

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

Oliver Pfaar, MD¹; Hendrik Wolf, PhD²; Ludger Klimek, MD¹; Jörg Schnitker, PhD³; and Eike Wüstenberg, MD²

¹Center for Rhinology and Allergology, Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Mannheim, Wiesbaden, Germany; ²ALK Arzneimittel GmbH, Wedel, Germany; and ³Institut für angewandte Statistik GmbH, Bielefeld, Germany

ABSTRACT

Background: International guidelines recommend that allergen-specific immunotherapy for pollen-induced rhinoconjunctivitis is initiated preseasonally. However, because subjects often present to physicians with allergy symptoms during the pollen season, “within-season” initiation of specific immunotherapy is of special interest.

Objective: We evaluated the immunomodulatory effects and tolerability of subcutaneous immunotherapy (SCIT) with Standardized Quality (SQ) 6-grass mix and rye allergen extract, using an 8-day intra-seasonal up-dosing schedule to 10,000 SQ-units (SQ-U).

Methods: In a 9-week, multicenter, randomized, double-blind, placebo-controlled trial, adults (mean age, 34.6 years; 99.3% whites) with grass pollen-induced rhinoconjunctivitis (mean disease duration, 15.1 years) were randomized 3:1 to receive SCIT or placebo. Treatment was initiated during the 2008 pollen season, with an 8-day up-dosing from 100 to 10,000 SQ-U (6 daily injections) followed by 2 maintenance injections of 10,000 SQ-U at intervals of 2 and 4 weeks, respectively. The primary end point examined immunologic effects, assessing the difference in IgE-blocking factor (serum components competing with IgE for allergen binding) between SCIT and placebo at week 9. Secondary/exploratory end points included the difference in IgE-blocking factor, specific IgG₄, and specific IgE at various times. Tolerability (adverse events, local and systemic allergic reactions) of the up-dosing schedule was also evaluated.

Results: Of the 148 treated subjects 144 (SCIT n = 109; placebo n = 35) were analyzed for the primary parameter. Immunologic response (significantly higher increase in IgE-blocking factor and IgG₄ levels) occurred with SCIT versus placebo at week 9 (IgE-blocking factor, $P = 0.0017$; IgG₄, $P = 0.0215$). Significant

differences were observed as early as week 3. AEs were reported in 60.7% of SCIT- and 30.6% of placebo-treated subjects, with no treatment-related serious AEs. Local allergic reactions occurred in 46.4% of SCIT and 8.3% of placebo subjects (χ^2 test, $P < 0.0001$). No significant difference was observed between groups in the incidence of systemic reactions (7.1% SCIT vs 5.6% placebo; χ^2 test, $P = 0.7413$).

Conclusions: This trial provides the first description of short (8-day) intra-seasonal up-dosing with SCIT, which induced immunologic effects after only 3 weeks, and was generally well tolerated, although it induced a marked increase in the rate of local reactions compared with placebo. ClinicalTrials.gov identifier NCT00807547; ALK trial ID SHX0562. (*Clin Ther.* 2012;34:2072–2081) © 2012 Elsevier HS Journals, Inc. All rights reserved.

Key words: 6-grass mix and rye, allergic rhinoconjunctivitis, intra-seasonal up-dosing, safety, subcutaneous immunotherapy (SCIT).

INTRODUCTION

Specific immunotherapy (SIT), including subcutaneous immunotherapy (SCIT), is the only available treatment

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for patients with allergic rhinoconjunctivitis (ARC) which targets the underlying cause of the disease.^{1,2} SIT is applied subcutaneously in a large number of patients in many countries, and in Germany most patients receiving immunotherapy are treated with SCIT. For pollen allergens, it is generally recommended that SCIT up-dosing is performed outside the pollen season to avoid concurrent exposure to natural pollen, because the risk of developing systemic side effects with SCIT is highest during the up-dosing period.^{2,3} Up-dosing SCIT during the pollen season, when the patient is naturally exposed to pollen allergens (“priming-effect”), may overburden the immune system and consequently reduce the tolerability of treatment. Starting SCIT within allergen seasons is thus not recommended by the European Academy of Allergy and Clinical Immunology, and no respective data have been published.³ However, many patients with allergies make their first visit to the physician during the pollen season, prompted by their symptoms. In this situation, physicians can currently only offer symptomatic therapy and request that the patient returns after the season for initiation of SCIT. Because patients are likely to be less motivated to return when the pollen season is over, few patients actually receive SIT. It would, therefore, be interesting to establish whether in-season initiation of SCIT is tolerable and whether it induces early changes in the immune system; to our knowledge, in-season initiation of SIT has previously only been investigated with a sublingual immunotherapy drop product,⁴ and the grass pollen allergy immunotherapy tablet.⁵ Furthermore, the length of the up-dosing period is relevant for patient convenience and tolerability.^{6,7} Although conventional up-dosing schedules involve weekly injections over several weeks, alternative regimens (rush or cluster schedules) use shorter up-dosing periods.⁷ This trial, therefore, investigated the immunologic changes and tolerability associated with a short (8-day) intra-seasonal up-dosing schedule for SCIT versus placebo.

METHODS

Trial Design

This was a multicenter, randomized, parallel-group, double-blind, placebo-controlled Phase III trial, conducted in 15 centers (allergy practices) in Germany. Patient enrollment began April 2008, with the last subject completing the study October 31, 2008.

Treatment was started after the beginning of the grass pollen season, defined as at least 3 consecutive days of moderate grass pollen counts (>5 grains/m³) according to the forecast by the German National Meteorological Service (Deutscher Wetterdienst). Subjects were screened and then randomized 3:1 to receive active SCIT (Alutard SQ; ALK, Hørsholm, Denmark) or placebo at visit 1. Alutard SQ is a range of purified, qualitatively, and quantitatively standardized allergen immunotherapy products, presented as sustained-release formulations for subcutaneous injection, for the treatment of ARC and mild-to-moderate allergic asthma. Alutard SQ “grasses and rye” was used as the active treatment in this trial, and it contains a suspension of equal quantities of allergens from 6 grasses and rye (*Dactylis glomerata*, *Lolium perenne*, *Avena elatior*, *Phleum pratense*, *Poa pratensis*, *Festuca pratensis*, and *Secale cereale*) adsorbed to aluminum hydroxide. The allergen extracts applied in the trial are expressed in the manufacturer’s Standardized Quality-units (SQ-U)⁸ and were supplied in vials of 1000 and 10,000 SQ-U/mL.

Placebo was identical to SCIT in appearance and content but without allergens, and the investigational medicinal products (IMPs) were labeled with a randomization number. Subjects were assigned the lowest available randomization number and received the correspondingly assigned IMP. Allocation of the randomization numbers to treatment groups was performed by the Contract Research Organisation (CRO) Institut für angewandte Statistik (IAS) GmbH, Bielefeld, Germany (which was responsible for biometrical planning, data management, and statistical analysis of the trial) with the use of the SAS random number generator (SAS Institute, Cary, North Carolina) and a block-wise randomization. The trial centers were supplied with sealed randomization code envelopes, which were only to be opened in case of an emergency. Investigators and subjects were blinded to treatment allocation throughout the trial.

Injections were administered by the investigator with the use of 1.0-mL syringes with tuberculin needles, applied strictly subcutaneously to the upper arm after aspiration and sterilization of the skin. The trial lasted for 9 weeks and involved an 8-day up-dosing period with 6 SCIT injections (100, 300, 1000, 3000, 6000, and 10,000 SQ-U; visits 1–6), or matching placebo, at daily intervals (apart from the

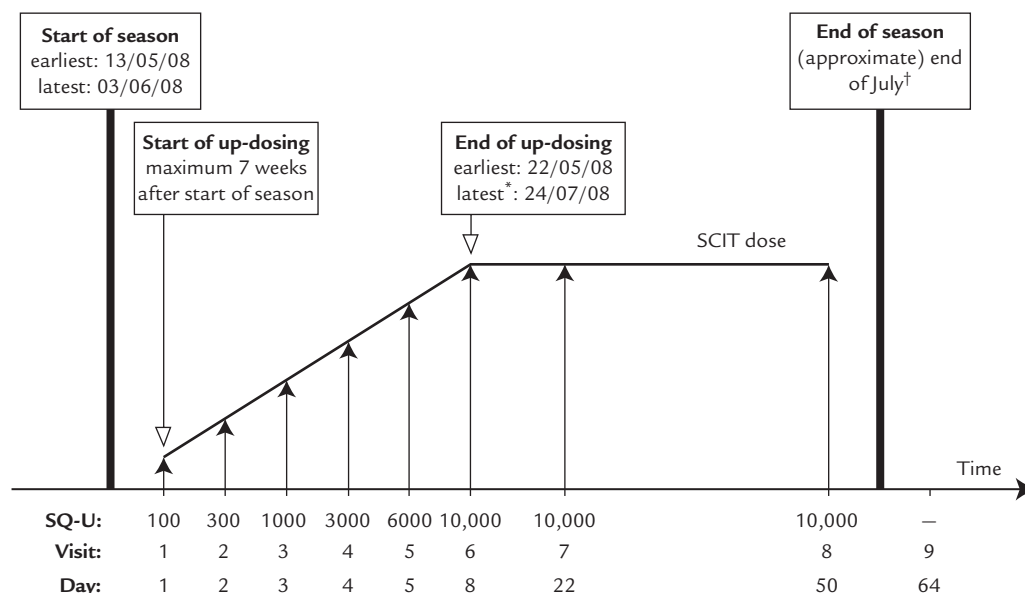


Figure 1. Therapy protocol of short (8-day) intra-seasonal up-dosing for subcutaneous immunotherapy (SCIT). The interval of 3 days between visits 5 and 6 was planned in accordance with the weekend. SQ-U = Standardized Quality-unit. *Latest date for the end of up-dosing, apart from 2 subjects with a delayed study course (up-dosing ended August 4, 2008, and August 11, 2008, respectively). †Definite date for the end of season is not available because the pollen count was not followed up after July 31, 2008, in most representative pollen stations.

weekend, eg, injection given on a Friday, visit 5, followed by the next injection on Monday, visit 6). Trial centers were advised to start treatment during the first 7 weeks of the pollen season to ensure that the up-dosing was completed no later than the last day of the season. The 8-day up-dosing period was followed by 2 maintenance injections with 10,000 SQ-U after intervals of 2 and 4 weeks, respectively (visits 7 and 8; **Figure 1**). A final visit (visit 9, after the pollen season) was made at approximately 2 weeks after the last injection of the IMP. The injection intervals could be prolonged, depending on the tolerability of the previous injections. All subjects were monitored by a physician for 30 minutes after each injection.³ It was intended to up-dose subjects from 10,000 SQ-U to the recommended target maintenance dose of 100,000 SQ-U after the end of the trial, outside the grass pollen season.

Subjects could take concomitant symptomatic medication for their rhinitis and/or asthma symptoms, such as nasal/inhaled corticosteroids, oral/topical antihistamines, and nasal decongestants. Subjects could also receive symptomatic “premedication” before SCIT in-

jections to minimize allergic reactions. Written informed consent was obtained from each subject before entering the trial. The trial protocol received full ethical approval from the Independent Ethics Committee of the Landesärztekammer Hessen and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Subjects

Main inclusion criteria were male and female patients 18 to 65 years of age, clinical history of grass-pollen induced ARC (≥ 2 years) that required treatment during the grass pollen season, and a positive skin-prick test (SPT) response to *Phleum pratense* (wheal diameter ≥ 3 mm). Main exclusion criteria were forced expiratory volume at 1 second $< 70\%$ of predicted value at screening, history of emergency hospital visits or admission for asthma in the previous 12 months, history of a known high degree of sensitivity to grass pollen, previous immunotherapy with grass pollen allergens or any other allergen within the past 5 years, and history of anaphylactic shock or angioedema.

Outcome Measures and Assessments

The primary end point of the trial was the level of IgE-blocking factor at visit 9 (9 weeks after the first injection) in the SCIT group compared with the placebo group. The IgE-blocking factor is a dimensionless number that varies theoretically from 0 (no presence of any IgE-blocking components) to 1 (all IgE blocked from binding to allergen).^{9,10} IgE-blocking factor (and IgG₄ and IgE, see below) was determined with the ADVIA Centaur immunoassay system (Siemens Medical Solutions, Diagnostics, Tarrytown, New York) as previously described.⁹ Analysis was performed by the Department of Bioanalytics of ALK. The method used was validated, and quality control of the analysis and data processing was performed.

Secondary end points included differences in levels of IgE-blocking factor between SCIT and placebo at visits 6 and 7 (in the grass pollen season, approximately 1 and 3 weeks after start of up-dosing) and differences in specific IgG₄-levels in arbitrary units (AU/L) at visits 6, 7, and 9 (weeks 1, 3, and 9). Specific IgE levels in the 2 treatment groups at visits 6, 7, and 9 were assessed as an exploratory end point, as were titrated SPTs and nasal provocation tests (NPTs) with the use of *Phleum pratense* allergens at visit 9 to evaluate skin and nasal reactivity. Titrated provocation tests at skin and nose were performed according to Klimek et al.¹¹ SPT was considered valid if the reaction to the positive control histamine was a wheal size of ≥ 3 mm. The SPT was evaluated by means of the area under the curve of wheal areas after 1, 3, and 10 histamine equivalent prick (HEP) ALK-prick SQ *Phleum pratense*, related to the wheal after 10 $\mu\text{g/mL}$ histamine. The end point of the NPT was defined as the threshold dose in the sequence of the following challenge doses: 10, 100, 1000, 10,000, and 100,000 SQ-U/mL Aquagen SQ *Phleum pratense*.

Further exploratory variables included the safety profile and tolerability of intra-seasonal up-dosing of SCIT. All adverse events (AEs) observed by the investigator or reported by the subject were recorded along with their severity, seriousness, and relation to trial medication and were coded with the use of the Medical Dictionary for Regulatory Activities. Local and systemic allergic reactions were recorded per subject and per injection and were categorized as “immediate” or “delayed” reactions (≤ 30 or > 30 minutes after injection, respectively).³

Statistical Analysis

Sample size for the difference in IgE-blocking factor levels between the SCIT and placebo groups at visit 9 (primary end point) was estimated prospectively, based on results from a previous clinical trial.⁸ In that previous trial, IgE-blocking factor was measured after a 7- to 8-week up-dosing period, giving mean (SD) values of -0.095 (0.15) for placebo and 0.005 (0.18) for 10,000 SQ-U, resulting in a standardized treatment difference of 0.60 .⁸

$$\Delta = (\text{mean}_{\text{active}} - \text{mean}_{\text{placebo}}) / \sqrt{(\text{SD}_{\text{active}}^2 + \text{SD}_{\text{placebo}}^2) / 2} = (0.005 + 0.095) / \sqrt{(0.15^2 + 0.18^2) / 2} = 0.60$$

Therefore, with a power of 0.8 and a $1:1$ allocation, at least 45 subjects should complete the trial to detect this standardized difference at the 0.05 significance level, and for the allocation ratio $3:1$ (active treatment to placebo), there should be at least $2/3 \times 45 = 30$ completers in the placebo group.¹² With a dropout rate of 15% , approximately 36 subjects should be randomly assigned to the placebo group and 108 subjects to the active group, giving 144 subjects in total.

Immunologic changes were analyzed in the full analysis set (FAS), which consisted of all subjects who received the trial medication at least once and who provided at least one immunologic measurement on treatment (intention-to-treat population). Baseline demographic characteristics and tolerability were assessed in all subjects who received the trial medication at least once.

The primary statistical analysis aimed to find a higher level of IgE-blocking factor with SCIT than with placebo at visit 9. The last observation carried forward (LOCF) approach was used to handle dropouts/missing data, using a t test with IgE-blocking factor as outcome and treatment as group variable. The levels of IgE-blocking factor were also analyzed with a Mann-Whitney-Wilcoxon U test, using an observed cases (OC) approach at visits 6, 7, and 9 and in a repeated measurement model (ANCOVA) with visit 1 as a covariate and baseline adjustments.

Changes in specific IgG₄ and IgE at visit 9 and repeated measures at visits 6, 7, and 9 were analyzed in the same way as IgE-blocking factor. However, because of the log-normal distribution of specific IgG₄ and specific IgE, t tests and ANCOVAs of

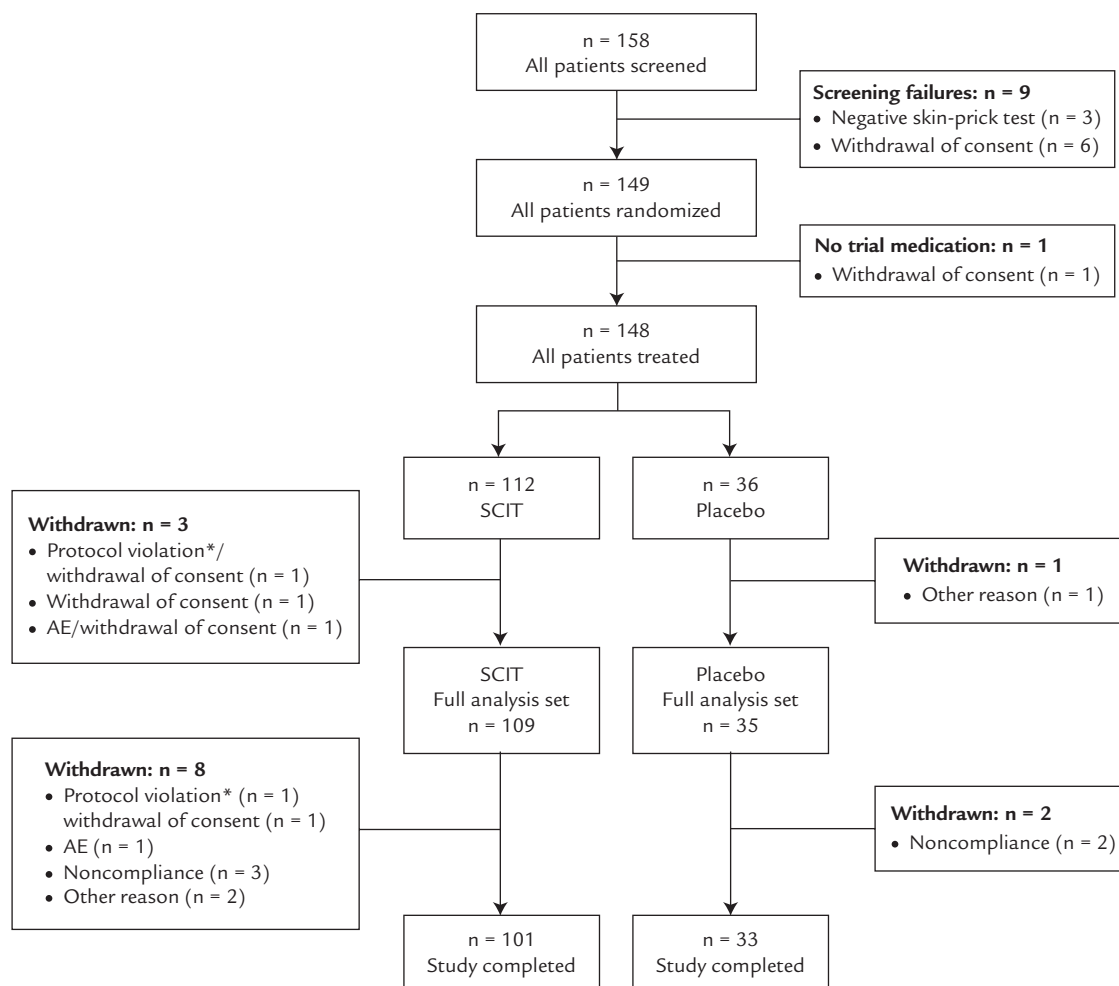


Figure 2. Trial flow chart. AE = adverse event; SCIT = subcutaneous immunotherapy. *Treatment with immunotherapy within the previous 5 years.

both variables were performed with log-transformed data.

The hypothesis testing of all primary and secondary end points was 2-sided, with a significance level of $\alpha = 0.05$.

Safety profile results were quantified by incidences of AEs and compared between trial groups with the χ^2 test.

RESULTS

Of 158 subjects screened, 149 were randomly assigned. One subject withdrew before receiving the IMP, and 148 received at least 1 dose (safety population). Subsequently, 14 treated subjects withdrew (11 SCIT; 3 placebo) and 134 subjects completed the trial (101 SCIT; 33 placebo).

The FAS comprised 144 subjects (SCIT, $n = 109$; placebo, $n = 35$) (Figure 2).

The groups were well balanced at baseline (Table I). The level of premedication use did not differ significantly between groups in terms of subjects (SCIT, 25/112 [22.3%]; placebo, 3/36 [8.3%]; χ^2 test, $P = 0.0623$), or injections (SCIT, 77/881 [8.7%]; placebo, 10/283 [3.5%]; generalized estimating equation model, $P = 0.1693$).

In total 77/112 (68.8%) SCIT subjects and 24/36 (66.7%) placebo subjects used symptomatic medication during the course of the study (ATC codes: antihistamines for systemic use [44.6%], nasal preparations [25.0%], ophthalmologicals [14.2%], drugs for obstructive airway diseases [21.6%]).

Table I. Demographic characteristics and symptom duration for the treatment groups.

Treatment Group	SCIT (n = 112)	Placebo (n = 36)	Total (n = 148)
Age, y			
Mean (SD)	34.2 (11.6)	35.7 (12.9)	34.6 (11.9)
Range	18–64	18–65	18–65
Sex, no. (%)			
Male	53 (47.3)	21 (58.3)	74 (50.0)
Female	59 (52.7)	15 (41.7)	74 (50.0)
Race no. (%)			
White	111 (99.1)	36 (100.0)	147 (99.3)
Other	1 (0.9)	0	1 (0.7)
Allergy no. (%)			
Rhinoconjunctivitis	112 (100.0)	36 (100.0)	148 (100.0)
Bronchial asthma	32 (28.6)	12 (33.3)	44 (29.7)
Atopic dermatitis	12 (10.7)	4 (11.1)	16 (10.8)
Other allergic diseases	36 (32.1)	12 (33.3)	48 (32.4)
Symptom duration, mean (SD), y			
Rhinoconjunctivitis	14.6 (10.3)	16.6 (11.3)	15.1 (10.5)
Bronchial asthma	5.1 (5.2)	6.1 (5.7)	5.4 (5.3)
Atopic dermatitis	9.6 (8.0)	11.3 (11.3)	10.0 (8.5)
Other allergic diseases	13.2 (10.7)	9.5 (8.9)	12.3 (10.3)
Grass pollen-specific IgE, mean (SD), kU/L	28.41 (45.53)	30.55 (56.87)	28.92 (48.23)

SCIT = subcutaneous immunotherapy.

Immunologic Effect

The level of IgE-blocking factor (primary parameter) was significantly higher at visit 9 with SCIT (mean [SD], 0.10 [0.28]) than with placebo (0.08 [0.26]; *t* test, *P* = 0.0017; FAS, LOCF). This was confirmed in the OC analysis (SCIT: 0.11 [0.29], *n* = 94; placebo: −0.08 [0.27], *n* = 30; *U* test, *P* < 0.0001; FAS), and in the ANCOVA for repeated measures with the use of baseline as covariate (Figure 3A). Significant differences in IgE-blocking factor were detected as early as 3 weeks after treatment initiation (visit 7) (Figure 3A). Furthermore, on the basis of these FAS LOCF data, the estimate of standardized difference determined an effect size of 0.67, which confirmed the effect size of the reference data (0.60) used to calculate sample size for the study.

Specific IgG₄ levels were significantly higher at visit 9 with SCIT (geometric mean [SD], 55.13 AU/L

[19.45–156.29 AU/L]) than with placebo (38.27 AU/L [18.85–77.71 AU/L]; *t* test, *P* = 0.0215; FAS, LOCF). This was confirmed in the OC analysis (SCIT: 57.23 AU/L [20.07–163.15 AU/L], *n* = 100; placebo: 37.36 AU/L [18.29–76.33 AU/L], *n* = 33; *U* test, *P* = 0.0158; FAS) and in the ANCOVA for repeated measures of the log-transformed data with the use of the baseline of log(specific IgG₄) as covariate (Figure 3B). On the basis of the ANCOVA (log-transformed least squares mean data/geometric mean), significant differences were detected as early as 3 weeks after treatment initiation (visit 7) (Figure 3B).

Levels of specific IgE at visit 9 were only slightly numerically higher with SCIT (geometric mean [SD] 16.46 kU/L [2.01–135.02 kU/L]) than with placebo (8.08 kU/L [0.88–73.90 kU/L]; *t* test, *P* = 0.0881; FAS, LOCF). However, differences were significant in both the FAS OC analysis (SCIT: 16.52 kU/L [1.98–

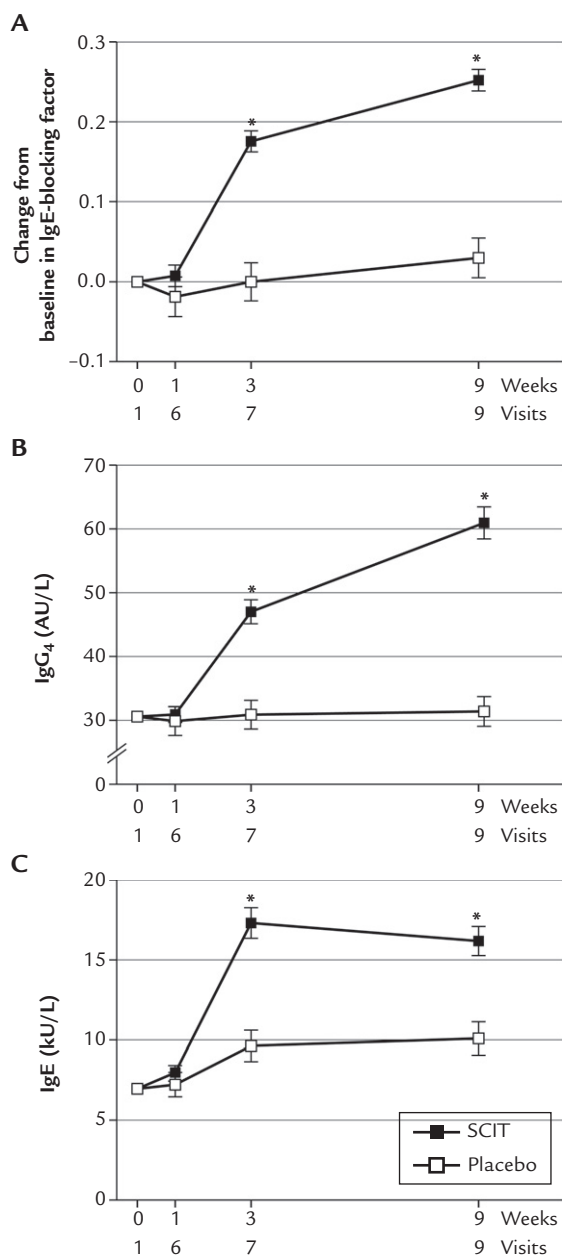


Figure 3. Baseline adjusted means (SEs) for changes from baseline in (A) IgE-blocking factor and baseline-adjusted geometric means and geometric standard errors (log-transformed data) for allergen-specific (B) IgG₄ and (C) IgE; ANCOVA (full analysis set). SCIT = subcutaneous immunotherapy. *The adjusted mean differences between treatment groups were statistically significant (Mann-Whitney-Wilcoxon *U* test, $P < 0.0001$) after 3 weeks and 9 weeks of treatment.

137.79 kU/L], $n = 101$; placebo: 7.58 kU/L [0.80–72.34 kU/L], $n = 33$; *U* test, $P = 0.0440$) and in the ANCOVA of log-transformed data, at visit 9, with significant differences observed from 3 weeks of treatment (visit 7) (Figure 3C).

The LOCF method did not favor SCIT, as was shown by sensitivity analyses (OC, ANCOVA) which all were more powerful than the LOCF analyses.

The titrated NPT was performed in a subgroup of patients only (SCIT, 69/112 [61.6%]; placebo, 21/36 [58.3%]). The median threshold dose was 1000 SQ-U/mL in both groups (*U* test, $P = 0.7257$). The difference in titrated SPT was also insignificant: the median wheal area related to the histamine area was 0.90 with SCIT and 1.01 with placebo (*U* test, $P = 0.8544$).

Safety and Tolerability

More subjects reported AEs in the SCIT group than in the placebo group in the course of the trial (68/112 [60.7%] SCIT vs 11/36 [30.6%] placebo; χ^2 test, $P = 0.0016$). The only system organ class from the Medical Dictionary for Regulatory Activities in which AEs occurred in significantly more subjects who received SCIT, compared with placebo, was “General disorders and administration site conditions” (50/112 [44.6%] SCIT vs 1/36 [2.8%] placebo; χ^2 test, $P < 0.0001$). The difference was because of injection site reactions (placebo: none; SCIT: pain, $n = 2/112$; pruritus, $n = 5/112$; swelling, $n = 48/112$). AEs that were considered possibly/probably related to the IMP were experienced by more subjects who received SCIT (54/112 [48.2%]) than placebo (5/36 [13.9%]; χ^2 test, $P = 0.0003$) because of injection site reactions in the SCIT group.

The incidence of local allergic reactions was markedly increased with SCIT than with placebo (52/112 [46.4%] vs 3/36 [8.3%] subjects; and 205/881 [23.3%] vs 5/278 [1.8%] total injections; χ^2 test both, $P < 0.0001$). The intensity of local reactions (diameter of swelling) after SCIT injection is described in Table II.

The incidence of systemic reactions was low and did not differ significantly between groups (SCIT vs placebo: 8/112 [7.1%] vs 2/36 [5.6%] subjects, χ^2 test, $P = 0.7413$; 10/881 [1.1%] vs 2/283 [0.7%] injections; χ^2 test, $P = 0.5348$) (Table III). In subjects with premedication, no systemic reactions were observed. Of the 8 SCIT-treated subjects who experienced systemic reactions, 4 reported delayed reactions and 4 had immediate, mild systemic reactions.

Table II. Intensity of local reactions (diameter of swelling) observed in the SCIT group.

Intensity of Local Reaction (diameter)	No. of Reactions (% of total number of SCIT injections), n = 881
No reaction	676 (76.7)
>0 cm, ≤5 cm	97 (11.0)
>5 cm, <8 cm	26 (3.0)
≥8 cm, ≤12 cm	61 (6.9)
>12 cm, ≤20 cm	18 (2.0)
>20 cm	3 (0.3)

SCIT = subcutaneous immunotherapy.

In the placebo group the reactions remained ≤5 cm in all cases.

Most AEs were of mild-to-moderate severity. Serious AEs were reported in 3 subjects (all SCIT) but were not judged as related to treatment. One subject had laryngeal carcinoma, 1 subject developed erysipelas, and 1 subject had a biliary colic. All 3 subjects were hospitalized but did not terminate treatment. Only 2 subjects (both SCIT) withdrew because of AEs (problems with circulation in 1 subject; local swelling plus unspecific systemic reaction in another subject), which were not assessed as serious.

DISCUSSION

According to current practice and consistent with the literature on practical application, initiation of SCIT is recommended outside the pollen season³ before patients experience allergic symptoms triggered by pollen exposure. However, without symptoms, many patients lack motivation to visit the physician for allergy treatment and wait until symptoms are present. This is the first large-scale, double-blind, placebo-controlled trial on the immunomodulatory effects and safety profile of short (8-day) intra-seasonal up-dosing of SCIT. The immunomodulatory effects, efficacy, favorable tolerability profile, improved quality of life, and cost-effectiveness of grass pollen SIT with the identical allergen extract initiated preseasonally, have been reported in several studies.^{8,13–16} The initiation of SCIT during the season with the use of a short up-dosing schedule may improve treatment convenience for both patient and physician, as well as patient adherence, if it is proven well tolerated. For tolerability, some studies suggest

that raised baseline levels of IgE/specific IgE after SCIT administration are linked with an increased risk of systemic AEs,^{17,18} although other studies do not concur.¹⁹

In our trial, the primary parameter, level of IgE-blocking factor, was significantly higher with SCIT than with placebo after 9 weeks of therapy, as were the levels of allergen-specific IgG₄ (secondary parameter). These changes are consistent with those seen in previous studies of preseasonally up-dosed SCIT.^{10,15,20–22} Significant differences between the treatment groups were seen for both IgE-blocking factor and specific IgG₄ as early as week 3, indicating an early onset of immunologic changes during up-dosing of SCIT within the pollen season. Although clinical efficacy was not assessed, IgE-blocking factor levels have been found to be significantly correlated with clinical improvement, as published recently.²³

Another important finding of our trial was the favorable safety profile of intra-seasonal SCIT initiation. Most AEs were of mild-to-moderate severity, no serious AEs were related to treatment, and the incidence of systemic allergic reactions was low (1.1% of SCIT injections). Only 2 subjects treated with SCIT withdrew from the trial because of AEs. Although SCIT was started within the grass pollen season, and thus subjects were exposed to exogenous pollen, the tolerability profile appears similar to that seen in some studies that involved preseasonal up-dosing of SCIT with intact allergen formulations.^{8,24} Note, however, that these results cannot be extrapolated to patients with a known high degree of sensitivity to grass pollen, because such patients were excluded from the trial.

The results of this study were accepted by the Paul-Ehrlich Institut (German medical regulatory body) as a variation of the marketing authorization, with the short intra-seasonal up-dosing regimen included as a

Table III. Occurrence of systemic reactions.

	Per Subject, n/N (%)	Per Injection, n/N (%)
SCIT	8/112 (7.1)	10/881 (1.1)
Placebo	2/36 (5.6)	2/283 (0.7)
χ^2 test, <i>P</i>	0.7413	0.5348

SCIT = subcutaneous immunotherapy.

treatment option alongside the Summary of Product Characteristics' recommendations.

CONCLUSIONS

Short (8-day) intra-seasonal up-dosing of SCIT with Alutard SQ 6-grass mix and rye increased immunologic parameters as early as 3 weeks after treatment initiation in this trial. It was well tolerated in subjects with grass pollen-induced rhinoconjunctivitis and was not associated with a high level of systemic allergic reactions, although there was a marked increase in local reactions relative to placebo. Thus, it may become a useful option in SCIT, improving both convenience and patient adherence. Furthermore, by allowing patients to initiate immunomodulatory treatment within the season when symptoms are present, more patients may have access to causal treatment.

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ALK-Germany assumed overall responsibility for the trial; it was responsible for trial design, data management, and analysis. Laboratory analyses were performed by ALK's Bioanalytical Departments in Spain and Denmark.

Dr. Klimek was coordinating investigator of the trial. Dr. Pfaar participated in the trial as recruiting investigator. Dr. Wolf was the sponsor's project manager for the trial and was involved in trial design and conduct. Dr. Wüstenberg was the sponsor's medical representative and was involved in trial design and conduct. Dr. Schnitker was responsible for biometrical planning, data management, and statistical analysis of the trial. In addition, all authors contributed to the manuscript preparation from the draft stage by reviewing, commenting, critically revising the text where ap-

plicable, and approving journal submission. Dr. Pfaar took overall responsibility for manuscript finalization and submission.

CONFLICTS OF INTEREST

Drs. Pfaar and Klimek have received research grants from ALK, Denmark; Allergopharma, Germany; Stallergènes, France; HAL, Netherlands; Artu Biologicals, Netherlands; Allergy Therapeutics/Bencard, Great Britain/Germany; Hartington, Spain; Lofarma, Italy; Novartis/Leti, Germany/Spain; Roxall, Germany; GlaxoSmith-Kline (GSK), Great Britain; Essex-Pharma, Germany; Cytos, Switzerland; Curalogic, Denmark; Biomay, Austria and have served as advisors and on the speaker's bureau for some of the above-mentioned pharmaceutical companies. Dr. Pfaar is a consultant of HAL-Allergy, The Netherlands. Dr. Pfaar has received travel grants from HAL Allergy, Netherlands/Germany, and Allergopharma, Germany. Dr. Wolf and Dr. Wüstenberg are employees of ALK Arzneimittel GmbH, Wedel, Germany. Dr. Schnitker (biometrist) was representative of a CRO (IAS GmbH, Bielefeld, Germany).

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Address correspondence to: Oliver Pfaar, MD, Center for Rhinology and Allergology, Department of Otorhinolaryngology, University Hospital Mannheim, An den Quellen 10, D-65183 Wiesbaden, Germany. E-mail: oliver.pfaar@allergiezentrum.org