

Safety and Tolerability of an SQ-Standardized GRAss ALlergy Immunotherapy Tablet (GRAZAX®) in a Real-Life Setting for Three Consecutive Seasons – The GRAAL Trial

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Abstract

Background and Objectives: GRAZAX® (*Phleum Pratense*, 75 000 SQ-T/2 800 BAU, ALK, Denmark), an SQ-standardized grass allergy sublingual immunotherapy tablet for the desensitization of grass pollen-induced rhinoconjunctivitis, has been developed to facilitate patient access to specific immunotherapy (SIT), while minimizing the risk of serious treatment-related adverse events. As a minimum duration of 3 years is recommended for SIT treatment, the GRAAL trial aimed to assess the safety profile of GRAZAX® in real-world conditions during long-term treatment of patients with grass pollen-induced allergic rhinoconjunctivitis (ARC).

Methods: A multicentre, prospective, open-label, observational trial was conducted over three consecutive grass pollen seasons from November 2007 to October 2010 in France. A total of 130 physicians included 628 patients with previously documented ARC. Patients received one tablet daily (no up-titration) for at least 4 months before the expected start of the pollen season (pre-season), which was then maintained throughout the entire season (co-season). The primary endpoint was safety and tolerability (immediate, i.e. each year at first tablet administration, and long-term) after pre- and co-seasonal exposure to GRAZAX®.

Results: Patients were treated for an average of 5.5 months per year. After administration of the first tablet, immediate tolerable reactions (defined as benign, local, of short duration [<30 minutes] and not requiring any symptomatic treatment) were experienced by 54.6%, 38.4% and 33.6% of the

patients during the first, second and third years of treatment, respectively. Immediate intolerable reactions (required study discontinuation, symptomatic medication or lasted >30 minutes) occurred in 14 patients (2.2%) during GRAZAX[®] initiation, and one patient (0.3%) at treatment reintroduction during the second year. Adverse events considered to be related to GRAZAX[®] were reported by 46.2%, 14.4% and 1.8% of patients, during the first, second and third years of treatment, respectively. The most frequently reported adverse events were mild-to-moderate local events (at the oral and pharyngeal mucosa levels). These symptoms mainly occurred within the first month of treatment initiation and subsequent tablet reintroduction.

Conclusion: Daily administration of GRAZAX[®] for three consecutive years was generally safe and well tolerated. An improvement in the incidence of adverse events related to treatment was observed at reintroduction of GRAZAX[®] and during the course of treatment.

Trial Registration: <http://clinicaltrials.gov> (NCT01433510).

Introduction

Allergic rhinoconjunctivitis (ARC) is a common respiratory disorder that appears to be experienced by an increasing number of individuals. Recent estimates report clinically confirmed ARC in 17–29% of European adults,^[1] and a large epidemiological survey conducted in 2006 found the overall prevalence in the French adult population was 31%.^[2] Although it is sometimes viewed as a benign ailment, the burden associated with this highly prevalent condition is considered to be substantial, making it a significant health issue. Due to the frequency and duration of the disease, the symptoms of ARC may cause extreme discomfort and hence considerably impair daily activities, social interactions, school activities and quality of life.^[3,4] Moreover, it is often associated with co-morbidities such as conjunctivitis, concomitant allergic disease and ear, nose and throat or respiratory disorders, and is regarded as one of the major risk factors for the development of asthma.^[5,6]

Besides avoidance measures, current practice guidelines point out the important role of long-term approaches such as specific immunotherapy (SIT) in the management of ARC.^[6,7] In contrast with symptomatic medications, SIT is the only available therapy that treats the cause of allergic

disease, providing long-term benefits with a sustained reduction in symptoms and the need for relief medications.^[8] SIT has also been shown to prevent sensitivity to other inhaled allergens, and to reduce the risk of progression to asthma.^[5,9–11]

Grass pollen is the most common cause of seasonal respiratory allergies and is associated with more than 50% of ARC cases.^[1] Although rare, traditional subcutaneous SIT is associated with the risk of life-threatening anaphylactic reactions, as well as clinic visits during the initial up-dosing phase, and injection-related discomfort.^[12] Sublingual immunotherapy (SLIT) minimizes the risk and practical constraints linked to injection-based immunotherapy. GRAZAX[®] (*Phleum Pratense*, 75 000 SQ-T/2 800 BAU; ALK, Denmark), a fast-dissolving grass allergy immunotherapy tablet for once-daily sublingual administration, was developed in this context. Its new formulation was designed to ease patient access to SIT by allowing self-administration at home. The clinical efficacy of GRAZAX[®] together with a good safety profile was demonstrated in a large-scale development programme initiated in 2001.^[13–19] GRAZAX[®] was subsequently approved in 30 European countries for the treatment of grass pollen-induced rhinitis and conjunctivitis in adults and children over 5 years of age with clinically relevant symptoms, and who have been diagnosed

with a positive skin prick test and/or specific IgE test to grass pollen.

This phase IV, prospective, open-label, observational trial was designed to enlarge current knowledge of GRAZAX® tolerability in real-world conditions and in regular clinical practice. Initially intended to cover a single pollen season (November 2007–October 2008), the GRass Allergy (GRAAL) trial was extended twice, allowing the assessment of safety over three consecutive seasons of grass pollen exposure. Tolerability results from the first year of the study have been previously published;^[20] this paper details tolerability data from the second and third years of the study, in addition to an analysis of the cohort of patients who received GRAZAX® throughout the entire 3 years. Continuation of the trial enabled safety evaluation at each re-introduction of the medication after an interruption of approximately 6 months each year, which is typical of the pre- and co-seasonal administration that occurs in France.

Patients and Methods

Trial Population

Adults aged >18 years, presenting with grass pollen-induced ARC previously documented with a positive diagnostic test (skin prick test [wheal diameter ≥ 3 mm] and/or specific IgE assay ≥ 0.70 KU/L), and for whom SLIT was planned by the physician, were eligible for inclusion. Written informed consent was obtained from all participants. Patients with severe, unstable or uncontrolled asthma (forced expiratory volume in 1 second [FEV₁] <70%), known hypersensitivity to one of the tablet's components, autoimmune disease, cancer, inflammatory disease of the oral cavity, ongoing or planned pregnancy, and/or ongoing treatment contraindicating SIT initiation (for instance, tricyclic antidepressants, monoamine oxidase inhibitors) were excluded from the trial. Since this study was designed to reflect a real-life setting, patients with previous grass pollen allergen immunotherapy, and those receiving concomitant allergen preparations or other medications such as β -adrenoceptor antagonists (β -blockers) or

angiotensin-converting enzyme (ACE) inhibitors, were not excluded.

Trial Design

This national, phase IV, open-label, multicentre, prospective, interventional, non-comparative observational trial was conducted in a routine practice setting between November 2007 and October 2010. Investigators were randomly recruited from a list of allergologists and pulmonologists (non-hospital-based) across France; a pre-specified number of investigators were recruited from all regions to ensure the sample was representative of all climatic and pollen conditions. Each investigator was asked to make a systematic inventory of all eligible patients in a centralized registry during an initial 2-month epidemiological phase.

During an initiation visit (Visit 1), the investigator had to call an interactive voice response system to allocate the patient into one of two groups: (1) enrolled or (2) not enrolled. This procedure was implemented to limit investigator-related bias for patient selection, and make possible the extrapolation of results to the general population. Enrolled patients began GRAZAX® (provided by ALK, since this agent was not otherwise available in France at the time) in accordance with the Summary of Product Characteristics criteria (one tablet daily, no up-dosing).^[21] Administration of the first tablet was performed under medical supervision for about 30 minutes, followed by daily administration on an out-patient basis. Treatment was initiated ≥ 4 months before the expected start of the 2008 grass pollen season and was maintained throughout the entire season. After this initiation visit, during the first year of SLIT, patients attended a follow-up visit at day 28 ± 2 (Visit 2) and an end-of-pollen season consultation (Visit 3; ≥ 180 days after initiation).

The trial was extended twice (once in 2009, and again in 2010) to allow patients to continue treatment whilst GRAZAX® was commercially unavailable, which is why GRAZAX® was given as a pre- and co-seasonal regimen. Patients were deemed non-compliant if they missed three or more tablets in any month. It was proposed that patients compliant with treatment during the first

year would continue with GRAZAX[®] during the following year in January 2009, and that patients adherent to treatment in 2009 would finish treatment in January 2010. In the 2009 pollen season (second year of treatment), GRAZAX[®] was initiated during an initial consultation (Visit 1) 2–4 months before the pollen season, and was continued up until the end of the pollen season when an evaluation visit was performed (Visit 2; ≤ 8 months after administration of the first tablet). The same procedure was applied to the 2010 pollen season (third year of treatment). Throughout the study, unscheduled intermediary visits could be performed at any time at the request of the patient or investigator. The trial followed the declaration of Helsinki and Good Clinical Practice, and was approved by the Committee for the Protection of Persons (Independent Ethics Committee) of Ouest IV, Nantes, France. The study is registered in a publicly available database: <http://clinicaltrials.gov> (NCT01433510).

Data Collection

Tolerability was the primary criterion of the trial. During the first year of treatment, patients were required to complete a hard copy follow-up diary each day of month 1 (diary no.1 received at Visit 1 to record treatment compliance and adverse events), and then each week for 8 weeks from 28 April 2008 to 22 June 2008 (diary no.2 received at Visit 2 to record ARC symptoms during the pollen season, their impact on daily activities, and any adverse events). Safety assessment was based on the collection of all adverse events reported spontaneously by patients and/or subsequent to physician inquiries (clinical interview, physical examination, review of the patient's diaries during the first year of treatment) throughout the treatment period. Follow-up diaries were collected and assessed at Visits 2 and 3, or at any intermediary visits. Study data were collected by electronic or paper case report form as per investigator preference at each visit. All recorded adverse events were classified according to MedDRA (Medical Dictionary for Regulatory Activities) version 13 terminology extrapolated from the spontaneous wording used by the investigator. The seriousness

and severity of adverse events were defined according to International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline E2A, Step 5.^[22] A severe adverse event was defined as having considerable interference on the subject's daily activities, while a serious adverse event was defined as any medical occurrence/effect that was life threatening; required hospitalization or prolongation of hospitalization; resulted in persistent or significant disability or incapacity; resulted in death, congenital abnormalities or birth defects; or any other event judged medically important.

Acute (immediate) tolerability was evaluated under medical supervision (≤ 30 minutes after first tablet intake and again after treatment reintroduction) and was subject to a separate analysis. All reactions were classified as tolerable/intolerable. A tolerable reaction was defined as benign, local, of short duration (< 30 minutes) and not requiring symptomatic treatment. Any reaction falling outside this definition, i.e. any reaction lasting more than 30 minutes after administration, requiring symptomatic treatment or resulting in discontinuation, was classified as intolerable. Other data collected included:

- General and medical patient characteristics (demography, ARC classification and history, SIT history, presence of asthma/polysensitization, co-morbidities, concomitant treatments)
- Treatment compliance (assessed both by counting the remaining tablets during the end-of-season visit and by a qualitative evaluation at each visit)
- Overall satisfaction with GRAZAX[®] (as assessed by an item about perception of efficacy on ARC symptoms during the grass pollen season by the investigator and the patient).

Statistical Methods

Statistical analyses were performed using SAS[®] software, version 8.2 (SAS Institute, Cary, NC, USA). Descriptive statistics consisted of the usual parameters: mean, standard deviation, minimum, maximum and number of observations for the continuous variables; frequencies and percentages for the categorical variables. Exploratory analy-

ses were carried out using statistical tests as appropriate (chi-squared [χ^2] or Fisher's exact test for modular variables, Student's t-test or non-parametric Wilcoxon test for quantitative variables). For the subgroup of 277 patients who received GRAZAX® throughout the 3 years, an inter-annual retrospective comparison of adverse event incidence rates was performed using a generalized linear model (logit link function and binomial distribution) with repeated measures. For all data, statistical significance was set at $p < 0.05$.

Results

Overall, 130 participating physicians (103 allergologists and 27 pulmonologists) initially registered 833 patients with documented grass pollen-induced ARC. From the registry cohort, 628 patients were randomly included in the trial and began GRAZAX® before the 2008 pollen season (figure 1).

Patient Characteristics

Baseline characteristics were comparable between the initial cohort and the sub-groups of patients who re-initiated treatment at years 2 and 3 (table I). At the first visit, most patients presented with a moderate-to-severe allergic rhinitis ('annoying' for the patient with regard to daily activities and sleep; 92.4%). Almost all patients (93.6%) received one or more symptomatic medication(s) during the previous pollen season (oral antihistamines for 91.5% and local corticosteroids for 51.2% of treated patients). Among patients receiving SIT at inclusion, 96.9% were generally being treated in a pre- and co-seasonal manner.

A total of 70.2% ($n = 367/523$) and 78.9% ($n = 277/351$) of patients who completed the trial according to protocol in 2008 and 2009, respectively, continued with treatment during the following year; i.e. a total of 230 patients (36.6%) were lost between treatment periods. Inter-annual patient loss was mostly due to the late implementation of the study in 2009 and 2010, at a time when a number of physicians had already prescribed alternative medications for their patients ($n = 143$); other reasons included the

withdrawal of 25 investigators ($n = 50$), and the scheduled end of immunotherapy ($n = 33$). Over the three seasons, 78 patients (12.4%) were withdrawn from the study due to adverse events. There was a marked decline in the drop-out rate as the years progressed (16.9%, 4.4% and 1.8% during the first, second and third years, respectively). This was attributed to a significant decrease in the proportion of patients who discontinued GRAZAX® for safety reasons (11.1%, 1.9% and 0.4% for the first, second and third years of treatment, respectively).

Safety Analysis

Treatment Exposure

Trial medication exposure was similar each year, with a mean annual value of 5.5 months per year (Year 1: 5.5 ± 1.9 ; Year 2: 5.6 ± 1.4 ; Year 3: 5.5 ± 1.2 months). The cumulative patient exposure for the three consecutive periods of treatment was 576 patient-years (cumulative number of years of treatment for the patient population over the study period). The majority of patients who continued on GRAZAX® during the second and third years were treated on a pre- and co-seasonal basis (95.4% and 97.1%, respectively), while the remaining patients received year-round treatment (GRAZAX® during the study period, and an allergen extract solution during the remainder of the year).

Immediate Reactions on First Administration and Reintroduction

About half of patients ($n = 343$; 54.6%) experienced a tolerable reaction within the 30 minutes following first administration of GRAZAX®, while 14 patients (2.2%) experienced an intolerable reaction requiring symptomatic treatment and/or discontinuation.^[20] At reintroduction of the tablet in the second year, 141 patients (38.4%) experienced a tolerable reaction, and an intolerable reaction was experienced by only one patient. Similarly, at the third reintroduction, 93 patients (33.6%) experienced tolerable reactions and no intolerable reactions were reported.

Adverse Events

As reported previously^[20] during the first year of the trial, 53.8% of patients experienced ≥ 1 adverse

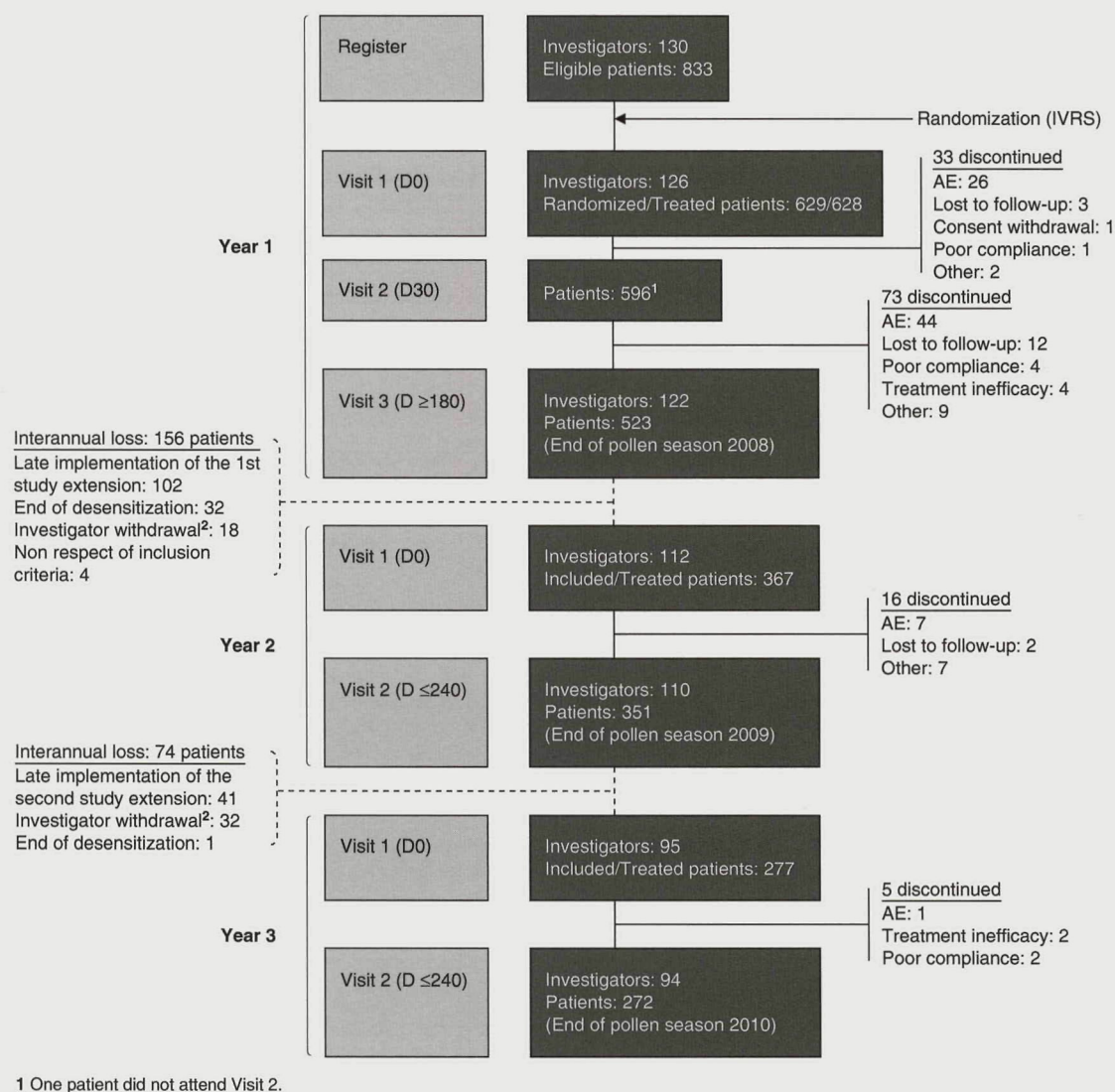


Fig. 1. Patient disposition. AE = adverse event; D = day; IVRS = Interactive Voice Response System.

event; this was reduced to 17.7% during the second year and to 4.7% during the third year (table II). Oral pruritus (6.3%), oral paraesthesia (2.2%) and throat irritation (1.6%) were the most frequent adverse events during the second year, affecting about three times fewer patients compared with the previous year (figure 2). Similarly,

the majority of adverse events during the second year of treatment were local events, related to GRAZAX[®] and mild-to-moderate in severity. Local, moderate-to-severe adverse events were less frequent during the second and third years of treatment (18.3% in 2008, 4.9% in 2009 and 1.1% in 2010). During the second year, only one patient

presented at first administration with an intolerable oropharyngeal pruritus requiring medication. Two other patients had one serious adverse event each (moderate supraventricular tachycardia and fatal cardiac arrest) which were considered by the investigator to be unrelated to GRAZAX®. Adverse events were infrequent during the third year of treatment, and mild or moderate in severity. No severe systemic reactions were observed over the entire trial period.

In addition, patients (n = 260; 41%) who switched during the first year from SIT had a 1.5-fold less risk of reporting an adverse event than patients (n = 368) who were SIT naïve (odds ratio [OR] = 0.67; 95% confidence interval [CI] 0.49, 0.93; p = 0.015),^[20] although it was unknown whether some patients switched their SIT to GRAZAX® for tolerability reasons.

Subgroup Analyses

In the subgroup of 277 patients who received GRAZAX® over three consecutive seasons, 50.5% did not experience any adverse events, while the remaining 49.5% mainly presented with

application site-related adverse events (oral pruritus, oral paraesthesia, oropharyngeal irritation, mouth oedema). None of these patients experienced a serious adverse event. A specific analysis of this subgroup showed that the overall incidence of adverse events was significantly decreased during the second and third years of treatment, compared with the first year (table III). A similar pattern was observed for treatment-related adverse events, loco-regional events, and those occurring during the first day of treatment (all p < 0.001). In particular, the incidence of local moderate-to-severe adverse events was reduced over time (11.2% in 2008, 4.3% in 2009, and 1.1% in 2010). Likewise, the incidence of immediate reactions was significantly decreased at first and second GRAZAX® reintroduction (table III). The most frequent adverse events usually manifested within the first month of GRAZAX® initiation, with infrequent appearance during the 5 months thereafter (figure 3). Few patients experienced these adverse events during the second and third years of treatment, except during the first day of GRAZAX® reintroduction in the second year (7.9%).

Table 1. Patient characteristics

Characteristic	Year 1 (n = 628)	Year 2 (n = 367)	Year 3 (n = 277)
Sex, n (%)^a			
Female	315 (50.2)	171 (46.6)	128 (46.2)
Male	313 (49.8)	196 (53.4)	149 (53.8)
Mean (± SD) age, y	35.0 (11.1)	37.2 (10.5)	38.6 (10.4)
Range, y	18–74	19–71	20–72
Physical examination, n (%)^a			
Not performed	36	27	11
Normal	573 (97.0)	337 (99.1)	259 (97.4)
Abnormal	18 (3.0)	3 (0.9)	7 (2.6)
Patient subgroups, n (%)^a			
Mild-to-moderate asthma	200 (31.9)	125 (34.1)	88 (31.8)
Polysensitization	451 (71.8)	254 (69.2)	188 (67.9)
Confirmation of grass pollen sensitivity, %			
Skin prick test positive ^b	99.8		
IgE positive ^c	38.3		

a Percentages calculated on the number of available data.

b Wheal diameter ≥3 mm.

c ≥0.70 KU/L

SD = standard deviation.

Table II. Summary of adverse events (AEs) [Year 1 data have been published previously^[20]]

AE	Year 1 (n=628)		Year 2 (n=367)		Year 3 (n=277)	
	n (%) patients	n events	n (%) patients	n events	n (%) patients	n events
Any AE	338 (53.8)	750	65 (17.7)	111	13 (4.7)	21
Related to GRAZAX®	290 (46.2)	629	53 (14.4)	91	5 (1.8)	13
Reported as serious AE	3 (0.5)	4	2 (0.5)	2	0 (0.0)	0
Causing trial withdrawal	70 (11.1)	130	7 (1.9)	15	1 (0.4)	3
Most frequently reported AEs^a						
<i>Gastrointestinal disorders</i>	214 (34.1)	343	41 (11.2)	52	5 (1.8)	8
Oral pruritus	106 (16.9)	129	23 (6.3)	29		
Oral paraesthesia	48 (7.6)	50	8 (2.2)	8		
Mouth oedema	40 (6.4)	44				
Swollen tongue	14 (2.2)	14				
<i>Respiratory, thoracic and mediastinal disorders</i>	116 (18.5)	176	20 (5.4)	26	3 (1.1)	3
Throat irritation	28 (4.5)	30	6 (1.6)	6		
Asthma, asthma exacerbation	18 (2.9)	21				
Cough	16 (2.5)	18				
Pharyngolaryngeal discomfort	16 (2.5)	18				
Allergic rhinitis	14 (2.2)	16	5 (1.4)	5		
Sneezing	14 (2.2)	14				
<i>Infections</i>	44 (7.0)	57			5 (1.8)	5
Rhinitis	13 (2.1)	14				
<i>Eye disorders</i>	40 (6.4)	44				
Conjunctivitis	18 (2.9)	21				
Eye pruritus	13 (2.1)	13				
<i>Ear and labyrinth disorders</i>	19 (3.0)	21				
Ear pruritus	19 (3.0)	21				

a AEs reported by ≥2% of patients during the first year, and ≥1% of patients during the second and third year of GRAZAX® treatment.

Further patient subgroup analyses showed that the incidence of adverse events was similar in mono- and polysensitized patients over the 3 years of treatment (table IV). A slightly higher proportion of patients with one or more adverse events was observed in asthmatic versus non-asthmatic patients (24.0% vs 14.5%; $p=0.023$) during the second year of treatment, while no significant difference was visible during the first or third years. Based on a generalized linear model, neither the asthmatic nor the polysensitization status of the 277 patients treated during three consecutive pollen seasons had a significant impact on the incidence of adverse events over time, particularly loco-regional events (asthma: OR=1.35, 95% CI 0.83, 2.20; polysensitization: OR=1.27, 95% CI 0.77, 2.08). Likewise, these specific conditions did not influence the incidence and tolerability of

immediate reactions to the product. No aggravation of asthma was seen at any point.

Compliance Assessment

The overall estimated rate of compliance with treatment was 71.8% during the first year, which increased to approximately 90% during the next 2 years (table V). Omission (61.2%) was the main reason stated for non-compliance, followed by adverse events (24.7%). The contribution of adverse events to non-compliance was notably decreased from one year to the next.

Satisfaction Rating

A similar proportion of investigators and patients (86.1% and 85.0%, respectively) declared being 'satisfied' or 'very satisfied' with GRAZAX®

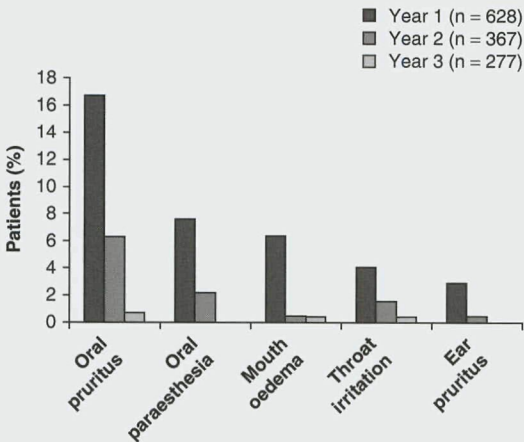


Fig. 2. Most common GRAZAX®-related adverse events

during the first year of treatment.^[20] The medication was also considered ‘easy to use’ or ‘very easy to use’ by 93.7% of patients.^[20] Patient and investigator satisfaction rates increased to over 90% during the second and third years of treatment.

Discussion

The GRAAL trial was intended to assess the tolerability profile of GRAZAX® under real-

world conditions. Its prospective, open-label, observational design allowed the evaluation of usual medical practice, as well as the patient’s own use in a real-life setting. Published results of first-year data,^[20] in addition to the data presented in this paper, show that GRAZAX® was well tolerated over a 3-year, long-term period in patients agreeing to restart treatment each year. More importantly, administration on a pre- and co-seasonal basis over three consecutive pollen seasons was associated with a significant yearly improvement in the incidence of treatment-related adverse events, particularly during tablet re-introduction at the physician’s office. However, it is important to note that these results were observed in patients who continued in the study beyond the first season, and were therefore better able to tolerate treatment.

Over 3 years of seasonal GRAZAX® treatment, only 12.4% of patients discontinued the study medication due to adverse events. These findings were consistent with previous experience of SLIT and GRAZAX®.^[13-17,23] Adverse events were reported in 338 patients (53.8%) in the first year,^[20] which is similar to if not lower than other studies.^[15,17,24] It is difficult to directly compare the results from the two subsequent seasons with those of other trials, as only one other study has

Table III. Adverse event (AE) analysis for patients treated on a pre- and co-seasonal basis over three consecutive years (n = 277)

Variable	Year 1 n (%)	Year 2 n (%)	Year 3 n (%)	Inter-annual comparison ^a		p-Value
				OR [95% CI]		
				Y2 vs Y1	Y3 vs Y1	
Overall AE						
At least one AE	121 (43.7)	41 (14.8)	13 (4.7)	0.22 [0.16, 0.32]	0.06 [0.04, 0.11]	p<0.0001
At least one AE related to GRAZAX [®]	107 (38.6)	31 (11.2)	5 (1.8)	0.20 [0.14, 0.30]	0.03 [0.01, 0.07]	p<0.0001
At least one loco-regional AE	92 (33.2)	31 (11.2)	5 (1.8)	0.25 [0.17, 0.37]	0.04 [0.02, 0.09]	p<0.0001
At least one AE at first GRAZAX [®] intake (during the first day of treatment)	58 (20.9)	23 (8.3)	2 (0.7)	0.34 [0.22, 0.53]	0.03 [0.01, 0.11]	p<0.0001
Immediate reaction (within 30 min) at first intake						
No	121 (43.7)	168 (60.6)	184 (66.4)	0.50 [0.39, 0.65]	0.39 [0.30, 0.51]	p<0.0001
Yes	156 (56.3)	109 (39.4)	93 (33.6)			

a Logistic regression with repeated measures.
CI = confidence interval; OR = odds ratio; Y = year.

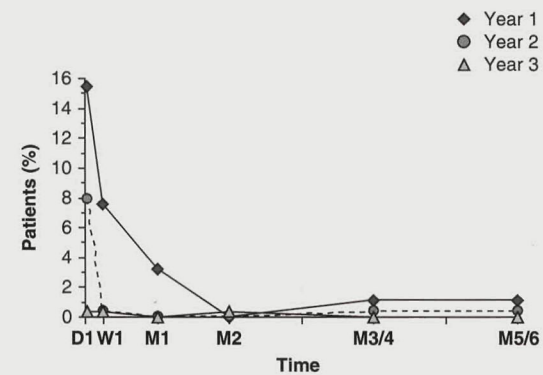


Fig. 3. Incidence over time of the most pertinent adverse events in patients treated on a pre- and co-seasonal basis over three consecutive years (n=277). Considered adverse events were oral pruritus, oral paraesthesia, mouth oedema, throat irritation and ear pruritus. Time-scale abbreviations: **D1** = during first day; **W1** = during first week (except D1); **M1** = during first month (except W1); **M2** = during second month; **M3/4** = during third and fourth months; **M5/M6** = during fifth and sixth months of treatment.

investigated pre- and co-seasonal administration.^[23] However, whilst both the GRAAL and the Didier et al.^[23] trials confirmed an improvement in tolerability over time with continuation of treatment, the results are still not directly comparable. In GRAAL the full maintenance dose was given from the outset, whereas the dose was progressively up-titrated to a target maintenance dose in the Didier et al. trial.^[23]

The most commonly reported adverse events in GRAAL were local and related to oral introduction of GRAZAX[®]. In the majority of patients, these symptoms began early during treatment and subsided spontaneously within a few weeks. It is noteworthy that 34.5% and 76.4% of all adverse events reported during the first year were experi-

enced within the day and the month following treatment initiation, respectively.

Patients remaining in the trial after the end of the first year (and indeed those treated previously with SIT) were generally better able to tolerate SLIT, and the results must be viewed in this context. Nevertheless, the progressive decrease in adverse events over time is consistent with results from other SLIT trials, including those using GRAZAX[®],^[13-17,23] and we assume that this phenomenon is a result of the continuing and potentially disease-modifying effects of SLIT.^[25] In support of this, recent published data demonstrated sustained clinical benefit with long-term grass allergy SLIT accompanied by immunological changes, indicative of progressive disease modification.^[24,26]

The acute (i.e. immediate) tolerability of GRAZAX[®] was also improved when treatment was reintroduced. Although reactions were observed in the majority of patients (56.8%) following the first administration of the product, these were tolerable in 96.1% of cases, and only six patients (1.7%) with an acute reaction discontinued GRAZAX[®] because of symptoms. Reintroduction over the next two seasons was associated with acute reactions in 38.7% and 33.6% of patients, respectively. In accordance with results from other studies of SLIT,^[13-17,23,27] these data emphasise the need to initiate and reintroduce GRAZAX[®] under medical supervision, enabling the patient and physician to discuss any adverse events related to treatment and possible actions. This preliminary step is needed to avoid patient discouragement and to optimize long-term management of ARC.

Table IV. Adverse event (AE) analysis in patient subgroups

Patient subgroups ^a	Year 1 (n = 628)		Year 2 (n = 367)		Year 3 (n = 277)	
	n (%)	p-Value	n (%)	p-Value	n (%)	p-Value
Mono- vs polysensitized						
Any AE	86 (48.6)/252 (55.9)	p = 0.10	15 (13.3)/50 (19.7)	p = 0.14	2 (2.2)/11 (5.9)	p = 0.24
GRAZAX [®] -related AE	73 (41.2)/217 (48.1)	p = 0.12	13 (11.5)/40 (15.7)	p = 0.29	1 (1.1)/4 (2.1)	p = 1.00
Non-asthmatic vs asthmatic						
Any AE	223 (52.2)/115 (57.5)	p = 0.22	35 (14.5)/30 (24.0)	p = 0.02	8 (4.2)/5 (5.7)	p = 0.60
GRAZAX [®] -related AE	192 (45.0)/98 (49.0)	p = 0.35	27 (11.2)/26 (20.8)	p = 0.01	3 (1.6)/2 (2.3)	p = 0.65

a Patients could be both polysensitized and asthmatic.

Table V. Compliance with GRAZAX® treatment

Variable	Year 1 (n=628)	Year 2 (n=367)	Year 3 (n=277)
Compliance, n (%)^a			
Did the patient satisfactorily follow GRAZAX® prescription? ^b			
Yes	446 (71.8)	316 (86.8)	250 (90.3)
No	175 (28.2)	48 (13.2)	27 (9.7)
Reasons for non-compliance, n (%)^a			
Omission	104 (61.2)	31 (64.6)	22 (81.5)
Adverse events	42 (24.7)	9 (18.8)	3 (11.1)
Other	24 (14.1)	8 (16.7)	2 (7.4)

a Percentages are calculated on the number of available data.
b Satisfactory compliance was defined as no more than two GRAZAX® tablets/month missing.

As polysensitization and/or allergic asthma often coexist in patients with ARC,^[28,29] we deemed it important to investigate the possible impact of such conditions on GRAZAX® tolerability. Previously published^[20] and current data from the GRAAL trial did not raise any specific safety concerns with regard to these patient subgroups. Although having mild-to-moderate asthma was associated with a significantly higher risk of developing an adverse event during the second year, this did not impact tolerability in a clinically relevant way. Moreover, we observed that the proportion of asthmatic patients continuing treatment during the second year (77.2%) was above that observed for the overall population, suggesting a comparable satisfaction rate for GRAZAX® in this subgroup. However, objective parameters (i.e. lung function tests, peak expiratory flow measurements, etc.) were not included in the present study.

Treatment compliance was high over the 3 years in the majority of patients, ranging from 71.8% (n=446) in the first year to 90.3% (n=250) in the final year of treatment. This is in line with other studies^[30] and is of particular significance as the results were obtained in a real-world setting, where treatment compliance is widely acknowledged to be poorer than in controlled trials.^[31] The convenience of the GRAZAX® formulation and the straightforward once-daily regimen are factors likely to optimize treatment compliance.

The limitations of the current trial are those of an open-label, observational, prospective study

of adverse events. Our aim was to investigate the tolerability of GRAZAX® in a real-world setting in France, and as such, a more controlled study was not appropriate. To attempt to control for investigator bias, patients were chosen randomly from the study registry, which was demonstrated to be representative of the sample as a whole. Although analysis of the effects of concomitant medication during the first year of the study have already been published,^[20] analysis of effects in the subgroup of patients who received GRAZAX® for 3 years was not possible. Also, carryover effects of other treatments received during the periods when GRAZAX® was not available cannot be ruled out. Determination of any correlations between duration of treatment and more formally assessed patient quality of life would have been interesting, but were not the focus of the current trial.

As noted, patients remaining in the trial during the second and third seasons were generally better able to tolerate treatment than those who withdrew after or during the first season. Compounding this potential for a ‘survival population’ bias is the relatively high overall drop-out rate. Although the number of patients withdrawing from the study decreased with each year, the overall drop-out rate (including inter-annual withdrawals) was greater than that observed during each treatment period (figure 1). A total of 356 patients (56.7%) withdrew from the study between the first study visit and the last, making it difficult to draw definite conclusions regarding the year-on-year

reduction in adverse events. However, given the evidence that supports similar progressive reductions in adverse events with continued SLIT,^[27] it is likely that the impact of any such bias is minimal.

Conclusion

The SQ-standardized grass allergy sublingual immunotherapy tablet was generally well tolerated in this real-world setting. Adverse events mostly occurred during the first month of initiation or re-initiation, and few reactions were severe. The incidence of mild reactions at first administration confirms the importance of treatment initiation at the physician's office. The key finding of this study is the need to perform re-introduction under medical supervision when GRAZAX[®] is prescribed according to a pre- and co-seasonal regimen. The good tolerability profile, ease of use and widespread availability of GRAZAX[®] in Europe favour improved treatment compliance.

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