Accelerated Dose Escalation with 3 Injections of an Aluminum Hydroxide-Adsorbed Allergoid Preparation of 6 Grasses Is Safe for Children and Adolescents with Moderate to Severe Allergic Rhinitis

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Abstract
A high-dose, accelerated escalation schedule during subcutaneous allergen-specific immunotherapy (AIT) is safe and well-tolerated in adults. However, there are no data in children and adolescents. The aim of the present trial was to assess safety and tolerability of an accelerated dose escalation schedule of an AIT with a grass pollen allergoid in children and adolescents with moderate to severe seasonal rhinoconjunctivitis in a multicenter, open-label, randomized phase II trial. The dose escalation scheme for patients in the One Strength Group included 3 injections with 1 strength B (10,000 TU/mL), whereas the dose escalation scheme for the Standard group included 7 injections with 2 strengths A (1,000 TU/mL) and B (10,000 TU/mL) of an allergoid grass pollen preparation. Overall, n = 50 children (n = 25 in each group; mean age 8.9 + 1.54 years) and n = 37 adolescents (n = 20 and n = 17; 14.2 + 1.62 years) were randomized. For all patients, the mean treatment duration was 59.4 days in the One Strength group and 88.6 days in the Standard group. Treatment-emergent adverse events (TEAEs) related to AIT were reported in 52 and 40% in children and 35 and 35.3% in adolescents, respectively. Systemic allergic reactions occurred in about 5% of our patients and were reported in more patients of the One Strength group (6.7 vs. 2.4%). All systemic reactions were classified as WAO Grade 1. Accelerated high-dose escalation with an aluminum hydroxide-adsorbed grass pollen allergoid can be initiated with a safety and tolerability profile comparable to the standard dose escalation schedule in children and adolescents with allergic rhinitis with or without asthma.

Keywords
Allergen-specific immunotherapy · Allergic rhinitis · Children · Cytokines · Nasal allergy tolerance/suppression
Introduction

Allergen-specific immunotherapy (AIT) is the spearhead of our limited arsenal of sustainable treatment options fighting the epidemic of allergic diseases [1]. For allergic rhinitis (AR) and/or allergic asthma, sublingual and subcutaneous administration of AIT has been shown to be efficacious and saves treatment options. However, the acceptance and adherence of subcutaneous AIT is limited by long-term updosing and maintenance phases [2]. During the last years, a number of clinical trials became available demonstrating that accelerated high-dose escalation schedules can be applied in patients with AR with or without asthma with a comparable safety and tolerability profile as the standard escalation schedules. Recently, Chaker et al. [3] have demonstrated that an accelerated 4-dose escalation scheme of a grass pollen allergoid starting with 200 therapeutic units (TU) can be given with a beneficial safety profile comparable to the standard 7-dose escalation regime starting with 100 TU. Taking a step forward, we were able to demonstrate that also an accelerated high-dose escalation schedule of a grass pollen allergoid starting with 5 times higher initial dose (1,000 TU) can be safely administered. Eighty percent of the patients in the high-dose escalation group reached the first AIT injection of the maintenance phase without dose adjustment [4]. While a slightly higher number of patients in the high-dose escalation group reported systemic allergic reactions (n = 4; 8.9%) compared to the standard dose escalation group (n = 1; 2.4%), all systemic allergic symptoms were classified as mild (WAO Grade 1 or Grade 2). However, all these observations are limited to adult populations and data in the pediatric and adolescent subgroups are sparse. Therefore, we performed a multicenter, open-label, randomized phase II clinical trial in pediatric patients with rhinitis or rhinoconjunctivitis caused by grass pollen sensitization and applied two different updosing regimes of a grass pollen allergoid.

Methods

Patients

This multicenter, open-label, randomized, parallel, active-controlled phase II trial was conducted in pediatric patients (5 to <18 years of age) with rhinitis or rhinoconjunctivitis caused by grass pollen. Patients between 5 and <18 years of age with the diagnosis of immunoglobulin E (IgE)-mediated seasonal moderate to severe AR according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline [5] or rhinoconjunctivitis with or without allergic asthma caused by grass pollen could be enrolled after providing informed consent. Further inclusion criteria included a positive skin prick test (≥3 mm in diameter) and specific IgE (≥0.70 kU/L) against grass pollen. In addition, patients had to experience AR or rhinoconjunctivitis symptoms triggered by grass pollen exposure for at least 1 month in the period from May to August, and they had to receive previous antiallergic treatment for at least two seasons prior to enrollment. In cases with a diagnosis of asthma, the asthma had to be diagnosed and classified as "well-controlled" according to the Global Initiative for Asthma (GINA) guideline [6]. Exclusion criteria included prior history of confirmed anaphylaxis after an AIT injection with grass pollen within the last 5 years, current treatment with any kind of immunotherapy, and uncontrolled/partly controlled asthma according to the Global Initiative for Asthma (GINA) guideline. Moreover, patients with autoimmune diseases, β-blocker use, and contraindication for the use of adrenaline could not be enrolled.

Patients were randomized into a group with accelerated dose escalation (Group I or “One Strength group”) and a group with standard dose escalation (Group II or “Standard group”) in a 1:1 ratio within each site. In order to achieve a balanced distribution of patients within each treatment group according to the two different age-groups (5 to <12 years and 12 to <18 years), patients were stratified according to their age.

The trial was conducted in autumn and winter, that is, prior to the grass pollen season. All patients were recruited between October 2018 and March 2019. No placebo group was included in this trial (EudraCT 2018-000548-25).

Trial Design and Treatment

This was a multicenter, open-label, randomized, parallel, active-controlled phase II trial in pediatric patients with rhinitis or rhinoconjunctivitis caused by grass pollen. It was conducted in Germany, Poland, Russia, and Spain.

The grass pollen allergoid (Allergovit® 6-grasses; Allergopharma GmbH and Co. KG, Reinbek, Germany) contains a mixture of allergens from 6 grass pollen species (Holcus lanatus, Dactylis glomerata, Lolium perenne, Phleum pratense, Poa pratensis, and Festuca pratensis). The allergoid is coprecipitated with aluminum hydroxide. The preparation is provided in two strengths: A (1,000 TU/mL) and B (10,000 TU/mL). The approximate estimation of major allergen content for Phleum pratense (Ph p 5) is 25 μg equivalent/mL in Allergovit® 6-grasses (in strength 10,000 TU) [7].

The One Strength group received 3 injections of one strength (B) of the grass pollen allergoid (0.1 mL of 1,000 TU, 0.3 mL of 3,000 TU, and 0.6 mL of 6,000 TU) at weekly intervals. The Standard group started with 1/10 of the dose of the One Strength group and received 7 injections (strength A: 0.1 mL of 100 TU, 0.2 mL of 200 TU, 0.4 mL of 400 TU, and 0.8 mL of 800 TU; strength B: 0.15 mL of 1,500 TU, 0.3 mL of 3,000 TU, and 0.6 mL of 6,000 TU). When the maintenance dose had been reached, both groups received 2 maximum-dose injections (0.6 mL of 6,000 TU) of strength B after 14 and 28 days. After each injection, patients in both groups were supervised for at least 120 min to monitor potential adverse reactions. Dosage modification was performed if local and/or systemic adverse events (AEs) occurred, based on a predefined regime. The WAO grading system was used to decide on dose modification in case of an systemic reaction. Briefly, if the patient experienced a systemic allergic reaction of any WAO grade following the first injection or a WAO Grade 3 or 4 reaction, then the patient must be discontinued from the trial. A WAO Grade 1 reaction resulted in a reduction by 1 dose step of the last applied
dose; a WAO Grade 2 resulted in a reduction by 2 dose steps of the last applied dose. If the first dose reduction was not tolerated in case of a WAO Grade 1 or 2 reaction, a second dose reduction by 1 dose step of the last applied dose was administered. No more than 2 dose reductions per patient due to an AE were tolerated during the trial.

Assessment of AR and Asthma

To assess the severity of the patient’s AR, the symptomatic history according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline was documented by the investigator at the screening visit. Peak flow measurements were also performed. The asthma status of all patients was monitored by the Asthma Control Questionnaire.

Assessment of Safety and Tolerability End Points

Safety and tolerability end points focused on treatment-emergent AEs (TEAEs), defined as any AE that started or worsened after the first intake of trial medication until 30 days after the last administration of the investigational medicinal product (IMP) or trial-related procedure. An adverse drug reaction was defined as all untoward and unintended responses to the IMP related to any dose administered. A local adverse reaction was defined as an AE related or not related to the IMP and occurring at the injection site. A systemic allergic reaction was defined as an AE related or not related to the IMP and graded as systemic according to the WAO grading system based on the organ systems involved and the severity of the reaction.

Apart from AE data, changes in laboratory values (hematology, clinical chemistry, and urinalysis) measured before and after the treatment phase, changes in vital signs and lung function measured before and after the treatment phase, and the assessment of overall tolerability, by the investigator and the patient, using a 5-point Likert scale (1 = very bad; 5 = very good) were documented. The trial was supervised by an independent Data and Safety Monitoring Board.

Statistical Analysis

Due to the exploratory design of the trial, there was no formal estimation of sample size. It was planned to randomize 35 patients per age and treatment group, which equals a total of 140 patients (children/adolescents and group I [One Strength]/group II [Standard]), to guarantee a probability of 95% that AEs with a true incidence rate of 8.6% occur at least once in the respective treatment group [8].

The patients were assigned to the following sets before starting the analysis: the “All-Patients Set” comprised patients that gave their informed consent. For this group, the patients’ disposition and reasons for premature trial termination are described. The “Safety Set” (SAF) was the group of patients who received at least 1 dose of trial medication. It is the basic analysis set for all assessments of safety and tolerability. For this set, exposure to IMP was analyzed.

Numbers and incidence rates of AEs and severe AEs with causal relationship to the IMP are reported separately for both age groups. Statistical tests (Fisher’s exact test, χ² test, and Wilcoxon-Mann-Whitney U test) were performed when adequate. Otherwise, the analysis was performed descriptively and explained by comparing events and frequencies between groups. For all statistical tests, a significance level of α = 5% was chosen.

Results

Patients

A total of 115 patients (children and adolescents) were enrolled in this trial, 60 children and 55 adolescents. Of the 60 screened children, 50 were randomized (safety set), 25 patients to the One Strength group and 25 patients to the Standard group (Fig. 1). A total of 3 randomized pediatric patients prematurely discontinued the trial, 1 in the One Strength group (AE: injection site swelling) and 2 in the standard group (AE: varicella and other reasons). In total, 37 adolescent patients were randomized, 20 patients to the One Strength group and 17 patients to the Standard group (Fig. 1). Two adolescent patients prematurely discontinued the trial, 1 in the One Strength group (AE: urticaria) and 1 in the Standard group (personal reasons).

For both children and adolescents, demographic characteristics were generally comparable between groups (Table 1). The incidence of patients’ allergy-specific history was generally comparable between groups. Almost all pediatric patients experienced nasal (98.0%) and ocular symptoms (86.0%). Wheezing, shortness of breath, and cough was reported for nearly half of the patients (ranged from 40.0 to 46.0%); chest tightness was reported for 32.0% of the pediatric patients (see online suppl. Table 1; see www.karger.com/doi/10.1159/000512561 for all online suppl. material). The mean and median duration of symptoms was generally comparable between the groups. All adolescent patients experienced nasal symptoms, and the majority of patients experienced ocular symptoms (78.4%). Wheezing, shortness of breath, and cough was reported for about one-sixth of the patients (ranged from 16.2 to 18.9%); chest tightness was reported for 13.5% of the adolescent patients. The incidence of patients’ allergy-specific history was generally comparable between groups; incidence in wheeze (25.0 vs. 11.8%), shortness of breath (30.0 vs. 5.9%), and chest tightness (20.0 vs. 5.9%) was higher in the One Strength group than in the Standard group.

For both children and adolescents, immunological profiles (total and specific IgE, i.e., mugwort, rye, birch, *P. pratense*, grass mix/early bloom, *D. farinae*, and *D. pteronyssinus*) did not differ significantly between treatment groups at baseline (Table 1). In the One Strength group, the majority of patients received 5 injections in total (children: 92.0%; adolescents: 85.0%) and in the standard group, 9 injections (children: 80.0%; adolescents: 94.1%). Accordingly, the median treatment duration was shorter in the One Strength group compared to
that in the Standard group for children (One Strength group: 61 days; Standard group: 87 days) and adolescents (One Strength group: 61 days; Standard group: 85 days). Median compliance was 100% for children and adolescents in both treatment groups.

**Adverse Events**

Overall, \( n = 51 \) (58.6%) patients reported at least 1 TEAE. The proportion of patients with at least 1 TEAE during the trial was similar in both groups (One Strength group: 60.0%; Standard group: 57.1%).

In the subgroup of children, \( n = 34 \) (68.0%) patients reported at least one TEAE (Table 2). The proportion of pediatric patients with at least one TEAE during the trial was slightly higher in the One Strength group than in the Standard group (72.0 vs. 64.0%; \( p = 0.7624 \)). In the subgroup of adolescents, 17 (45.9%) patients reported at least one TEAE. The proportion of adolescent patients with at least one TEAE during the trial was similar between groups (One Strength group: 45.0%; Standard group: 47.1%; \( p = 1.0000 \); Table 2).
### Table 1. Demographic data and baseline characteristics: SAF

|                        | Children |                   | Adolescents |                   |
|------------------------|----------|-------------------|-------------|-------------------|
|                        | One Strength | Standard | One Strength | Standard |
|                        | n = 25                 | n = 25                | n = 20               | n = 17               |
| Age, years             |                        |                     |                      |
| Mean (SD)              | 8.9 (1.76)             | 8.9 (1.32)           | 13.9 (1.41)          | 14.6 (1.80)          |
| Median                 | 9.0                    | 9.0                  | 14.0                | 15.0                |
| Min.–max.              | 5–11                  | 6–11                 | 12–16               | 12–17               |
| Gender, n (%)          |                        |                     |                      |
| Male                   | 15 (60.0)              | 17 (68.0)            | 14 (70.0)           | 9 (52.9)            |
| Female                 | 10 (40.0)              | 8 (32.0)             | 6 (30.0)            | 8 (47.1)            |
| Asthma (yes), n (%)    | 15 (60.0)              | 14 (56.0)            | 5 (25.0)            | 3 (17.6)            |
| Among them, n (%)      |                        |                     |                      |
| Inhaled steroids (yes) | 13 (86.7)              | 10 (71.4)            | 3 (60.0)            | 3 (100)             |
| Inhaled steroids (no)  | 2 (13.3)               | 4 (28.6)             | 2 (40.0)            | 0                   |
| Ethnicity, n (%)       |                        |                     |                      |
| White                  | 25 (100)               | 25 (100)             | 20 (100)            | 17 (100)            |
| BMI, kg/m²             |                        |                     |                      |
| Mean (SD)              | 17.7 (2.46)            | 18.3 (3.95)          | 20.0 (3.24)         | 20.6 (3.35)         |
| Median                 | 17.5                  | 17.1                 | 19.5                | 20.0                |
| Min.–max.              | 13–22                 | 13–29               | 15–29               | 17–29               |
| Pet contact, n (%)     |                        |                     |                      |
| No                     | 20 (80.0)              | 19 (76.0)            | 14 (70.0)           | 11 (64.7)           |
| Intermittent           | 3 (12.0)               | 0                    | 0                    | 0                   |
| Permanent              | 2 (8.0)                | 6 (24.0)             | 6 (30.0)            | 6 (35.3)            |
| Total IgE, kU/L        |                        |                     |                      |
| Median                 | 352.00                | 428.00               | 262.50              | 220.00              |
| Min.–max.              | 16.2–845.0            | 55.0–3,615.0         | 37.8–6,734.0        | 58.6–3,113.0        |
| Specific IgE, kU/L for grass mix/early bloom |                        |                     |                      |
| Median                 | 32.500                | 45.600               | 16.300              | 27.500              |
| Min.–max.              | 1.39–100.00           | 0.76–100.00          | 0.71–100.00         | 1.30–100.00         |
| Specific IgG4 for Phleum pratense, mg/L |                        |                     |                      |
| Median                 | 0.240                 | 0.340                | 0.250               | 0.330               |
| Min.–max.              | 0.07–1.79             | 0.07–6.28            | 0.07–0.93           | 0.07–1.57           |

N, number of patients; n (%), number (percentage) of patients with data; SAF, safety set.

### Table 2. Overview of TEAEs

|                        | Children |                   | Adolescents |                   |
|------------------------|----------|-------------------|-------------|-------------------|
|                        | One Strength | Standard | One Strength | Standard |
|                        | n = 25                 | n = 25                | n = 20               | n = 17               |
| TEAEs                  | 18 (72.0)             | 16 (64.0)            | 9 (45.0)            | 8 (47.1)            |
| TEAEs related to IMP   | 13 (52.0)             | 10 (40.0)            | 7 (35.0)           | 6 (35.3)            |
| Local reactions        | 10 (40.0)             | 10 (40.0)           | 6 (30.0)            | 5 (29.4)            |
| Systemic allergic reactions | 2 (8.0)             | 0                    | 1 (5.0)             | 1 (5.9)             |
| Other type of events   | 14 (56.0)             | 10 (40.0)            | 6 (30.0)           | 5 (29.4)            |
| TEAEs leading to discontinuation | 1 (4.0)             | 1 (4.0)              | 1 (5.0)            | 1 (5.9)             |
| Treatment-emergent SAE | 0                     | 0                   | 1 (5.0)            | 1 (5.9)             |
| Treatment-emergent SAE related to IMP | 0                     | 0                   | 1 (5.0)            | 1 (5.9)             |

e, number of events (TEAEs); IMP, investigational medicinal product; n, number of patients; n (%), number (percentage) of patients with at least one TEAE; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
In the subgroup of children, of the 117 reported TEAEs, 48 TEAEs were assessed as related to IMP by the investigators and occurred in 23 (46.0%) patients. Slightly more pediatric patients experienced at least one IMP-related TEAE in the One Strength group than in the Standard group (52.0 vs. 40.0%; \(p = 0.5709\)) with slightly smaller absolute and relative number of events in the One Strength group than in the Standard group (21 vs. 27, ratio of TEAE per patient: 1.6 vs. 2.7). In the subgroup of adolescents, of the 98 reported TEAEs, 71 TEAEs were assessed as related to IMP by the investigators and occurred in 13 (35.1%) patients. The number of adolescent patients who experienced at least one IMP-related TEAE was comparable between groups (One Strength group: 35.0%; Standard group: 35.3%; \(p = 1.0000\)) with slightly more events in the One Strength group than in the Standard group (39 vs. 32, ratio of TEAE per patient 5.6 vs. 5.3). An overview of TEAEs related to the IMP is presented in Table 3 for the subgroup of children and adolescents.

For both children and adolescents, most of the reported TEAEs related to IMP were local reactions: 105 local reactions were reported with an equal distribution in both groups (One Strength group: 53 TEAEs; Standard group: 52 TEAEs). The number of affected patients was similar between both groups (One Strength group: 35.6%; Standard group: 35.7%; \(p = 1.0\)).

### Table 3. TEAEs related to IMP and intensity of TEAEs

| | One Strength | | Standard | | One Strength | | Standard |
|---|---|---|---|---|---|---|---|
| | \(n = 25\) | | \(n = 25\) | | \(n = 20\) | | \(n = 17\) |
| Overall | 13 (52.0) | 21 | 10 (40.0) | 27 | 7 (35.0) | 39 | 6 (35.3) | 32 |
| Mild | 18 | 25 | 12 | 12 | 5 (25.0) | 13 | 4 (23.5) | 10 |
| Moderate | 3 | 2 | 12 | 3 | 3 (15.0) | 11 | 3 (17.6) | 7 |
| Severe | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| General disorders and administration site conditions | 10 (40.0) | 17 | 10 (40.0) | 27 | 6 (30.0) | 36 | 5 (29.4) | 25 |
| Injection site swelling | 8 (32.0) | 11 | 8 (32.0) | 11 | 5 (25.0) | 13 | 4 (23.5) | 10 |
| Injection site erythema | 2 (8.0) | 3 | 3 (12.0) | 11 | 3 (15.0) | 11 | 3 (17.6) | 7 |
| Injection site pruritus | 2 (8.0) | 2 | 3 (12.0) | 3 | 4 (20.0) | 8 | 2 (11.8) | 8 |
| Injection site edema | 0 | 0 | 1 (4.0) | 1 | 0 | 0 | 0 | 0 |
| Injection site pain | 0 | 0 | 1 (4.0) | 1 | 3 (15.0) | 3 | 0 | 0 |
| Swelling | 1 (4.0) | 1 | 0 | 0 | 1 (5.0) | 1 | 0 | 0 |
| Injection site discomfort | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Investigations | 1 (4.0) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Forced expiratory volume decreased | 1 (4.0) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | 1 (4.0) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pain in extremity | 1 (4.0) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nervous system disorders | 1 (4.0) | 1 | 0 | 0 | 0 | 0 | 1 (5.9) | 2 |
| Headache | 1 (4.0) | 1 | 0 | 0 | 0 | 0 | 1 (5.9) | 1 |
| Somnolence | 0 | 0 | 0 | 0 | 0 | 0 | 1 (5.9) | 1 |
| Respiratory, thoracic and mediastinal disorders | 0 | 0 | 0 | 0 | 2 (10.0) | 2 | 1 (5.9) | 1 |
| Cough | 0 | 0 | 0 | 0 | 0 | 0 | 1 (5.9) | 1 |
| Rhinitis, allergic | 0 | 0 | 0 | 0 | 1 (5.0) | 1 | 0 | 0 |
| Sneezing | 0 | 0 | 0 | 0 | 1 (5.0) | 1 | 0 | 0 |
| Skin and subcutaneous tissue disorders | 1 (4.0) | 1 | 0 | 0 | 1 (5.0) | 1 | 1 (5.9) | 2 |
| Dermatitis, allergic | 1 (4.0) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Urticaria | 0 | 0 | 0 | 0 | 1 (5.0) | 1 | 1 (5.9) | 1 |
| Pruritus | 0 | 0 | 0 | 0 | 0 | 0 | 1 (5.9) | 1 |
| Eye disorders | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Conjunctival edema | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Infections and infestations | 0 | 0 | 0 | 0 | 0 | 1 (5.9) | 1 |
| Rhinitis | 0 | 0 | 0 | 0 | 0 | 0 | 1 (5.9) | 1 |

e, number of events (TEAEs); IMP, investigational medicinal product; \(n\), number of patients; \(n\) (%), number (percentage) of patients with at least one TEAE; PT, preferred term; SAF, safety set; SOC, system organ class; TEAE, treatment-emergent adverse event.
In the subgroup of children, 44 local reactions related to IMP occurred slightly less frequently in the One Strength group than in the Standard group (17 vs. 27 TEAEs). The number of affected patients was equal in both groups (One Strength group: 40.0%; Standard group: 40.0%; \( p = 1.0 \)). In the subgroup of adolescents, 61 local reactions related to IMP occurred slightly more frequently in the One Strength group than in the Standard group (36 vs. 25 TEAEs). The number of affected patients was similar between both groups (One Strength group: 30.0%; Standard group: 29.4%; \( p = 1.0 \)).

No deaths and no suspected unexpected serious adverse reactions were reported during the trial. Only in the subgroup of adolescents, serious AEs occurred in 1 patient of the One Strength group and another patient of the Standard group. Overall, 3 patients experienced TEAEs leading to premature discontinuation from the trial (One Strength group: 2 patients, Standard group: 1 patient). One adolescent in the One Strength group suffered from a systemic allergic reaction (urticaria) which was related to study medication. One child in the One Strength group suffered from non-serious adverse drug reactions (injection site swelling, swelling, and pain) which were related to study medication. Another child in the Standard group suffered from a non-serious AE (varicella) which was not related to study medication. All these patients were included in final computation.

**Systemic Adverse Reactions**

Overall, systemic allergic reactions occurred in 4 (4.6%) patients, 3 (6.7%) patients in the One Strength group and 1 (2.4%) in the Standard group (\( p = 0.6171 \)). In the subgroup of children, 2 systemic allergic reactions related to IMP occurred in 2 patients, all of which were reported in the One Strength group: forced expiratory volume decreased and allergic dermatitis. There was no statistically significant difference between groups (\( p = 0.49 \)). Both systemic allergic reactions in pediatric patients were assessed as non-serious.

In the subgroup of adolescents, 6 systemic allergic reactions related to IMP occurred in 2 patients. Of the 6 reported events, 1 (urticaria) occurred in 1 patient of the One Strength group, and 5 systemic TEAEs were reported from 1 patient of the Standard group. The allergic reactions were conjunctival edema, cough, pruritus, rhinitis, and urticaria. There was no statistically significant difference between groups. All 6 systemic allergic reactions in adolescent patients were assessed as serious.

**Time to Onset of TEAEs Related to IMP**

Overall, most of the TEAEs related to IMP were reported during these escalation phases. For both children and adolescents in the One Strength group, most IMP-related TEAEs occurred after the second IMP administration with a decrease in the number of IMP-related TEAEs with further IMP injections (Fig. 2). In contrast, for children and adolescents in the Standard group, the number

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**Fig. 2.** TEAEs related to IMP in relation to individual injections – pooled analysis (children, adolescents, and adults). IMP, investigational medicinal product; TEAE, treatment-emergent adverse event.
of IMP-related TEAEs after the first and second IMP doses was lower compared to the One Strength group; here, the peak of IMP-related TEAEs occurred between the fifth and seventh IMP injection.

For both children and adolescents, most of the IMP-related TEAEs occurred up to 6 h after IMP administration (children: 30 of 48 TEAEs; adolescents: 48 of 71 TEAEs). In the subgroup of children, a slightly fewer number occurred in the One Strength group than in the Standard group (12 TEAEs vs. 18 TEAEs). In the subgroup of adolescents, a slightly higher number occurred in the One Strength group than in the Standard group (28 TEAEs vs. 20 TEAEs). In children and in adolescents, after 6 h, the number of TEAEs decreased continuously. Further analyses suggest that there was no influence of the reaction type (local reaction or systemic allergic reaction) on the time to onset, neither in children nor in adolescents. A more detailed analysis of the onset period >30 min to ≤6 h in both populations revealed that the majority of TEAEs related to IMP occurred up to 2 h (children) and 3 h (adolescents), respectively, after IMP injection.

Tolerability and Other Safety Parameters

All investigators (children) and the majority of investigators (adolescents), respectively, assessed the overall tolerability at the end of the escalation phase as “very good” or “good” (children: 75.0 and 25.0%; adolescents: 80.6 and 13.9%, Fig. 3). Similar results were obtained for the patient’s assessment (children: 87.5 and 12.5%; adolescents: 80.6 and 16.7%). The investigators judged the tolerability for children in the One Strength group after the last dose of the escalation phase slightly inferior to the Standard group (very good: 62.5 vs. 87.5%). This difference was statistically significant (p = 0.0494). All other assessment results were similar for both the One Strength group and the Standard group (p > 0.05). Furthermore, the investigators’ and patients’ assessments at the final visit revealed similar results.

For all patients (children and adolescents), there were no notable differences between the asthmatic and non-asthmatic patients. Furthermore, there were no clinically relevant differences between the treatment groups in terms of changes in clinical chemistry, hematology, and urinalysis values during the trial. The immunological profile was assessed at baseline and at the final visit. During the course of the trial, the mean amount of IgG4 against Timothy grass pollen increased notably over time in both treatment groups for children and adolescents (p < 0.0001). The comparison of the mean changes from baseline revealed no notable difference between treatment groups at final visit for children and adolescents (p > 0.05).

Discussion

Administration of grass pollen allergoid preparations using the standard dose escalation scheme is an efficacious and safe treatment option in children and adolescents with AR and/or allergic asthma [9]. The use of alternative dose escalation schemes with fewer injections is increasingly common in daily practice. Since reported reactions were mainly local and mild of intensity, the use of an accelerated dose escalation should be expected to be safe and comparable to standard schemes with regard to the appearance, frequencies, and severity of side effects [10]. However, up to now, there are only limited data about side effects of shortened escalation schemes with higher injection doses in children and adolescents. In this open-label, randomized, active-controlled trial, we were able to demonstrate that an accelerated high-dose escalation schedule using 3 injections of a grass pollen allergoid can be applied with a comparable safety profile as the standard escalation schedule using 7 injections. Nearly 90% of all randomized patients reached the first AIT injection of the maintenance phase without dose adjust-
ional IgG4 antibodies are induced by AIT [15]. We hy-

For all patients, children, and adolescents, most of the
reported TEAEs related to AIT were local reactions with an
equal distribution in both groups. Local reactions from AIT are common during the updosing and maintenance
phase [11]. In our study, not only the absolute number of TEAS but also the number of affected patients was similar
between both groups. Overall, the most commonly re-
ported local reactions related to AIT were injection site
swelling, followed by injection site erythema and injec-
tion site pruritus. These data fit precisely with the results
of our recently published clinical trial in adults [4]. How-
ever, all local symptoms were reported more frequently
in adults compared to children and adolescents. The local
side effects of the grass pollen allergoid was in the lower
quartile compared with data from recently published
studies, showing that as many as 26–86% of the patients
receiving SCIT experience local reactions [12].

Systemic allergic reactions occurred in about 5% of our
patients and were reported in more patients of the One
Strength group (6.7 vs. 2.4%). Again, these data are in line
with data published in adults [4, 12]. In our population,
all systemic allergic reactions were classified as WAO
Grade 1 reactions. All pediatric and adolescent patients
reported TEAEs of mild or moderate intensity, and no
TEAE was classified as severe. The frequency and the in-
tensity of TEAEs were overall not considered a safety con-
cern, and no change in the benefit risk profile of the me-
dicinal product was regarded necessary.

Current asthma guidelines now recommend sublin-
gual and/or subcutaneous AIT as an add-on therapy for
asthma in adults and children based on results from re-
cent clinical studies [6, 13]. However, uncontrolled asth-
amia is still a contraindication for AIT, and patients with
asthma are believed to be at higher risk for systemic side
effects [14]. With respect to the subpopulation of asth-
matic patients, our analyses revealed that there were no
significant safety signals or other findings compared to
the whole trial population. Nevertheless, our subgroup
comprised only 29 children and 8 adolescents with AR
and asthma. Even if our results are in line with recently
collected data in adults [4], a larger population must be
recruited to make a valid and evidence-based conclusion
for asthmatic patients in this age-group.

A number of clinical studies have shown that func-
tional IgG4 antibodies are induced by AIT [15]. We hy-
pothesize that an accelerated dose schedule might offer
the opportunity to gain clinical and immunological toler-
ance faster compared to standard dose escalation. There-
fore, we assessed the change of specific IgG4 for P. pratense
between the screening visit and the final visit as an explor-
atory end point. For children and adolescents, the mean
amount of IgG4 against Timothy grass pollen increased
significantly over time in both groups. The comparison
between both groups revealed slightly higher IgG4 con-
centration in the One Strength group; however, this dif-
fERENCE was not statistically significant.

Recently, Zissler et al. [16] reported data of an observ-
ational real-life, case-controlled, and long-term clinical
cohort. They proposed 3 phases of the tolerogenic process
during AIT and reported a correlation of the ratio of IL-
10+ B-cells and Th17 cells during the early initiation
phase to symptom improvement after 3 years of treat-
ment. The hypothesis of a different tolerogenic effect
might be supported by the clinical observation of a spe-
cific pattern of AEIs in relation to the number of the indi-
vidual injection. While the highest number of AEIs in the
high-dose escalation group occurred after the first and
second injections in weeks 1 and 2, the number of AEIs
peaked in the standard dose escalation group in weeks 5
and 6. Hypothetically, these data might point toward a
faster tolerance induction in the high-dose escalation
group.

Beyond clinical trials, adherence to both subcutaneous
and sublingual AIT is limited. Recently, Kiel et al. [2]
showed that real-life persistence is better in subcutaneous
AIT than in sublingual AIT in the Netherlands with 23
and 7% of the users that reached the optimal duration of
treatment of 3 years, respectively. One potential barrier
that might be opposed to a better adherence to AIT is the
length of treatment. In this context, the advantage of a
shortened AIT therapy is that administration of fewer in-
jections is comfortable and more convenient for the pa-
tients having fewer visits in doctor’s practice. In addition,
less absenteeism from school or from leisure activities
of children and adolescents is especially relevant for pedi-
atic patients. For all patients in our trial, the mean treat-
mament duration was 59.4 days in the One Strength group
compared to 88.6 days in the Standard group.

An additional aspect of better adherence to AIT is the
concept of “shared decision-making” [17]. Applied to AIT
administration, health-care providers keep information
on treatment options, that is, conventional versus acceler-
ated updosing regimes of AIT and their potential benefits
and harms. The patients’ perspective addresses the cur-
rent social situation and lifestyle preferences. Putting
these aspects together, this approach can lead to a shared decision-making, which might improve adherence and consecutively also clinical outcomes [17]. The accelerated updosing of AIT versus the conventional scheme of AIT might be a perfect example how health-care providers might initiate a process of shared decision-making. Future clinical trials should assess the impact of this tool on treatment adherence as well as treatment efficacy.

The strength of our clinical trial is that we recruited a good characterized clinical cohort of children and adolescents with AR with or without asthma and that we recorded the AEs comprehensively based on clearly defined clinical standards [18]. One weakness of our study is the open-label design, although blinding was not applicable with an acceptable amount of effort. Moreover, the efficacy of AIT was not measured in this study. Again, while measuring the clinical efficacy after 60 or 90 days might not be appropriate, prolonging our study over 1 or 2 years was not feasible. Finally, the number of recruited patients is quite small. Even if there were no new safety issues and no changes in the safety profile of the grass pollen allergoid, additional data in larger cohorts of children and adolescents are necessary for the confirmation of the overall good safety profile in our high-dose escalation group.

In conclusion, our results show that regardless of dosing schedule, AIT with grass pollen allergoid was safe and well-tolerated in children and adolescents with rhinitis or rhinoconjunctivitis with or without comorbid asthma. TEAEs were comparable between high-dose and standard dose escalation and predominantly local reactions. Systemic reactions were observed in about 5% in the One Strength group, but all of them were graded as WAO Grade 1. Altogether, the accelerated updosing scheme with a grass pollen allergoid offers an additional treatment option of AIT in children, adolescents, and adults.

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Statement of Ethics

The trial design was approved by the Ethics Committees of the University of Lübeck. The trial was conducted in accordance with the trial protocol, the International Conference on Harmonization guideline for Good Clinical Practice, applicable local regulations, and the Declaration of Helsinki. Patients willing to participate in the trial were asked to provide written informed consent after being given sufficient time to consider participation.

Conflict of Interest Statement

X. Bovermann has nothing to declare. I. Ricklefs has nothing to declare. C. Vogelberg has received a speaker honorarium or consultant fees from the following companies: Alimmune, ALK-Abelló, Allergopharma, AstraZeneca, Bencard Allergie, Boehringer Ingelheim, DBV Technologies, HAL, InfectoPharm, LETI Pharma, Novartis Pharma, Sanofi-Aventis, and Stallergenes. L. Klimek reports grants and personal fees from Allergopharma, Germany, personal fees from MEDA, Sweden, grants and personal fees from Novartis, Switzerland, grants and personal fees from Allergopharma, Germany, grants and personal fees from Bionorica, Germany, personal fees from Boehringer Ingelheim, Germany, grants and personal fees from GSK, Great Britain, grants and personal fees from Lifolmat, Italy, grants from Biomay, Austria, grants from HAL, The Netherlands, grants from LETI Pharma, Spain, grants from Roxxall, Germany, and grants from Bencard, Great Britain, outside the submitted work. M.V. Kopp has received a speaker honorarium or consultant fees from the following companies: ALK-Abelló, Allergopharma, Boehringer Ingelheim, Chiesi, Glaxo, InfectoPharm, Sanofi-Aventis, LETI Pharma, Novartis Pharma, and Vertex.

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Author Contributions

X.B. enrolled the study population and was part of the writing team; I.R. was part of the writing team; C.V. analyzed the data and revised the manuscript; L.K. analyzed the data and revised the manuscript; M.V.K. designed the clinical trial, analyzed the data, and wrote the manuscript.

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