throat and mouth area, with oral pruritus being the most frequent (20.9%). Specific AEs occurring in at least 5% of all subjects are presented in Table 5. All are mentioned as occurring with very common to uncommon frequency for the 5-grass pollen tablet in the SPC. Compared with the FAS-P, treatment-emergency AEs occurring more frequently in the FAS-D included throat irritation, tongue edema, dyspnea, and paresthesia.

## Discussion

This study was designed to evaluate the use of SLIT with a 5-grass pollen tablet in a real-life AR population and to determine treatment persistence and reasons for treatment discontinuation.

In this study, 64% of investigators were ear, nose, and throat physicians, and the patient population treated was a classic AR population.<sup>3,4,6,7</sup> Patients were on average approximately 30 years of age, had moderate to severe rhinoconjunctivitis, 67% had polysensitivity, and 32% had concomitant asthma. Although the percentage of patients with polysensitivity was comparable, the percentage of patients with asthma was somewhat larger in this

**Table 4**

Subject symptoms after studied grass pollen season at end of study (visit 4)

| Variable           | FAS (n = 196) | FAS-P (n = 137) | FAS-D (n = 59) |
|--------------------|---------------|-----------------|----------------|
| Nasal complaints   |               |                 |                |
| Missing            | 41            | 0               | 41             |
| None               | 27 (17.4%)    | 27 (19.7%)      | 0              |
| Mild               | 74 (47.7%)    | 65 (47.4%)      | 9 (50.0%)      |
| Moderate           | 42 (27.1%)    | 35 (25.5%)      | 7 (38.9%)      |
| Severe             | 12 (7.7%)     | 10 (7.3%)       | 2 (11.1%)      |
| Eye complaints     |               |                 |                |
| Missing            | 43            | 1               | 42             |
| None               | 53 (34.6%)    | 50 (36.8%)      | 3 (17.6%)      |
| Mild               | 62 (40.5%)    | 54 (39.7%)      | 8 (47.1%)      |
| Moderate           | 27 (17.6%)    | 24 (17.6%)      | 3 (17.6%)      |
| Severe             | 11 (7.2%)     | 8 (5.9%)        | 3 (17.6%)      |
| Lung complaints    |               |                 |                |
| Missing            | 48            | 6               | 42             |
| None               | 109 (73.6%)   | 98 (74.8%)      | 11 (64.7%)     |
| Mild               | 27 (18.2%)    | 22 (16.8%)      | 5 (29.4%)      |
| Moderate           | 8 (5.4%)      | 7 (5.3%)        | 1 (5.9%)       |
| Severe             | 4 (2.7%)      | 4 (3.1%)        | 0              |
| ≥1 other complaint |               |                 |                |
| Missing            | 36            | 0               | 36             |
| Yes                | 24 (15.0%)    | 23 (16.8%)      | 1 (4.3%)       |
| No                 | 136 (85.0%)   | 114 (83.2%)     | 22 (95.7%)     |

Abbreviations: FAS, full analysis set; FAS-D, discontinued-treatment population; FAS-P, persistent-treatment population.

**Table 5**Treatment-emergency adverse events occurring in at least 5% of all subjects<sup>a</sup>

| Adverse event     | FAS (n = 196)   | FAS-P (n = 137) | FAS-D (n = 59)  |
|-------------------|-----------------|-----------------|-----------------|
| Oral pruritus     | 41 (20.9%) [45] | 27 (19.7%) [31] | 14 (23.7%) [14] |
| Throat irritation | 35 (17.9%) [40] | 21 (15.3%) [26] | 14 (23.7%) [14] |
| Oral edema        | 25 (12.8%) [30] | 16 (11.7%) [18] | 9 (15.3%) [12]  |
| Oral paresthesia  | 19 (9.7%) [26]  | 12 (8.8%) [17]  | 7 (11.9%) [9]   |
| Pharyngeal edema  | 15 (7.7%) [15]  | 10 (7.3%) [10]  | 5 (8.5%) [5]    |
| Tongue edema      | 14 (7.1%) [14]  | 3 (2.2%) [3]    | 11 (18.6%) [11] |
| Dyspnea           | 13 (6.6%) [13]  | 5 (3.6%) [5]    | 8 (13.6%) [8]   |
| Nausea            | 13 (6.6%) [15]  | 7 (5.1%) [8]    | 6 (10.2%) [7]   |
| Ear pruritus      | 12 (6.1%) [13]  | 11 (8.0%) [12]  | 1 (1.7%) [1]    |
| Lip edema         | 10 (5.1%) [10]  | 6 (4.4%) [6]    | 4 (6.8%) [4]    |
| Paresthesia       | 10 (5.1%) [13]  | 4 (2.9%) [4]    | 6 (10.2%) [9]   |
| Stomatitis        | 10 (5.1%) [11]  | 8 (5.8%) [9]    | 2 (3.4%) [2]    |

Abbreviations: FAS, full analysis set; FAS-D, discontinued-treatment population; FAS-P, persistent-treatment population.

<sup>a</sup>Data are presented as number of subjects experiencing an adverse event (percentage) [number of adverse events].

cohort compared with those reported in larger randomized studies performed using the 5-grass pollen tablet.<sup>30–33</sup>

The overall study duration was 7 months, which is slightly longer than that seen in similar real-life studies.<sup>25,28,37,38</sup> After 1 month, 85% of all patients persisted with treatment, and 70% persisted after 7 months. This is comparable to a recent real-life study that described a dropout rate of 30% after 4 months of treatment with pollen SLIT and higher than that described in a large Dutch study in which the persistence of SLIT at 6 months was approximately 60%.<sup>25,28</sup> For those patients who continued treatment throughout the study, improvement in their disease status was reported (by physician and patient assessments) in 80% of cases. Furthermore, 80% reported they would continue treatment with the 5-grass pollen immunotherapy in the following season. This suggests that in most patients, treatment is well tolerated and associated with clinical benefit in physician opinion and in patient perception. In addition, because data from randomized studies suggest that continued therapy with AIT provides a sustained benefit in symptom control and quality of life, this level of treatment persistence is reassuring.<sup>10–14</sup> These data add to those from larger randomized trials and more recent real-life studies in adults and children that support the use of 5-grass SLIT in the management of AR.<sup>31–38</sup>

Real-life studies often focus on year-to-year adherence as the treatment duration of a course of immunotherapy, which is at least 3 years.<sup>22–24,28</sup> Much less is known about persistence during the first few months of treatment. In this study, half the patients who discontinued treatment did so within 4 weeks of therapy. This is in line with results obtained from randomized controlled trials with the 5-grass pollen tablet<sup>36</sup> and those described by others.<sup>25</sup> Another real-life study found that the largest decrease in persistence occurred during the first few months of a treatment follow-up of 3 years, after which persistence decreased more slowly over time.<sup>28</sup> Therefore, to improve overall persistence, it is important to understand why patients discontinue therapy during the first month(s) of treatment. Overall, 17% of patients withdrew owing to side effects. However, of patients who discontinued treatment from V2 to V3 (ie, ≤4 weeks), 87% withdrew because of AEs. For those who discontinued treatment from V3 to V4, 65% reported AEs as the reason for stopping therapy. Other real-life studies have reported side effects as a main cause of early discontinuation.<sup>25,30</sup> In general, in real-life and randomized studies, adherence is negatively influenced by AEs and poor tolerability.<sup>24,29</sup>

There were no clear differences in the type of AEs reported by the FAS-D and FAS-P, although the frequency of some AEs was higher in the FAS-D (most notably throat irritation, tongue edema, dyspnea, and paresthesia) and the FAS-D reported more AEs. In the

2 groups, most AEs were well recognized as associated with SLIT and local to the site of sublingual administration. The most frequently occurring AEs were the same as those observed in a recently published real-life study with the 5-grass pollen tablet in children.<sup>38</sup> As can be expected, the intensity of a relatively large percentage of AEs in the FAS-D was described as “severe” (28.2% vs 10.1% in the FAS-P). In other words, when patients describe their AE as “severe,” there is an increased risk they will discontinue their treatment. The authors’ experience is consistent with data from clinical studies reporting that local AEs are a major cause of SLIT discontinuation in adults and children.<sup>22,24,29</sup>

The AEs experienced by patients and associated with discontinuation in this study were local to the site of sublingual administration and well recognized as associated with the 5-grass pollen tablet and with other SLITs.<sup>11,24,27,36</sup> A cornerstone in the strategy to decrease treatment discontinuation should be patient education on such events, and this is supported by improved compliance in clinical studies. For example, in one study, a group of patients received detailed information on self-administration of SLIT, whereas the other group attended a short educational course about treatment outcomes, potential side effects, and problems related to the use of SLIT. This study found that patients in the latter group had greater persistence after 6 months of treatment.<sup>30</sup> In another real-life study, patients receiving an educational plan and regular contact by phone, e-mail, and a prearranged visit at 4 months showed significantly greater adherence compared with those receiving no follow-up plan. Importantly, the first month of treatment was identified as crucial, with the highest rate of discontinuation during this period.<sup>25</sup> A study by Vita et al<sup>40</sup> also found a correlation between the number of yearly follow-up visits and the rate of adherence to SLIT.

Clearly, to improve adherence, effective communication between patient and physician is crucial. The main topics to be discussed openly are the evaluation of the available treatment options and their pros (eg, efficacy, time to onset of efficacy) and cons (eg, safety and tolerability issues and length of treatment). Other important factors are the willingness of the patient to share a therapeutic plan and the time taken for the visit.<sup>41</sup> Because physicians usually do not have sufficient time to arrange educational programs during routine visits, other health care professionals, such as nurses, are important in planning and executing a formal educational plan and regular follow-up contacts with the patient.

As is common in observational real-life studies, although this study was conducted in accordance with recommended Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (eTable 1),<sup>42</sup> the present study has some limitations. The analysis is descriptive only, and no formal analyses between treatment persistent (FAS-P) and treatment discontinuation (FAS-D) were planned or performed. The reporting of and recording of AEs were performed by the investigator based on the patient’s recollection of the event at the scheduled study visits, which in most cases was after the AE had occurred. This carries an associated recall bias and might underestimate the severity of such events. The less rigorous reporting requirements for AEs in postmarketing studies<sup>43</sup> also might have underestimated the frequency of such events. In addition, the authors have no data on AEs occurring in those patients lost to follow-up (all in the FAS-D).

This real-life study showed that most patients (70%) with AR treated pre-co-seasonally with a 5-grass pollen tablet persisted with treatment after the first pollen season, most of whom (80%) were willing to continue in the following season. Nevertheless, improving adherence in the first period of AIT is crucial to improve overall adherence over a longer treatment period. As such, patient education and communication between physician and patients, especially during the first month of treatment, and in particular as

to what can be expected in terms of local transient events, remains crucial to improve patient adherence to AIT over the treatment course.

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## Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2015.10.018>.

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**eTable 1**

STROBE Statement—checklist of items that should be included in reports of observational studies: persistence of treatment with 5-grass pollen tablets in patients with allergic rhinitis: a real-life study<sup>a</sup>

|                              | Item number     | Recommendation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Pages                                                                            |
|------------------------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Title and abstract           | 1               | (a) indicate study design with a commonly used term in the title or the abstract<br>(b) provide in the abstract an informative and balanced summary of what was done and what was found                                                                                                                                                                                                                                                                                                                                                                                                                                                 | abstract p 1<br>abstract p 1–2                                                   |
| Introduction                 |                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                  |
| Background and rationale     | 2               | explain the scientific background and rationale for the investigation being reported                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | manuscript p 1–2                                                                 |
| Objectives                   | 3               | state specific objectives, including any prespecified hypotheses                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | manuscript p 1–2                                                                 |
| Methods                      |                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                  |
| Study design                 | 4               | present key elements of study design early in the article                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | manuscript p 2                                                                   |
| Setting                      | 5               | describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | manuscript p 2                                                                   |
| Participants                 | 6               | (a) cohort study—provide eligibility criteria and sources and methods of selection of participants; describe methods of follow-up<br>case–control study—provide eligibility criteria and sources and methods of case ascertainment and control selection; provide the rationale for choice of cases and controls<br>cross-sectional study—provide eligibility criteria and sources and methods of selection of participants<br>(b) cohort study—for matched studies, provide matching criteria and number of exposed and unexposed<br>case–control study—for matched studies, provide matching criteria and number of controls per case | manuscript p 3<br><br>NA                                                         |
| Variables                    | 7               | clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers; describe diagnostic criteria, if applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | manuscript p 3                                                                   |
| Data sources and measurement | 8 <sup>b</sup>  | for each variable of interest, provide sources of data and details of methods of assessment (measurement); describe comparability of assessment methods if there is >1 group                                                                                                                                                                                                                                                                                                                                                                                                                                                            | manuscript p 3–4                                                                 |
| Bias                         | 9               | describe any efforts to address potential sources of bias                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | manuscript p 3–5                                                                 |
| Study size                   | 10              | explain how the study size was arrived at                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | NA                                                                               |
| Quantitative variables       | 11              | explain how quantitative variables were handled in analyses; if applicable, describe which groupings were chosen and why                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | manuscript p 3–4                                                                 |
| Statistical methods          | 12              | (a) describe all statistical methods, including those used to control for confounding<br>(b) describe any methods used to examine subgroups and interactions<br>(c) explain how missing data were addressed<br>(d) cohort study—if applicable, explain how loss to follow-up was addressed<br>case–control study—if applicable, explain how matching of cases and controls was addressed<br>cross-sectional study—if applicable, describe analytical methods taking account of sampling strategy<br>(e) describe any sensitivity analyses                                                                                               | manuscript p 3–5<br><br>NA<br>NA<br>described and included in analyses<br><br>NA |
| Results                      |                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                  |
| Participants                 | 13 <sup>b</sup> | (a) report numbers of subjects at each stage of study—eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in study, completing follow-up, and analyzed<br>(b) give reasons for nonparticipation at each stage<br>(c) consider use of flow diagram                                                                                                                                                                                                                                                                                                                                                  | manuscript p 5–6<br>manuscript p 5–6<br><a href="#">Figure 1</a>                 |
| Descriptive data             | 14 <sup>b</sup> | (a) provide characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders<br>(b) indicate number of participants with missing data for each variable of interest<br>(c) cohort study—summarize follow-up time (eg, average and total amount)                                                                                                                                                                                                                                                                                                                         | manuscript p 5; table<br>manuscript p 5–9; table                                 |
| Outcome data                 | 15 <sup>b</sup> | cohort study—report numbers of outcome events or summary measurements over time<br>case–control study—report numbers in each exposure category or summary measurements of exposure<br>cross-sectional study—report numbers of outcome events or summary measurements                                                                                                                                                                                                                                                                                                                                                                    | manuscript p 5–9; table<br>manuscript p 5–9; table                               |
| Main results                 | 16              | (a) provide unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval); make clear which confounders were adjusted for and why they were included<br>(b) report category boundaries when continuous variables were categorized<br>(c) if relevant, consider translating estimates of relative risk into absolute risk for a meaningful period                                                                                                                                                                                                                             | NA<br>NA<br>NA                                                                   |
| Other analyses               | 17              | report other analyses done (eg, analyses of subgroups and interactions and sensitivity analyses)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | NA                                                                               |

(continued on next page)

**eTable 1** (*continued*)

|                   | Item number | Recommendation                                                                                                                                                                | Pages              |
|-------------------|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Discussion        |             |                                                                                                                                                                               |                    |
| Key results       | 18          | summarize key results with reference to study objectives                                                                                                                      | manuscript p 9–12  |
| Limitations       | 19          | discuss limitations of study, taking into account sources of potential bias or imprecision; discuss direction and magnitude of any potential bias                             | manuscript p 12–13 |
| Interpretation    | 20          | provide a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | manuscript p 12–13 |
| Generalizability  | 21          | discuss generalizability (external validity) of study results                                                                                                                 | manuscript p 12–13 |
| Other information |             |                                                                                                                                                                               |                    |
| Funding           | 22          | present source of funding and role of funders for the present study and, if applicable, for the original study on which the present article is based                          | acknowledgments    |

Abbreviation: STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

<sup>a</sup>An explanation and elaboration article discusses each checklist item and provides methodologic background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the following Web sites: <http://www.plosmedicine.org/> [PLoS Medicine], <http://www.annals.org/> [Annals of Internal Medicine], and <http://www.epidem.com/> [Epidemiology]). Information on the STROBE initiative is available at <http://www.strobe-statement.org>.

<sup>b</sup>Provide information separately for cases and controls in case–control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.