



Year-round treatment initiation for a 6-grasses pollen allergoid in specific immunotherapy of allergic rhinoconjunctivitis and asthma

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Aim: Allergen immunotherapy (AIT) is an effective treatment for allergic diseases. We investigate whether treatment-initiation during the pollen season is safe. **Methods:** RCT-IIIb-trial of 6-grass-pollen-allergoid (Allergovit®) in grass pollen-allergic patients (18–65 years) with moderate–severe rhinitis/rhinoconjunctivitis ($\pm$ controlled asthma), randomized 2:1 to treatment-initiation during (Group-A) versus outside the pollen season (Group-B). **Results:** Of 240 patients (32.8 ± 9.9 years, 19.5% asthma) treated, 84.9% (Group-A) and 86.6% (Group-B) reached maintenance dose without delay. Treatment-emergent adverse events occurred in 108 (68.4%/Group-A) and 41 patients (56.2%/Group-B) leading to premature trial-termination in 11 patients (7%/A) versus 3 (4.1%/B). Across groups, physicians (for 190 patients; 85.2%) and patients (192; 86.1%) rated the tolerability as ‘very good’–‘good’. *Phleum pratense*-specific IgG4 increased in both groups ($p < 0.0001$). **Conclusion:** Year-round allergen immunotherapy-initiation with this preparation is safe.

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Keywords: allergoid • intra-seasonal treatment initiation • subcutaneous immunotherapy • year-round treatment initiation

Background

Allergen immunotherapy (AIT) is considered an effective treatment for patients with seasonal or perennial allergic rhinoconjunctivitis and asthma and is the only treatment that may take effect on the natural course of allergic diseases, and may prevent the development of asthma in patients with allergic rhinitis [1]. In a survey among specialist allergy societies and allergy patient support groups, as well as in patients who discontinued immunotherapy prematurely, the greatest obstacles for AIT were found to be accessibility and costs to the patient, including time missed from work and travel costs [2,3].

To date, according to current guidelines and marketing authorizations, in patients with allergic symptoms AIT is either initiated after or before the pollen season [1,4,5].

In order to allow a treatment start during the entire year without any time constraints, therapy initiation needs to be investigated during the months when patients are exposed to clinically relevant pollen loads. This is normal when the patient seeks medical attention and is highly motivated to start a disease modifying therapy. However, due to the time interval between this consultation and a preseasonal start of therapy, many patients lose their motivation to start AIT because they are free of symptoms at this time and no longer think about it. Therefore, a timely intra-seasonal initiation of the treatment regime appears to be more suited to the needs of the patients.

Aluminum-adsorbed, high-dose, 6-grasses pollen allergoid (Allergovit® 6-grasses) has been approved since 1992 and has since then been used routinely in subcutaneous AIT. Its efficacy and safety were investigated among other trials, in a 2-year, double-blind, multicenter, placebo-controlled, Phase III trial in 154 patients suffering symptoms

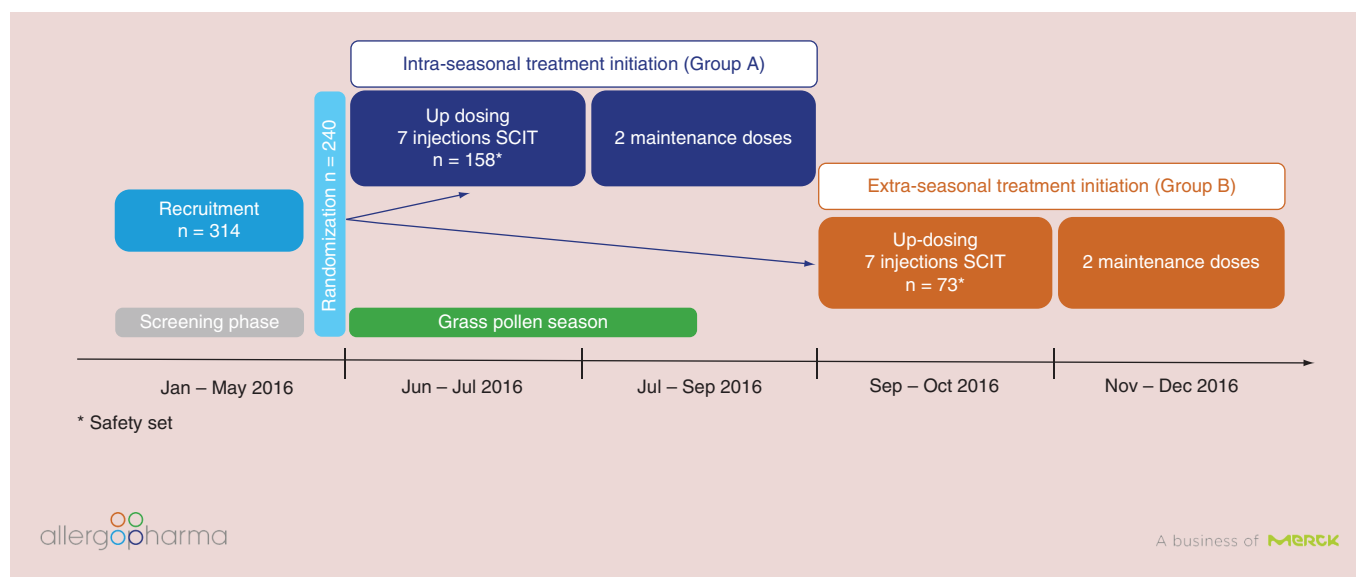


Figure 1. Trial design: treatment initiation of grass pollen allergen immunotherapy in group A (intra-seasonally) versus Group B (extra-seasonally).

of rhinoconjunctivitis with or without asthma [6]. A combined symptom and medication score raised in the first year of treatment showed a significant difference of 26.6% between the two treatment groups. It further improved after the second year of treatment when there was a significant 48.4% difference in the symptom and medication score between active and placebo treatment in favor of the allergoid. Highly significant increases in grass pollen allergen-specific IgG1 and IgG4 antibody concentrations were measured in association with active treatment [6].

Patients seek medical advice during the pollen season when they suffer from allergic symptoms. Although not recommended by AIT treatment guidelines yet, an immediate treatment initiation would be helpful to facilitate the uptake of this only disease-modifying therapy. A systematic review [7] identified eight clinical trial publications reporting subcutaneous AIT initiations at different times of the year in more than 900 patients including three direct comparisons between intra- and extra-seasonal initiations of subcutaneous immunotherapy (SCIT). From the existing published data, the perspective of initializing AIT outside or during pollen seasons seems to be practicable, both types of treatment initiations with a favorable safety profile [4,7].

We performed a multicenter, randomized, open-label, clinical trial to evaluate safety and tolerability of a year-round initiation of specific immunotherapy for a 6-grasses pollen allergoid focused on the comparison of dose escalation starting during the grass pollen season (Group A) versus a standard preseasonal dose regimen (Group B) starting outside the pollen season.

Methods

Design

This was a multicenter, randomized, controlled, open-label, Phase IIIb trial with two active treatment groups performed in Germany. Screening of patients was performed between January and May 2016 and eligible men and women were entered in June 2016. End of trial was 15 February 2017. EudraCT trial identifier is 2015-002409-13.

Patients in Group A (proof of principle for an intra-seasonal treatment initiation) started AIT during the grass pollen season (in June 2016) and patients in Group B (standard preseasonal dose regimen) started dose escalation outside the grass pollen season (in September 2016). A flowchart of the trial design is presented in Figure 1. Patients were randomized in a 2:1 ratio using block randomization, whereby the centers did not know the block size.

Patients

The full list of inclusion and exclusion criteria is shown in Online Supplementary File 1.

To be eligible for trial participation, all inclusion criteria had to be met by legally competent male or female outpatients: written informed consent, age 18–65 years, IgE-mediated seasonal allergic rhinitis or rhinoconjunctivitis

with or without controlled allergic asthma caused by grass pollen as confirmed by skin prick test (wheal for 6-grasses pollens ≥ 3 mm in diameter) or immunoassay result for specific IgE ≥ 0.70 kU/l to grass mix; main symptoms of allergic rhinitis or rhinoconjunctivitis between the months of May and August of at least 1 month with respective grass pollen exposure in the previous two seasons; previous treatment with antiallergic medication for at least two seasons prior to enrollment.

Main exclusion criteria included the following: previous AIT with grass pollen or with unknown allergen within the last 5 years; any present immunotherapy; any other AIT within the last 5 years; clinically relevant chronic rhinoconjunctival or respiratory symptoms related to other reasons than allergy; peak expiratory flow (PEF) $< 70\%$ of predicted normal (European Coal and Steel Community) under adequate asthma treatment according to the Global Initiative for Asthma (GINA) [8]; perennial and continuously treated asthma; rhinoconjunctival atopic symptoms for 20 years or longer; severe acute or chronic diseases or autoimmune diseases, immune defects including immunosuppression.

A number of restrictions during trial conduct applied. If a patient had received a vaccination against viral or bacterial pathogens, a period of at least 2 weeks had to be met between the vaccination and the start of the AIT. Before performing the skin prick test, use of any medication that could interfere with the skin reaction had to be discontinued. Such drugs had to be stopped for a period of time equivalent to the manufacturer-specified duration of action. Use of any short-acting antihistamines (e.g., diphenhydramine) had to be stopped for 3 days, and long-acting antihistamines (e.g., fexofenadine, cetirizine, loratadine or desloratadine) for 7 days prior to skin testing. During the treatment phase, it had to be considered that concomitant treatment with antiallergic drugs could affect the tolerance level of the patient and delay possible anaphylactic reactions or the diagnostic results. Topical treatment was preferred during the trial.

Patients should stop the use of any systemic antiallergic medication at least for 3 days before AIT administration, on the day of AIT administration and 1 day after. However, symptomatic treatment with topical antiallergic drugs could be continued. Medication for the treatment of rhinitis and rhinoconjunctivitis was permitted, but had to be documented as concomitant medication.

Treatments

Allergovit 6-grasses pollen is an aluminium-absorbed allergoid suspension for subcutaneous injection. Two different strengths were provided: A with 1000 TU/ml and B with 10,000 TU/ml.

Dose escalation was performed according to the recommended standard schedule of the product and could be adjusted according to the well-being of the individual patient. The maximum individually tolerated dose could vary between patients and could be lower than the maximum recommended dose. During dose escalation, weekly injections of 100, 200, 400, 800, 1500, 3000 and 6000 TU were administered. Intervals could be extended to a maximum of 14 days. During maintenance, the injection interval had to be 2 weeks at first maintenance visit, and a deviation of ± 3 days was allowed. The injection interval had to be 4 weeks at second maintenance visit, and a deviation of ± 7 days was allowed. After the maximum dose was reached, this dose was to be administered during maintenance treatment (Figure 2).

The World Allergy Organization (WAO) Systemic Reaction Grading System [9] was used for grading of adverse events (AEs) based on the organ systems involved and the severity of the reaction.

Concomitant & restricted medication

Medication for the treatment of rhinitis and rhinoconjunctivitis was permitted but had to be documented. Patients with bronchial asthma who required regular basic treatment of their allergic asthma had to be treated as recommended by GINA 2015 to control their asthma [8]. The start of additional asthma medication was not allowed. Beta blockers were not permitted.

End points

AEs and serious AEs were assessed by the investigator and coded using MedDRA version 19.0 [10] according to their primary system organ class and preferred term. Exploratory immunological parameters were the change in specific total IgG and specific IgG4 for *Phleum pratense* between screening visit and final visit. Safety end points were as follows:

- Local reactions at the injection site ≤ 5 cm (number);

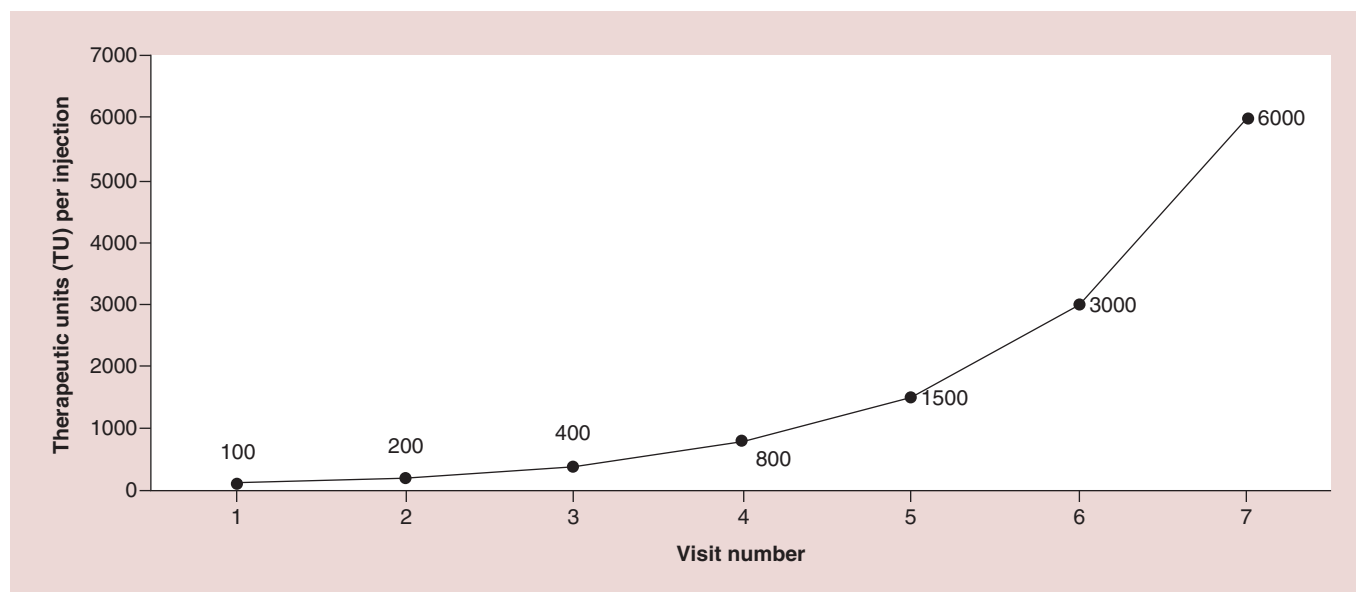


Figure 2. Dosing schedule (up-dosing phase).

- Incidence, type and intensity of local reactions >5 cm at the injection site (number);
- Incidence and intensity of systemic reactions after injections according to the WAO grading system [9], classification reviewed by the Data Safety Monitoring Board.
- Intensity of treatment-emergent AEs (TEAEs) as judged by the investigator (mild = transient symptoms, no interference with the patient's daily activities; moderate = marked symptoms, moderate interference with the patient's daily activities; severe = considerable interference with the patient's daily activities);
- Changes in laboratory values (hematology, clinical chemistry and urinalysis) before and after treatment;
- Changes in vital signs and lung function measured before, during and after treatment;
- Assessment of the overall tolerability of treatment by the investigator and the patient using a five-point Likert scale (1 = very bad and 5 = very good) was obtained at the final visit [11].

Statistical methods

In this safety and tolerability trial, no hypotheses were formulated, and the data were analyzed descriptively.

Due to the exploratory design of the trial, there was no formal estimation of sample size accounting type I error, rate, power, standard deviation and effect size. The samples size of 35 patients per treatment group was considered sufficient to guarantee a probability of 95% that AEs with a true incidence rate of 8.6% occur at least once in occurring AEs and to compare AE profiles as well as changes in vital signs and laboratory values. The basic analysis for all assessments of safety and tolerability was the safety set (SAF), which was defined as the group of patients who received at least one dose of trial medication.

Ethical conduct of the trial

The trial was conducted in accordance with the trial protocol, the International Council for Harmonization guideline for Good Clinical Practice, applicable local regulations and the Declaration of Helsinki. All patients provided written informed consent. Trial approval was obtained from the Ethics Committee of the University of Erlangen, Reference number: 217_15Az. Date of approval: 16 October 2015.

Results

Patient disposition & flow

Of the 314 patients screened, 240 were randomized to one of two treatment groups: 161 patients in Group A (started treatment in June) and 79 patients in Group B (started treatment after the pollen season) (Figure 3). Most of the 74 patients who failed screening did not meet all of the eligibility criteria.

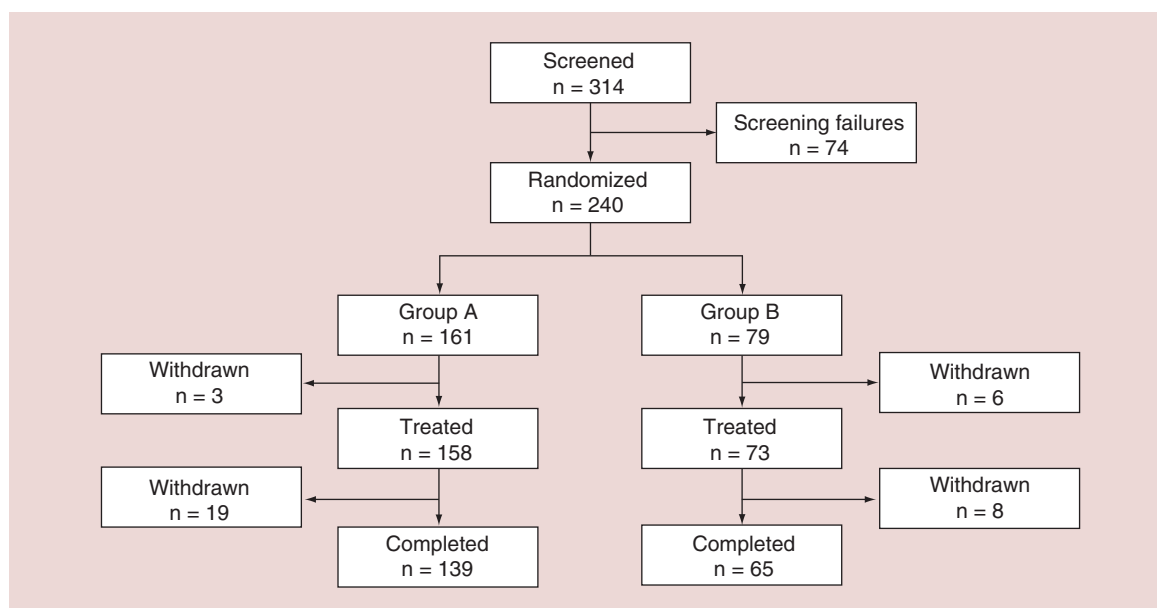


Figure 3. Patient disposition (safety set: n = 158 patient in Group A, n = 73 in Group B). Reasons for screening failure and withdrawals (number of patients): Screening failures (n = 74): Inclusion criteria not met/exclusion criteria met (n = 62), consent withdrawn (n = 5), adverse event (n = 1), lost to follow-up (n = 2), other reasons (n = 4). Withdrawals after randomization before treatment: Group A: consent withdrawn (n = 2), lost to follow-up (n = 1); Group B: consent withdrawn (n = 2), lost to follow-up (n = 3), unexpected work assignment abroad (n = 1). Withdrawals after randomization during treatment: Group A: lost to follow-up (n = 3), adverse event (n = 11), investigator decision (n = 2), prolonged interval (n = 1), consent withdrawn (n = 2). Group B: lost to follow-up (n = 4), adverse event (n = 2), prolonged interval (n = 2).

Table 1. Patient characteristics, allergy history and co-medication at baseline (safety set).

Characteristic	Intra-seasonal treatment initiation	Extra-seasonal treatment initiation
Number of patients (n)	158	73
Age range (years) mean ($\pm$ SD)	18–64 32.6 $\pm$ 9.5	19–64 33.6 $\pm$ 10.7
Sex, male female	85 (53.8) 73 (46.2)	38 (52.1) 35 (47.9)
Body Mass Index (kg/m ²)	25.5 $\pm$ 4.6	25.0 $\pm$ 5.1
Allergic-specific history		
Nose symptoms (%)	158 (100.0)	73 (100.0)
Eye symptoms (%)	150 (94.9)	69 (94.5)
Lung (%)	36 (22.8)	16 (21.9)
Asthma (%)	29 (18.4)	16 (21.9)
Antiallergic medications		
Antihistamines, systemic (%)	68 (43.0)	29 (39.7)
Nasal preparations (%)	35 (22.2)	18 (24.7)

Safety set, n = 231 patients. Values are patient numbers and percentages (in brackets) or mean values $\pm$ standard deviation.

Nine patients terminated the trial after randomization, but before the first investigational medicinal product (IMP) administration: three patients in Group A and six patients in Group B.

Demographics in the safety patient set at baseline

Patient characteristics and co-medication at baseline (SAF) are shown in Table 1. Somewhat more male than female patients participated in the trial (n = 123; 53.2% vs n = 108; 46.8%). The majority was Caucasian (n = 217; 93.9%). Mean age was 32.8 $\pm$ 9.9 years, with a range from 18 to 64 years. Mean BMI was 25.4 $\pm$ 4.8 kg/m². With respect to the named parameters, there were no significant differences between Groups A and B.

Asthma as comorbidity

Most patients did not have asthma at screening; 19.0% patients in Group A and 20.5% in Group B were classified as having controlled asthma according to GINA at screening.

Allergy-specific history & skin prick test

Allergic nasal symptoms were reported for all 231 patients, eye symptoms for 219 (94.8%) patients and lung symptoms for 52 (22.5%) patients. The percentage of patients with allergy-specific symptoms was similar between the treatment groups (Table 1).

Less than half of the patients had relatives with allergies. Other allergic diseases reported for >5% of the total patients were seasonal allergy (36.8%), allergy to animal (11.7%), house dust allergy (9.5%) and food allergy (8.7%).

Mean and median wheal sizes were similar for all allergens tested. Patients had the strongest reaction to the 6-grasses allergen with a mean size of 8.92 mm in Group A and 8.70 mm in Group B. A total mean size of 7.12 mm was reported for rye, 5.03 mm for birch, 2.77 mm for mugwort, 2.08 mm for *Dermatophagoides farinae* and 2.09 mm for *Dermatophagoides pteronyssinus*.

PEF was performed to determine the asthma status of patients at screening. Mean and median PEF were similar between all the groups at screening.

Out of 231 patients in the safety set, at least one medical history was reported by 104 (45.0%) patients. The most frequently reported medical history was asthma, followed by hypothyroidism (Table 1).

Specific IgG4 measurements *in vitro*

Immunological AIT effects were assessed by analyzing the serum concentrations of timothy grass pollen (*P. pratense*) specific IgG4 before and after treatment using ImmunoCAP (ThermoFisher Scientific, Uppsala, Sweden).

Concomitant medication

During the treatment phase, at least one concomitant medication was used by 93.5% (n = 216) of all subjects (safety set, n = 231). The most commonly used drugs were for the respiratory system used by 140 subjects (88.6%) in intra-seasonal Group A and 55 (75.3%) in extra-seasonal Group B (p = 0.018). Thereof, antihistamines for systemic use were most frequent (used by 67% [n = 106 subjects] from Group A and 64.4% [n = 47] from group B). In contrast, corticosteroids for systemic use were used rarely (3.2% [n = 5] in Group A and 1.4% [n = 1 subject] in Group B; p = 0.6197; for details see Online Supplementary Table 1).

Exposure to 6-grasses pollen allergoid

The mean total volume of injected 6-grasses pollen allergoid was similar between all the groups. The total volume ranged from 100 TU (the first dose level at the start of the dose escalation phase) to 39,000 TU. The majority of patients in the safety set reached the maintenance dose without any dose reductions (Table 2). The planned dose had to be adjusted in 62 patients: it was adjusted for more patients in Group A (n = 46; 30.3%) than in Group B (n = 16; 23.9%). This difference between Group A and Group B was however not statistically significant (p = 0.4161).

The most frequently reported reason (in n = 44, i.e., 71.0% of n = 62 patients) for adjustment to the planned dose was AEs. This was the case for 33 patients (out of n = 46 (71.7%)) from Group A and 11 (out of 16 patients (68.8%)) from Group B requiring dose adjustment (Table 2). The majority of patients (69.7% in Group A and 76.1% in Group B) received a total of nine injections.

Immunology

Mean change from baseline to the final visit in grass pollen specific IgG4 (available in 222 patients) was similar between the groups: 4.75 mg/l in Group A and 5.07 mg/l in Group B. The change from baseline to the final visit within each group was statistically significant (p < 0.0001).

Adverse events

A detailed overview on TEAE is provided in Table 3.

Table 2. Maintenance does and dose adjustments (safety set).

		Intra-seasonal treatment initiation	Extra-seasonal treatment initiation
Subject reached maintenance dose without back-dosing	Missing	12	6
	No	22 (15.1)	9 (13.4)
	Yes	124 (84.9)	58 (86.6)
	p-value [†]	0.8365	
Dose adjustment atleast once	Missing	6	6
	No	106 (69.7)	51 (76.1)
	Yes	46 (30.3)	16 (23.9)
	p-value [†]	0.4161	
Dose adjustment reason [‡]	Adverse event	33 (71.7)	11 (68.8)
	Not within timeframe	14 (30.4)	6 (37.5)
	Other [§]	3 (6.5)	1 (6.3)

[†]Two-sided p-value of the Fisher exact test used to compare Group A (Intra-seasonal treatment initiation) with Group B (Extra-seasonal treatment initiation).

[‡]Subjects counted once per category; multiple answers were possible.

[§]Comprises back-titration for one subject and reasons related to nonadherence to the timeframe for all other subjects.

Table 3. Summary of treatment-emergent adverse events (safety set).

	Statistic	Intra-seasonal treatment initiation (N = 158)	Extra-seasonal treatment initiation (N = 73)
TEAE related to IMP	N (%) / E	108 (68.4) / 605	41 (56.2) / 245
	95% CI	(60.5; 75.5)	(44.1; 67.8)
	p-value [†]	0.0777	
TEAE leading to trial discontinuation	N (%) / E	11 (7.0) / 15	3 (4.1) / 9
	95% CI	(3.5; 12.1)	(0.9; 11.5)
	p-value [†]	0.5570	
TEAE systemic reactions according to WAO	N (%) / E	5 (3.2) / 6	2 (2.7) / 3
	95% CI	(1.0; 7.2)	(0.3; 9.5)
	p-value [†]	1.0000	
TEAE local reactions related to IMP	N (%) / E	102 (64.6) / 577	40 (54.8) / 229
	95% CI	(56.6; 72.0)	(42.7; 66.5)
	p-value [†]	0.1907	
Serious TEAE	N (%) / E	1 (0.6) / 1	0 (0.0) / 0
	95% CI	(0.0; 3.5)	(0.0; 4.9)
	p-value [†]	1.0000	
Serious TEAE related to IMP	N (%) / E	0 (0.0) / 0	0 (0.0) / 0
	95% CI	(0.0; 2.3)	(0.0; 4.9)
	p-value [†]	-	

[†]Fisher exact test used to compare both groups.

CI: Confidence interval (according to Clopper Pearson for the number of subjects); E: Number of events; IMP: Investigational medicinal product; TEAE: Treatment-emergent adverse event; WAO: World Allergy Organization.

TEAEs were reported for 91.1% of patients in Group A and 78.1% in Group B ($p = 0.01$). At least one TEAE related to IMP by the investigator was reported for 108 (68.4%) patients in Group A and for 41 (56.2%) patients in Group B (p not significant, [Table 3](#)). During the trial, no serious AEs related to treatment occurred.

A slightly higher percentage of patients in Group A prematurely terminated the trial due to TEAEs than in Group B: 11 patients (7.0%) due to 15 TEAEs versus 3 patients (4.1%) due to 9 TEAEs (p not significant, [Table 3](#)). This difference was however not statistically significant. The most frequently reported TEAEs leading to withdrawal were injection site swelling (4.3% of total patients) and injection site erythema (2.6% of the total patients).

Table 4. Treatment-emergent local reactions related to investigational medicinal product by intensity (safety set).

Local reaction Intensity	Intra-seasonal treatment initiation (n = 158)	Extra-seasonal treatment initiation (n = 73)
Number (%) of patients with at least one adverse event	102 (64.6)	40 (54.8)
Mild	80 (50.6)	34 (46.6)
Moderate	37 (23.4)	12 (16.4)
Severe	8 (5.1)	4 (5.5)

Table 5. Treatment-emergent systemic reactions related investigational medicinal product by MedDRA system organ class, preferred term, World Allergy Organization grade (safety set).

System Organ Class Preferred term WAO Grade	Intra-seasonal treatment initiation (n = 158)	Extra-seasonal treatment initiation (n = 73)
Overall – Patients with at least one adverse event n (%)	5 (3.2)	2 (2.7)
Eye disorders – Conjunctivitis allergic – WAO Grade 1	1 (0.8)	
General disorders & administration site conditions – Injection site oedema – WAO Grade 1		1 (0.4)
Nervous system disorders – Headache – WAO Grade 1	1 (0.6)	
Respiratory, thoracic & mediastinal disorders – Rhinorrhoea – WAO Grade 1		1 (1.4)
Skin and subcutaneous tissue disorders – Rash – WAO Grade 1 – Urticaria – WAO Grade 1	1 (0.6) 1 (0.6)	
Immune system disorders – Anaphylactic reaction – WAO Grade 2	1 (0.6)	1 (1.4)

IMP: Investigational medicinal product; TEAE: Treatment-emergent adverse event; WAO: World Allergy Organization.

Local reactions

Of the total safety set, at least one local reaction occurred in 102 patients (64.2%) of Group A and 40 patients (54.8%) in Group B ($p = 0.1907$) (Table 4). All local reactions, except for three reactions in Group B, were considered related to 6-grasses pollen allergoid. A total of 114 patients had mild reactions, 49 had moderate and 12 had severe local reactions.

Systemic reactions

Six systemic reactions according to WAO were reported for five (3.2%) patients in Group A and three systemic reactions for two (2.7%) patients in Group B (Table 5). The differences between the groups were not statistically significant ($p = 1.0000$). All of these were considered by the investigator to be related to 6-grasses pollen allergoid.

Most reactions were WAO Grade 1 systemic reactions. Only two WAO Grade 2 systemic reactions were reported: one related anaphylactic reaction with difficulty in breathing and with urticaria and itching for one patient in Group A2 between 30 min and 6 h after administration, considered moderate in intensity (6-grasses pollen allergoid dose escalation was not continued and the dose was repeated, as recorded in the electronic case report form [eCRF]); and one related anaphylactic reaction with urticaria at the thigh and watery eyes for one patient in Group B between 6 and 24 h after administration, considered mild in intensity (6-grasses pollen allergoid administration discontinued). All other systemic reactions were only reported for one patient each. Most of these systemic reactions were considered mild in intensity, only one was reported as moderate and one other as severe.

Tolerability assessment

The great majority of physicians rated the tolerability of the immunotherapy as ‘very good’ (intra-seasonal treatment 41.2%; extra-seasonal treatment 54.3%) or ‘good’ (intra-seasonal treatment 43.1%; extra-seasonal treatment 32.9%). Moreover, most patients rated the tolerability accordingly: ‘very good’ (intra-seasonal treatment 38.6%; extra-seasonal treatment 42.9%) or ‘good’ (intra-seasonal treatment 46.4%; extra-seasonal treatment 45.7%) (Figure 4).

Laboratory parameters

There were no trends in the mean and median changes from baseline over time and between treatment groups or subgroups in any of the clinical chemistry, hematology or urinalysis laboratory parameters.

Comparison of subgroups with & without symptomatic medication

Approximately only 20% of the patients in this trial who started 6-grasses pollen allergoid 6-grasses treatment during the pollen season (Group A) frequently used systemic antiallergic co-medication. Other safety assessments, in other words, laboratory parameters, vital signs, physical examination findings and lung function tests were similar between the treatment groups. Outcomes with respect to tolerability and effectiveness (IgG4 antibody responses) in terms of preseasonal versus intra-seasonal treatment (starting treatment during the pollen season in this trial), were not different between subgroups.

Discussion

The present trial provides a rationale to initiate AIT at any time during the year: the findings of the study open for the possibility to initiate 6-grass allergoid AIT – besides already previously established treatment scheme starting pre- or post-seasonally – also intra-seasonally during the grass pollen season. The safety and tolerability of 6-grasses pollen allergoid in patients with rhinitis or rhinoconjunctivitis (with or without controlled allergic asthma) caused by grass pollen was similar regardless of the start of dose escalation relative to the pollen season. Initiation of this 6-grasses pollen allergoid is safe during the pollen season in this population.

The guideline of German Society for Allergology and Clinical Immunology (and other societies) on allergen-specific immunotherapy in IgE-mediated allergic diseases states that overall the evidence base on effectivity and tolerability of subcutaneous and sublingual immunotherapy for the treatment of allergic rhinitis and rhinoconjunctivitis due to pollen allergy is robust [5]. However, results of a given product (due to a substantial heterogeneity of allergens) or trial cannot be extrapolated to another product. Currently, a small fraction of patients (less than 10% on immunotherapy) initiate sublingual grass allergen products in-season (May–July) [12].

This open-label, Phase IIIb study focused on the safety and tolerability profile of intra-seasonal dose escalation versus post-seasonal dose escalation of a 6-grasses pollen allergoid (approved for pre- and post-seasonal treatment initiation).

Pollen counts from the investigated grass pollen season 2016 [13,14] indicate a regular grass pollen exposure during the season in Germany: Airborne pollen concentration measured during the vegetation period of 2016 in Munich identified start and end of grass pollen season (5 and 95% of year's total amount reached) on 18 May 2016 and 4 August 2016, highest grass pollen concentrations with up to 268 pollen/m³ per day were reached in the South of Germany between end of May and mid of June [13]. In contrast, in Berlin and the Brandenburg area, in 2016, the start and end of the pollen season was 13 May–26 July 2016 with peak pollen periods with up to 163 pollen/m³ per day reached between the end of May and the end of June [14]. Pollen counts were not recorded for the individual trial sites, but the study design ensured that the intra-seasonal treatment group (Group A) certainly experienced dose escalation during the grass pollen season (from June on), whereas an exposure to grass pollen was not present during dose escalation in Group B (from September on).

The majority of patients (>80%) in both groups reached the maintenance dose without any dose reduction, and the number of patients needing a dose adjustment did not significantly differ between groups. Also, no statistically significant difference for the number of patients prematurely terminating the trial due to TEAEs was observed between groups. The TEAE rate, as well as the rate of local reactions were numerically but not statistically significantly higher in Group A which in this trial started AIT during the grass pollen season compared with the preseasonal group (Tables 3 and 4). However, the study may be underpowered to detect a difference in rare systemic reactions in both groups as there is a clear nonsignificant trend toward higher mild TEAE in the intra-seasonal



Figure 4. Tolerability assessment by investigator and patient. Tolerability assessment by (A) investigator and (B) patient. Tolerability was assessed for n = 223 patients by investigators and by n = 223 subjects (safety set n = 231, 8 missing) using a five-point Likert scale (ranging from very bad [1] to very good [5]) at the final visit.

group A (Tables 3 & 4). After licensing, an acceptable safety profile is followed up through pharmacovigilance systems implemented on a national and European level [15].

No unexpected safety concerns were reported for any patients in both groups and the safety profile of 6-grasses pollen allergoid as described in the Summary of Product Characteristics (SmPC) was generally confirmed.

These results are in accordance with the safety data reported from other trials on other allergen preparations. SCIT using an unmodified grasses rye extract initiated during the pollen season did result no significant differences in the incidence of systemic reactions compared with placebo [4]. In the systematic review on intra-seasonal treatment initiation of AIT, for SCIT trials the frequency of systemic allergic reactions was 0–7% with ‘up to peak season’ or co-seasonal initiation, and 0–6% with ‘after peak season’ or out of season initiation of SCIT [7]. Also, from one trial included in [7], using a direct comparison of intra-seasonal with extra-seasonal SCIT initiation, low discontinuation rates (3% for ‘up to peak season’ and 2% for ‘after peak season’ initiation) have been reported.

In our trial, no placebo group was included, since the research focus was on the time schedule of treatment and on safety/tolerability of treatment initiation during the grass pollen season. Thus, the preseasonal routine schedule of the licensed medicinal product served as comparator, and 6-grasses pollen allergoid was administered, with a well-known safety profile for administration before and after the pollen season (based on the two pivotal trials AL0101AV and 98-03 [6,16]). Other than the starting time for dose escalation (during the grass pollen season in the intra-seasonal Group A, preseasonal in the other [Group B]) and the number of patients randomized in the two groups, there were no differences in the patient selection or dosing schedules between the groups. The dose and dose escalation in the trial were in line with the guidance in the SmPC of the marketed product 6-grasses pollen allergoid, which has a well-established safety and efficacy profile. All procedures performed in the trial, including lung function assessment, prick test and blood sampling, are routine procedures in clinical practice. The mentioned factors support the external validity of trial results.

With respect to efficacy, as a surrogate marker, the induction of allergen-specific (‘blocking’) IgG4 antibodies was used in this trial which has been considered as the most important immunological finding after specific immunotherapy [17–19].

Strengths of this trial include the stringent selection of participants in accordance with established clinical criteria specified in guidelines for grass pollen immunotherapy [20]. For the safety assessment of systemic reactions, the classification of the WAO was used [9].

Some limitations need to be considered when discussing the outcomes. To elucidate whether an initiation of AIT with 6-grasses pollen allergoid is possible during the pollen season similar to the established extra-seasonal treatment scheme the trial had an open-label, unblinded design. Theoretically, it would have been possible to blind patients and observers; however, this would have meant additional (sham or placebo) injections and was considered unethical. Differences in the use of symptomatic medications in and outside the pollen season might have eased potential side effects of the IMP therapy. Apart from the measurement of IgG4 as a surrogate marker for the immunological disease-modifying effects and the patientive assessment of patients which allowed a comparison across groups, efficacy was not assessed in further detail. The chosen trial design appeared feasible since efficacy data of the allergen preparation over placebo had previously been obtained with the standard preseasonal dosing scheme [21].

In terms of trial size, with 161 patients in the intra-seasonal group A, and 79 patients in the preseasonal group B, rare (0.01–0.1%) or very rare side effects (<0.01%) cannot be captured reliably due to low patient numbers [22]; however, the trial size is well in line with the other positive trials done with allergoid or nonmodified allergen preparations available in Germany as listed in the S2 guidelines (7 preparations, 12 trials, number of analyzable patients between 28 and 365 in each trial) [5]. Based on the data of this trial, a year-round treatment initiation with the high-dose grass pollen allergoid is a safe treatment option for patients suffering from an allergic rhinoconjunctivitis with or without bronchial asthma. By using this option, treatment in adult patients can be started immediately after diagnosis, even during the pollen season.

Based on the results of this trial, the year-round treatment including intra-seasonal initiation scheme for AIT using the 6-grasses pollen allergoid has been accepted for marketing authorization by the Paul-Ehrlich-Institut in Germany.

Conclusion

With this the study, having investigated in-season treatment initiation of grass pollen AIT compared with out-of-season/post-season treatment initiation, the gap of knowledge has been filled regarding the question of whether

AIT started during the pollen season is safe and tolerable. The findings of the study suggest that the intra-seasonal treatment initiation of AIT against grass-pollen with this formulation is equally safe and tolerable compared with an extra-seasonal treatment start, paving the path to a year-round treatment start in adults with this product, which has been approved as a variation to the existing marketing authorization in Germany, allowing for a treatment initiation during the season, which can be now considered in selected patients.

Summary points

- To date, according to current guidelines and marketing authorizations, in patients with allergic symptoms allergen immunotherapy (AIT) is either initiated after or before the pollen season.
- However, the patients' need to seek medical attention and motivation to start a disease modifying therapy seems to be facilitated by the burden of disease during the pollen season.
- No increase in adverse events (AE) of concern was found in a systemic review on co-seasonal initiation of subcutaneous immunotherapy or sublingual immunotherapy; however, additional data with standardized regimens and doses are needed.
- To allow for a year-round treatment start with Aluminum-adsorbed high-dose, 6-grasses pollen allergoid (Allergovit® 6-grasses) including the pollen season, safety and tolerability of intra-seasonal versus extra-seasonal AIT start was investigated in this multicenter, randomized, controlled, open-label, Phase IIIb study with two active treatment groups performed in Germany.
- Patients eligible according to defined inclusion/exclusion criteria were randomized 2:1 to treatment initiation during (Group A) versus outside the grass pollen season (Group B) 2016.
- The treated study population (safety set) consisted of 231 grass-pollen allergic patients (18-65y) with moderate-to-severe rhinitis or rhinoconjunctivitis (± controlled asthma): n = 158 in Group A, 73 in Group B.
- Patients in Group A (proof of principle for an intra-seasonal treatment initiation) started AIT during the grass pollen season (in June 2016; treatment period: 9 sc. injections from June–September) and patients in Group B (standard preseasonal dose regimen) started dose escalation outside the grass pollen season (in September 2016; treatment period from September–December 2016).
- Symptomatic treatment with topical antiallergic drugs could be continued. Medication for the treatment of rhinitis and rhinoconjunctivitis was permitted, but had to be documented as concomitant medication.
- AEs and serious AEs were assessed by the investigator and coded using MedDRA version.
- Safety end points were:
 - Local reactions at the injection site ≤5 cm (number);
 - Incidence, type and intensity of local reactions >5 cm at the injection site (number);
 - Incidence and intensity of systemic reactions after injections according to the World Allergy Organization grading system;
 - Intensity of treatment-emergent AEs (TEAEs) as judged by the investigator (mild = transient symptoms, no interference with the patient's daily activities; moderate = marked symptoms, moderate interference with the patient's daily activities; severe = considerable interference with the patient's daily activities);
 - Changes in laboratory values (hematology, clinical chemistry and urinalysis) before and after treatment;
 - Changes in vital signs and lung function measured before, during and after treatment;
 - Assessment of the overall tolerability of treatment by the investigator and the patient using a 5-point Likert scale (1 = very bad and 5 = very good).
- The majority of patients in the safety set (84.9% in Group A and 86.6% in Group B) reached the maintenance dose without a delay.
- Any adjustments had to be done in 62 patients: Group A (n = 46; 30.3%), Group B (n = 16; 23.9%) (difference not significant, p = 0.4161).
- *Phleum pratense* specific IgG4 increased in both groups (change to baseline p < 0.0001).
- During the treatment phase, at least one concomitant medication was used by 93.5% (n = 216) of all subjects (safety set, n = 231). The most commonly used drugs were for the respiratory system used by 140 subjects (88.6%) in Group A and 55 (75.3%) in Group B (p = 0.018). Thereof, antihistamines for systemic use were most frequent (used by 67% (n = 106 subjects) from Group A and 64.4% (n = 47) from group B).
- At least one TEAE occurred in 108 (Group A: 68.4%) and 41 patients (Group B: 56.2%) (p not significant).
- Premature terminations of the trial due to TEAEs occurred in 11 (7.0%) patients in Group A versus 3 (4.1%) in Group B (p not significant).
- The most frequently reported TEAEs leading to withdrawal were injection site swelling (4.3% of total patients) and injection site erythema (2.6% of the total patients).
- Six systemic reactions according to World Allergy Organization were reported for 5 (3.2%) patients in Group A and three systemic reactions for 2 (2.7%) patients in Group B (not statistically significant, p = 1.0000).
- The majority of physicians (for 190 patients; 85.2%) and patients (192; 86.1%) rated the tolerability of both treatment schemes as 'very good' or 'good'.

- With this the study, having investigated in-season treatment initiation of grass pollen AIT compared with out-of-season/post season treatment initiation, the gap of knowledge has been closed regarding the question whether AIT start with this investigational medicinal product during the pollen season is safe and tolerable.
- The findings of the study suggest, that the intra-seasonal treatment initiation of AIT against grass-pollen with this formulation is equally safe and tolerable compared with an extra-seasonal treatment start, paving the path to a year-round treatment start in adults with this product.
- Based on the data, a variation to the existing marketing authorization has been granted in Germany, allowing for a treatment initiation during the season that can be now considered in selected patients.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/imt-2019-0086

Authors contributions

V Mahler was involved in the development of the trial protocol and was the coordinating investigator of the trial. S Zielen participated as investigators at the trial sites with high levels of recruitment.

All authors contributed to the preparation of the manuscript by reviewing, commenting, and critically revising the text where applicable. All authors read and approved the final manuscript.

Financial & competing interests disclosure

The trial was funded by Allergopharma GmbH, Reinbek, Germany. The authors of this manuscript have the following competing interests: After completion of the trial, Vera Mahler, became employee of the Paul-Ehrlich-Institute, Langen, Germany. Measures are in place for unbiased marketing authorization procedures. S Zielen has received fees for lectures and advisory boards from Allergopharma GmbH, ALK-Abelló Arzneimittel GmbH, Allergy Therapeutics, HAL Allergy, Lofarma GmbH, bene-Arzneimittel GmbH, Biotest, Boehringer Ingelheim, GlaxoSmithKline GmbH, IMS Health GmbH & Co. OHG, Novartis AG and Vifor Pharma Deutschland GmbH. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Data sharing statement

The authors certify that this manuscript reports original clinical trial data: EudraCT trial identifier is 2015-002409-13. No individual participant data that underlies the results reported in the article will be available, and nor will information regarding the study protocol or statistical analysis, beyond what is reported in the text and the supplementary files.

References

Papers of special note have been highlighted as: • of interest

1. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Mallat H-J, Valovirta E. Standards for practical allergen-specific immunotherapy. *Allergy* 61(Suppl. 82), 1–20 (2006).
- **Provides a road map for quality assured practical daily routine for allergen-specific immunotherapy ensuring a high professional standard and an effective use of resources.**
2. Ryan D, van Gerth Wijk R, Angier E *et al.* Challenges in the implementation of the EAACI AIT guidelines: a situational analysis of current provision of allergen immunotherapy. *Allergy* 73(4), 827–836 (2018).
- **Illustrates the current situation of provision of allergen immunotherapy (AIT) which is administered too rarely.**
3. Vaswani R, Garg A, Parikh L, Vaswani S. Non-adherence to subcutaneous allergen immunotherapy: inadequate health insurance coverage is the leading cause. *Ann. Allergy Asthma Immunol.* 115(3), 241–243 (2015).
4. Pfaar O, Wolf H, Klimek L, Schnitker J, Wüstenberg E. Immunologic effect and tolerability of intra-seasonal subcutaneous immunotherapy with an 8-day up-dosing schedule to 10,000 standardized quality-units: a double-blind, randomized, placebo-controlled trial. *Clin. Ther.* 34(10), 2072–2081 (2012).

5. Pfaar O, Bachert C, Bufe A *et al.* Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergy and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). *Allergo. J. Int.* 23(8), 282–319 (2014).
- **The guideline for AIT developed by the German, Austrian and Swiss allergological Societies follows product-specific considerations and evidence.**
6. Corrigan CJ, Kettner J, Doerner C, Cromwell O, Narkus A. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy* 60(6), 801–807 (2005).
- **Provides the clinical evidence for the efficacy and safety for the investigational medicinal product previously investigated in a 2-year, double-blind, multicenter, placebo-controlled, Phase III with preseasonal treatment start.**
7. Creticos PS, Bernstein DI, Casale TB, Lockey RF, Maloney J, Nolte H. Coseasonal initiation of allergen immunotherapy: a systematic review. *J. Allergy Clin. Immunol. Pract.* 4(6), 1194–1204.e4 (2016).
- **Systematic review compiling evidence for co-seasonal AIT to validate or invalidate the perception of increased safety risk. No increase in adverse events of concern was observed with coseasonal initiation of subcutaneous immunotherapy or sublingual immunotherapy; however, the authors conclude that additional data with standardized regimens and doses are needed.**
8. Global Initiative for Asthma: GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION (2015). (2018). https://ginasthma.org/wp-content/uploads/2016/01/GINA_Report_2015_Aug11-1.pdf
9. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the world allergy organization subcutaneous immunotherapy systemic reaction grading system. *J. Allergy Clin. Immunol.* 125(3), 569–74, 574.e1–574.e7 (2010).
10. International Federation of Pharmaceutical Manufacturers and Associations. MedDRA (medical dictionary for regulatory activities). (2019). www.meddra.org/about-meddra/organisation/management-board/ifpma
11. Likert R. A Technique for the measurements of attitudes. *Arch. Psychol.* 140, 5–55 (1932).
12. McDonnell AL, Wahn U, Demuth D *et al.* Allergy immunotherapy prescribing trends for grass pollen-induced allergic rhinitis in Germany: a retrospective cohort analysis. *Allergy Asthma Clin. Immunol.* 11(1), 19 (2015).
13. Jung S, Estrella N, Pfaffl MW, Hartmann S, Handelshäuser E, Menzel A. Grass pollen production and group V allergen content of agriculturally relevant species and cultivars. *PLoS ONE* 13(3), e0193958 (2018).
14. Karatzas K, Katsifarakis N, Riga M *et al.* New European Academy of Allergy and Clinical Immunology definition on pollen season mirrors symptom load for grass and birch pollen-induced allergic rhinitis. *Allergy* 73(9), 1851–1859 (2018).
15. Mahler V, Esch RE, Kleine-Tebbe J *et al.* Understanding differences in allergen immunotherapy products and practices in North America and Europe. *J. Allergy Clin. Immunol.* 143(3), 813–828 (2019).
16. Frank E, Williams A, Cromwell O, Atkinson P, Rajakulasingam K. Effectiveness of a pre-seasonal allergoid immunotherapy in patients with seasonal allergic rhinitis due to grass pollen [abstract]. *J. Allergy Clin. Immunol.* 107(2), S260 (2001).
17. Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. *J. Allergy Clin. Immunol.* 140(6), 1485–1498 (2017).
- **Summarizes the current understanding of mechanisms underlying induction and persistence of tolerance, potential predictive biomarkers of clinical response and novel and more effective strategies for AIT.**
18. Shamji MH, Ceuppens J, Bachert C *et al.* Lolium perenne peptides for treatment of grass pollen allergy: a randomized, double-blind, placebo-controlled clinical trial. *J. Allergy Clin. Immunol.* 141(1), 448–451 (2018).
19. Wachholz PA, Durham SR. Mechanisms of immunotherapy: IgG revisited. *Curr. Opin. Allergy Clin. Immunol.* 4(4), 313–318 (2004).
20. Walker SM, Durham SR, Till SJ *et al.* Immunotherapy for allergic rhinitis. *Clin. Exp. Allergy* 41(9), 1177–1200 (2011).
21. Williams A, Henzgen M, Rajakulasingam K. Additional benefit of a third year of specific grass pollen allergoid immunotherapy in patients with seasonal allergic rhinitis. *Eur. Ann. Allergy Clin. Immunol.* 39(4), 123–126 (2007).
22. Council for International Organizations of Medical Sciences. Guidelines for Preparing Core Clinical-Safety Information on Drugs Second Edition – Report of CIOMS Working Groups III and V. (1999). cioms.ch/shop/product/guidelines-preparing-core-clinical-safety-information-drugs-second-edition-report-cioms-working-groups-iii-v/

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