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A One-Strength Dose Escalation Regimen for Birch Pollen SCIT Is Safe and Tolerable in Children, Adolescents, and Adults

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ABSTRACT

Background: Allergen immunotherapy is the only disease-modifying treatment for IgE-mediated diseases for patients 5 years and over. The question is often asked why children receive the same doses as adults. There is not a single dose-finding study including children and/or adolescents. Moreover, randomized controlled trials that include all age groups but report effects separately are rare.

Method: This randomized trial investigated the safety and tolerability of an accelerated dose escalation schedule (One-Strength group) compared to the standard regimen (Standard group) when using a birch pollen SCIT allergoid in patients aged 5–65 years.

Results: Overall, 201 patients were randomized to the two regimens: 87 adults, 52 adolescents, 62 children. Three hundred eighty-two treatment-related adverse drug reactions (ADRs) occurred in 81 patients (40.5%). A higher proportion of patients in the One-Strength group (48.5%) experienced at least one ADR compared to those in the Standard group (32.0%). The majority of ADRs were local (93.3%), and the majority were of mild intensity (95.8%). 3 patients in the One-Strength and 1 patient in the Standard group developed a total of 9 systemic ADRs, which all were classified as WAO grade 1 or 2 and most of mild intensity. No event of WAO grade 3 or higher was reported. No serious ADR occurred. Overall, tolerability was assessed as "very good" or "good" by more than 96% of investigators and patients. Safety and tolerability were comparable in the three age groups.

Conclusion: Birch pollen SCIT was safe and well-tolerated when administered using a One-Strength dose-escalation regimen in patients aged 5–65 years.

1 | Introduction

Pollen grains, which act as carriers of airborne allergens and contain potent allergenic proteins, are well-studied worldwide and represent a major cause of allergic rhinitis (pollinosis). The respiratory tract is the primary target of inhaled pollen and can be affected by IgE-mediated allergic diseases in genetically predisposed individuals. These conditions manifest

Abbreviations: ADR, adverse drug reaction; AE, adverse event; AIT, allergen immunotherapy; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; CI, Confidence Interval; FEV1, forced expiratory volume in 1 s; HDM, house dust mite; IMP, investigational medicinal product; MedDRA, Medical dictionary for Drug Regulatory Activities; PT, Preferred Term; SAF, Safety Set; SCIT, subcutaneous immunotherapy; SD, Standard Deviation; SLIT, sublingual immunotherapy; SOC, System Organ Class; TEAE, treatment-emergent adverse event; WAO, World Allergy Organization; WHO, World Health Organization.

clinically as allergic rhinitis (AR), conjunctivitis, or asthma. Most pollen-allergic patients experience rhinoconjunctivitis [1]. In Europe, the prevalence of confirmed AR in adults ranges from 17% to 28.5%, while 15%–38% of patients are also affected by asthma [2].

In Central and Northern Europe, tree pollens of the order Fagales (birch, alder, hazel, hornbeam, and oak) are major airborne allergens [3, 4]. In Germany, a survey reported that approximately 19% of the adult population was sensitized to tree pollen allergens [5]. Additionally, a skin prick test study found that 34.1% of German patients had a clinically relevant allergy to birch pollen [6]. Allergen immunotherapy (AIT) is the only causal treatment option for IgE-mediated allergic diseases, including allergic rhinitis, rhinoconjunctivitis, and asthma [7, 8]. Its efficacy and safety using birch pollen products for subcutaneous or sublingual immunotherapy were shown in several randomized clinical trials [9–13], while real-world database analyses proved long-term effectiveness for up to 6 years [14, 15].

Up to now, the majority of randomized controlled AIT trials showing efficacy and safety were primarily performed with adult patients and only a few exclusively included children [16–18]. According to the EAACI guideline on allergen immunotherapy in allergic rhinoconjunctivitis "many of the SCIT trials are now relatively old, many enrolled only a few children and/or did not present pediatric only analyses" [8]. Especially, there are no dose-finding trials investigating whether the same dose(s) and/or dose regimen are suitable for children. Therefore, randomized AIT trials, including children and adolescents, are still desirable and essential.

The aim of this randomized, two-arm, open-label multicenter trial was to investigate the safety and tolerability of an accelerated dose escalation regimen (One-Strength dose escalation) compared to the standard regimen (Standard dose escalation) when using a birch pollen SCIT allergoid. This study not only included children, adolescents, and adults simultaneously, but also provided results for each age group individually and examined the comparability of safety and tolerability across groups.

2 | Methods

2.1 | Trial Design

This was a multicentre, open label, randomized, phase II trial with two active treatment arms (EudraCT 2021-002317-34), which was performed in 15 sites in Germany and Poland. All patients were treated with an aluminum hydroxide-adsorbed birch pollen allergoid product for SCIT (Allergovit Birch; Allergopharma GmbH & Co. KG, Reinbek, Germany) in two different dose escalation regimens (Figure 1).

No premedication was planned during the trial.

After each injection, all patients were supervised for at least 120 min to monitor FEV1, vital signs, and potential treatment-emergent adverse events (TEAEs) related to the investigational medicinal product (IMP).

A dose reduction after an IMP-related TEAE followed a strict pattern (see Supporting Information).

Randomization was performed block-wise at each site in a 1:1 ratio, and patients were stratified into the respective age group according to their age on the day of their enrolment.

2.2 | Ethics

The trial was conducted in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki. Competent authorities in Poland and Germany and independent ethics committees approved the trial protocol, and written informed consent was obtained from the patient and the patient's legal representative, respectively.

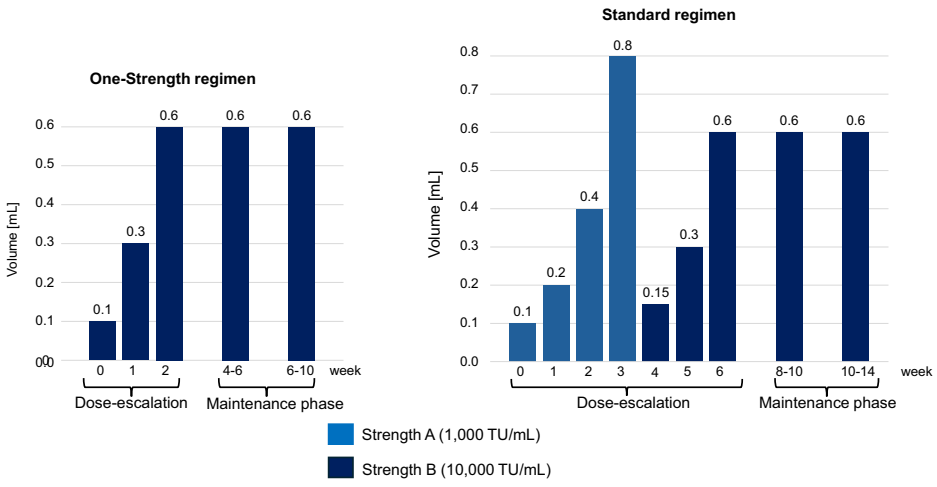

FIGURE 1 | Dose regimens in the one-strength and standard group during SCIT with the birch pollen allergoid. Dose escalation was administered in weekly intervals. Once the maintenance dose had been reached, two injections were administered at intervals of 2–4 weeks.

2.3 | Patients

Patients' inclusion criteria were:

- age: ≥5 to ≤65 years
- clinically relevant symptoms of moderate to severe rhinitis/rhinoconjunctivitis with or without asthma (well controlled acc. to [19]) caused by birch pollen confirmed by a positive skin prick test, birch pollen-specific IgE (≥0.7 kU/L), allergic symptoms from March to May and need of symptomatic anti-allergic medication for at least 2 seasons.

Main exclusion criteria are listed as Supporting Information.

2.4 | Endpoints

2.4.1 | Safety

Number and incidence of the following events were recorded:

- Adverse event (AE): any untoward medical condition that started or worsened at the day of the patient's signature on patient information consent until and including the final visit or premature termination visit.
- TEAE: any AE that started on the day of the patient's signature on patient informed consent and was performed until and including the final visit or premature termination visit.
- TEAE related to IMP, herein after referred to as adverse drug reaction (ADR): An untoward and unintended response to the IMP related to any dose administered. ADRs were differentiated into:
  - Local ADR: occurring at the injection site,
  - Systemic ADR: graded according to the WAO grading system based on the organ systems involved and the severity of the reaction [20],
  - 'Other type of ADR': ADR which could not be classified as local or systemic ADR.

Investigators recorded the time of onset for every ADR.

Moreover, the number of patients who reached the maintenance dose without dose adjustment due to ADRs was recorded.

Intensity of all ADRs was assessed by investigators based on the following criteria:

- 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.

2.4.2 | Tolerability

Overall tolerability of SCIT for every single patient was assessed at the final visit by investigators and patients/parents/legal guardians by using the 5-point Likert scale (1 = very bad; 5 = very good) [21].

2.4.3 | Immunology

Levels of birch pollen-specific IgG4 were measured both before the start of treatment and at the final visit.

2.4.4 | Other Clinical and Laboratory Parameters

Changes in laboratory values (hematology, clinical chemistry, and urinalysis), vital signs, and lung function were measured before and after the treatment phase.

2.5 | Statistics

The study assessed the safety and tolerability of two different dose-escalation schemes in an exploratory design. A total of 210 participants (35 per age and treatment group) were planned to be randomized, ensuring a 95% probability of observing at least one adverse event with a true incidence of 8.6% per group. All analyses were descriptive and exploratory; no formal hypothesis testing was performed. Continuous variables were summarized using standard descriptive statistics, and categorical data by absolute and relative frequencies. Comparisons between groups were exploratory, with two-sided significance levels set at $\alpha = 0.05$. Details on sample size determination, methodology and statistical approach are provided in the Supporting Information.

3 | Results

Overall, 200 patients received at least one SCIT injection and were assigned to the Safety Set (SAF). 103 of these patients were randomized to the One-Strength group and 97 patients to the Standard group. A total of 188 patients (93.5%) completed the trial, with 96 of them receiving SCIT with the One-Strength and 92 with the Standard regimen. For detailed information on patients' disposition see Figure S1.

3.1 | Patients' Demographic

For the total patient population, demographic characteristics in the SAF were generally comparable between groups. All patients suffered from moderate to severe symptoms of birch pollen-allergic rhinitis [1], see Table 1. Overall, 77.0% of patients also suffered from allergic conjunctivitis and 27.0% from well-controlled asthma. There was no statistically significant difference between the groups for any analyzed demographic parameter (all $p > 0.05$, multiple Fisher's Exact tests and Mann–Whitney U-tests) except for children's age ($p = 0.0345$). The distribution of asthmatic patients did not differ significantly between the two regimens across the three age groups ($p > 0.05$; Fisher's exact tests and Mantel–Haenszel test). In contrast, the proportion of asthmatics was notably higher among children than among adolescents and adults. Moreover, compared to adolescents and adults, the level of birch

TABLE 1 | Patients' demographic characteristics (SAF).

	Adults		Adolescents		Children	
	One-Strength group	**Standard group**	**One-Strength group**	**Standard group**	**One-Strength group**	**Standard group**
Number of patients, *n*	47	40	25	26	31	31
Age (years), mean (SD)	36.2 (11.1)	37.2 (9.4)	14.2 (1.4)	14.2 (1.4)	8.7 (2.0)	7.9 (1.7)
Gender, *n* (%)						
Female	19 (40.4%)	20 (50.0%)	17 (68.0%)	10 (38.5%)	13 (41.9%)	12 (38.7%)
Male	28 (59.6%)	20 (50.0%)	8 (32.0%)	16 (61.5%)	18 (58.1%)	19 (61.3%)
Patients with allergic rhinitis, *n* (%)	47 (100%)	40 (100%)	25 (100%)	26 (100%)	31 (100%)	31 (100%)
Duration of symptoms, mean years (SD)	9.8 (9.6)	9.8 (7.4)	4.4 (2.3)	5.2 (3.1)	3.5 (1.4)	3.3 (1.6)
Patients with allergic conjunctivitis, *n* (%)	39 (83.0%)	28 (70.0%)	20 (80.0%)	19 (73.1%)	25 (80.6%)	23 (74.2%)
Duration of symptoms, mean years (SD)	10.7 (10.3)	11.3 (7.7)	3.9 (2.4)	5.3 (3.5)	3.5 (1.4)	3.7 (1.6)
Patients with asthma, *n* (%)	13 (27.7%)	7 (17.5%)	4 (16.0%)	6 (23.1%)	13 (41.9%)	11 (35.5%)
Skin prick test, longest wheal diameter in mm, median (min–max)	10.0 (5–24)	10.0 (4–25)	9.0 (5–16)	9.0 (5–15)	10.0 (5–16)	9.0 (4–16)
Birch pollen specific IgE, median kU/L (min–max)	16.300 (1.09–100.00)	14.800 (1.47–100.00)	38.900 (2.94–100.00)	37.700 (3.51–100.00)	100.00 (5.54–100.00)	100.00 (1.19–100.00)

pollen-specific IgE was highest in children, with a median value of 100 kU/L, indicating that they were highly allergic. For further information on patients' demographic characteristics, see Table 1.

3.2 | Safety

For the total population, 75.7% of patients in the One-Strength group received 5 injections while 84.5% in the Standard group received 9 injections, consistent with the expected regimens without dose adjustment. In the One-Strength group, 77.4% of children, 88% of adolescents, and 68% of adults received 5 injections.

Four patients terminated the trial prematurely due to non-serious TEAEs related to the IMP, which affected two patients in each treatment regimen. One further patient, randomized to the One-Strength group, discontinued the trial due to a serious TEAE, not related to the IMP. This patient developed food allergic symptoms several hours after the IMP injection.

Overall, 382 ADRs occurred in 81 (40.5%) patients. The proportion of patients having experienced at least one ADR was significantly higher in the One-Strength group (50 (48.5%)) compared to the Standard group (31 (32.0%)) (95% CI [3.2%; 30.0%], $p < 0.05$). No serious ADR was reported during the trial course. For further details on TEAEs and ADRs in the three age groups, see Table 2.

95.8% of all ADRs were of mild intensity, which occurred slightly less often in the One-Strength (94.3%) than in the Standard group (97.7%). No ADR was of severe intensity. A comparable picture emerged across the three age groups.

Overall, 356 (93.2%) out of the 382 ADRs were local reactions which occurred in significantly more patients of the One-Strength (47 patients (45.6%) with 202 events) than of the Standard group (31 patients (32.0%) with 154 events) (95% CI [0.3%; 27.0%], $p < 0.05$). Also, in the subgroup of adults significantly more patients were affected by at least one local ADR in the One-Strength (46.8%) compared to the Standard group (20.0%) (95% CI [7.9%; 45.7%], $p < 0.05$), while no significant differences were present in the subgroups of adolescents and children. In contrast to adults and adolescents, children in the One-Strength group showed fewer local ADRs compared to the Standard group (Figure 2).

A total of 9 systemic ADRs occurred in 4 patients. The symptoms observed were those typically seen during AIT: nasal pruritus, hypersensitivity, sneezing, tiredness, flushing, or rash. One adult, one adolescent, and one child each of the One-Strength group experienced one systemic ADR, while 1 child of the Standard group developed 6 events. There was no significant difference in the number of patients affected between the One-Strength and Standard groups for any age

TABLE 2 | Number and proportion of adults, adolescents and children having experienced any treatment-emergent adverse event (TEAE) and any adverse drug reaction (ADR) as well as the number of respective events.

	Adults		Adolescents		Children	
	One-Strength group	Standard group	One-Strength group	Standard group	One-Strength group	Standard group
Treatment-emergent adverse events (TEAEs)						
Patients with at least 1 TEAE, *n* (%)	30 (63.8%)	18 (45.0%)	16 (64.0%)	15 (57.7%)	22 (71.0%)	21 (67.7%)
p value	n.s.		n.s.		n.s.	
Events, *n*	153	84	79	87	92	189
Adverse drug reactions (ADRs)						
Patients with at least 1 ADR, *n* (%)	24 (51.1%)	8 (20.0%)	15 (60.0%)	11 (42.3%)	11 (35.5%)	12 (38.7%)
p value	95% CI [12.1%; 50.0%], $p < 0.05$		n.s.		n.s.	
Events, *n*	110	41	63	35	38	95
Intensity of ADRs						
Events with intensity of, *n* (%)						
Mild	101 (91.8%)	39 (95.1%)	61 (96.8%)	34 (97.1%)	37 (97.4%)	94 (98.9%)
Moderate	9 (8.2%)	2 (4.9%)	2 (3.2%)	1 (2.9%)	1 (2.6%)	1 (1.1%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

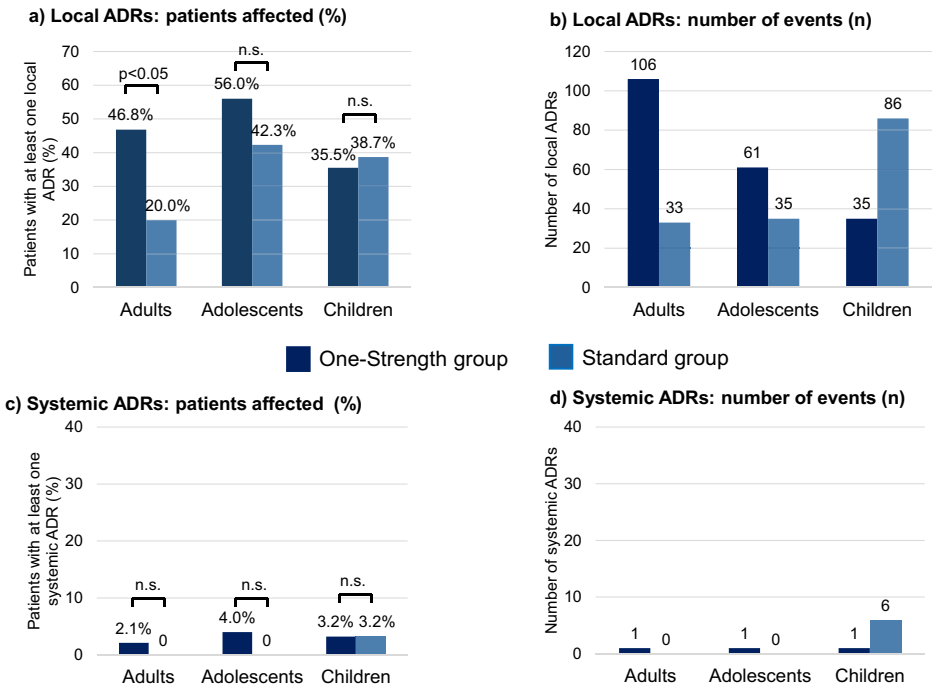

FIGURE 2 | Proportion of adults, adolescents and children affected by (a) local and (c) systemic adverse drug reactions (ADR) and the respective number of (b) local and (d) systemic ADRs in each age group.

group. Seven of the 9 systemic ADRs, which developed in 3 patients, were classified as WAO grade 1 reactions, while 2 events in 2 patients (1.0%) were classified as WAO grade 2 reactions. No events of WAO grade 3 or higher were reported. 8 of the 9 systemic ADRs were rated as mild, while one in an adolescent patient of the One-Strength group was rated to be of moderate severity. For details on the number of patients affected and events see Figure 2.

Seventeen ADRs classified as "other type of event" occurred in 8 (4.0%) patients and included headache, feeling cold, fever, tiredness as stand-alone symptom as well as pain and weakness in the extremity. Six "other types of events" affected 5 (4.9%) patients of the One-Strength group, while 11 events occurred in 3 (3.1%) patients of the Standard group. There was no statistically significant difference in the number of patients affected between the two treatment groups.

Overall, dose adjustment due to ADRs was necessary in 12.6% of patients in the One-Strength and 4.1% of patients in the Standard group.

3.3 | Time to Onset of ADRs

In the total population, 93.8% of ADRs in the One-Strength and 89.5% of ADRs in the Standard group occurred within 24 h after injection. The results were comparable in the two treatment arms within the three age groups.

Analyzing the occurrence of the number of ADRs in relation to the individual IMP administration per visit shows that for the total population, the majority of ADRs occurred during the dose escalation phase (Figure 3). In the One-Strength group, most ADRs occurred after the 1st and 2nd injections with a consecutive decrease thereafter. In contrast, in the Standard group, the number of ADRs was lower than in the One-Strength group and remained nearly constant throughout the dose escalation phase.

There is no notable difference in the number of ADRs in relation to the individual IMP administration per visit between the three age groups.

3.4 | Safety in Patients With Asthma

A total of 27.0% of patients had allergic asthma. Table 3 shows that the proportion of asthmatic patients developing local or systemic ADRs was comparable to that of the non-asthmatics. Moreover, the kind of systemic ADRs did not differ noticeably between asthmatics and non-asthmatics. The only asthmatic patient developing a systemic ADR developed sneezing after one SCIT injection during the One-Strength dose escalation, which was classified as a WAO grade 1 reaction. No trend toward increased intensity of local ADRs was observed in patients with asthma.

3.5 | Tolerability

Overall tolerability of both regimens was assessed as "very good" or "good" by more than 96% of investigators. Assessments for the Standard regimen were marginally better than for the One-Strength regimen (Figure 4). More than 97% of patients of all age groups rated the tolerability of both regimens as "very good" or "good." Results were similar for the three age groups.

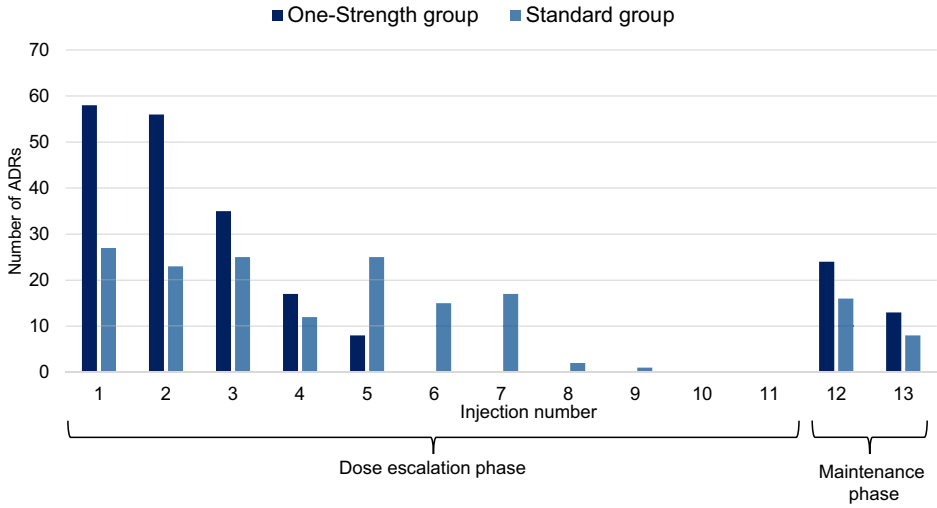

FIGURE 3 | Adverse drug reactions (ADRs) in relation to individual investigational medicinal product (IMP) administration per visit.

TABLE 3 | Number and proportion of asthmatic and non-asthmatic patients having experienced local and systemic adverse drug reactions (ADRs) as well as the number of respective events.

	Asthmatics		Non-asthmatics	
	One-Strength ($n=30$)	**Standard ($n=24$)**	**One-Strength ($n=73$)**	**Standard ($n=73$)**
Local adverse drug reactions (ADRs)				
Patients with at least 1 local ADR, *n* (%)	13 (43.3%)	7 (29.2%)	34 (46.6%)	24 (32.9%)
Events, *n*	67	43	135	111
Systemic ADRs				
Patients with at least 1 systemic ADR, *n* (%)	1 (3.3%)	0	2 (2.7%)	1 (1.4%)
Events, *n*	1	0	2	6

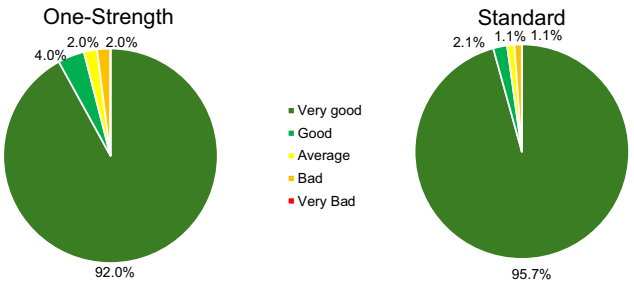

FIGURE 4 | Overall tolerability of the One-Strength and Standard regimens for birch pollen SCIT, as assessed by the investigators in the total population.

3.6 | Birch-Pollen Specific IgG4

For the total population and each of the three age groups, levels of birch pollen-specific IgG4 increased significantly from baseline to the final visit ($p<0.0001$ for all comparisons; Wilcoxon signed-rank test). At the final visit, the comparison of the changes from baseline revealed no significant difference between the One-Strength and the Standard group for the total population and the three age groups ($p>0.5$, each, van Elteren test or Mann–Whitney *U*-test). Figure 5 shows the results for birch pollen-specific IgG4 for the total population.

3.6.1 | Other Clinical and Laboratory Parameters

There were no significant changes in laboratory values (hematology, clinical chemistry, and urinalysis), vital signs, and lung function from before to after the treatment phase.

4 | Discussion

AIT is one of the rare treatment options in which children and adults receive the same medication dosage, even for starting doses, dose escalation regimens and maintenance doses. Up to now, no phase II trial investigating dose response relationship in terms of efficacy and safety in children and adolescents has been performed. The trial at hand investigated safety and tolerability of a new One-Strength dose escalation regimen compared to the

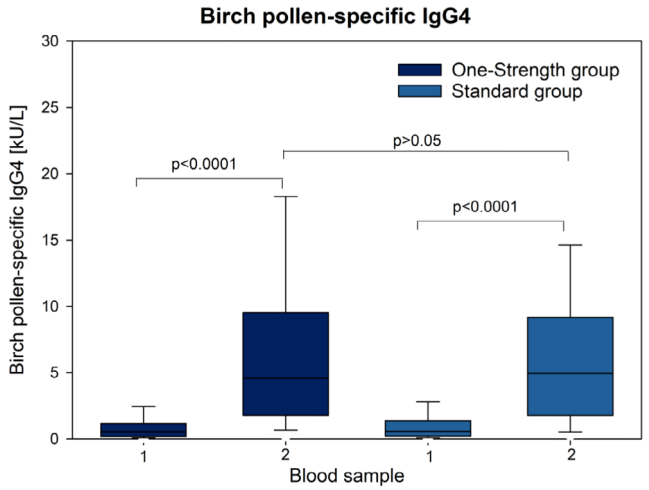

FIGURE 5 | Level of birch pollen-specific IgG4 before starting dose escalation with the birch pollen allergoid (blood sample 1) and after dose escalation and two injections of the maintenance dose (blood sample 2). The boxes show the 25th percentile (bottom), the 75th percentile (top); error bars show the 10th percentile (bottom) and the 90th percentile (top).

Standard regimen when using a birch pollen SCIT allergoid. The trial is unique in that it included not only adults, but also adolescents and, notably, children. In addition, the three age groups were each analyzed separately, and the results compared with each other.

The trial showed that a One-Strength dose escalation regimen, comprising 3 injections from the higher of two strengths, was as safe and tolerable as the Standard regimen, which consists of 7 injections from 2 strengths, in patients aged 5–65 years. The One-Strength regimen caused more ADRs, but there were no differences in the kind and intensity of ADRs compared to the Standard regimen. Moreover, all reported ADRs were known and already described for the birch pollen SCIT product. No serious ADR was reported during the trial course. More than 93% of all ADRs were local reactions at the injection site, like swelling, pruritus, erythema, and pain. No systemic ADR of WAO grade 3 or higher occurred. Most ADRs were of mild intensity, and asthma was not a risk factor for more or more severe ADRs. Overall, asthmatics did not show a divergent safety profile. The subgroups of adults, adolescents, and children showed similar safety and tolerability results overall. In contrast to adults and adolescents, children in the One-Strength group showed considerably fewer ADRs, indicating potentially better tolerability. As expected, starting SCIT with only the highest of 2 strengths and respectively a 10-fold higher dose in the One-Strength regimen compared to the Standard regimen caused more ADRs already after the first injection(s). Comparable observations were made in two randomized trials investigating the safety and tolerability of a grass pollen SCIT allergoid when administered using the One-Strength regimen, both in adults [22] and in children and adolescents [23]. There were also trends toward more ADRs in the One-Strength group compared to the Standard regimen; however, most ADRs were local reactions at the injection site, predominantly of mild intensity, and the proportion of patients experiencing systemic ADRs was small. There was also no systemic ADR of WAO grade 3 or higher. When summarizing the results of the three randomized phase II trials investigating the safety of the grass and birch pollen SCIT allergoid in the One-Strength regimen, involving a total of 193 patients, two patients in the grass pollen SCIT group experienced serious ADRs—one adolescent with urticaria and one adult with severe erythema and swelling at the injection site.

An analysis of the occurrence of ADRs in relation to the individual IMP showed that with the One-Strength scheme, more ADRs appear after the first two injections than with the Standard scheme. This was also observed in the two trials investigating the same regimens using a grass pollen allergoid [22, 23]. As already discussed for a One-Strength scheme using a house dust mite SCIT product, this shift of the highest number of ADRs per administration may hint at a faster tolerance induction in the One-Strength group [24]. This hypothesis is underlined by the significant increase in birch pollen-specific IgG4 levels from baseline to the final visit, without significant differences between the two regimens, indicating that both were able to induce an immunological response toward an immune tolerance. To further strengthen this observation, assessing the functional capacity of IgG4 antibodies using the IgE-facilitated allergen binding assay and the basophil activation test would have been of particular interest [25, 26].

In recent years, several randomized controlled trials have been conducted to investigate the safety of accelerated dose escalation for various SCIT products [22–24, 27–31]. Only one trial included children [23] after safety and tolerability of the One-Strength regimen for a grass pollen allergoid was shown for adults [22]. This regimen was then approved in Germany in 2022 for patients aged 5 years and older. Most other studies were limited to the adolescent and adult age groups, or even solely on adults; hence, the use in children would constitute off-label use [27–31]. Ultimately, the current trial resulted in the approval for the One-Strength dose escalation regimen in Germany in April 2024 for the birch pollen allergoid AIT in patients aged 5 years and above. Thus, both the grass and birch pollen allergoids are now approved in Germany for all age groups, in both the Standard and One-Strength regimens.

The One-Strength regimen improves patient convenience by reducing the number of doctors' visits. This may enhance patient adherence, which is crucial for achieving optimal AIT outcomes. Non-adherence threatens the clinical effectiveness of AIT both during the treatment phase and in the long term, as well as its potential to modify the disease [7, 8]. Based on real-world database analyses, the adherence rate after 3 years ranged between 10% and 55% [32, 33]. Moreover, patients' adherence to SCIT was generally higher than to sublingual immunotherapy (SLIT) [14, 34, 35]. Inconvenience is a key factor affecting adherence to treatment [36, 37]. A particularly relevant study demonstrated that shortening the dose escalation phase of SCIT significantly improved patient adherence. Even after the first year, significantly fewer patients discontinued SCIT when treated with an accelerated versus a conventional dose escalation regimen—and this positive effect persisted for at least 3 years [35].

This trial has some limitations. Rare ADRs or safety risks may not be observed in the rather small patient population. The results may not be generalizable to the broader population as

the sample may not be sufficiently representative. In addition, the trial was not powered to detect statistically significant differences in systemic ADRs between the two dose escalation regimens. Therefore, data for larger patient cohorts can contribute to confirming the positive benefit–risk profile of the One-Strength regimen. Another aspect is that physicians were not blinded to the regimen, which could have influenced their evaluation of tolerability and the intensity of ADRs. This could have resulted in a worse evaluation of the One-Strength compared to the Standard regimen because they assumed worse safety and tolerability due to the 10-fold higher starting dose. Nevertheless, physicians' evaluation of tolerability and intensity of events was comparable between the two regimens.

5 | Conclusion

The trial demonstrated that SCIT with the birch pollen allergoid is safe and well-tolerated when dose escalation is performed using the One-Strength regimen. No differences in the safety profile were observed between children, adolescents, and adults. There was no trend toward more or more severe ADRs in asthmatic patients compared to non-asthmatics. This regimen improves patient convenience in the short term, potentially enhancing adherence over the course of 3–5 years of treatment course, although this association has yet to be fully established.

Author Contributions

All authors contributed to the study concept and design, and/or the analysis or interpretation of data. All authors had access to the trial data, reviewed the manuscript, revised the content critically, and approved the final version for submission. All authors agree to be accountable for all aspects of the work.

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Conflicts of Interest

Marek Jutel reports personal fees from ALK-Abello, Allergopharma, Stallergenes, Anergis, Allergy Therapeutics, Leti, HAL, GSK, Novartis, Teva, Takeda, Chiesi, Pfizer, Regeneron, Astra Zeneka, Lallemand, Shire, CELLTRION Inc. Genetech, Roche, Verona, Lek Pharmaceuticals, Arcutis Biotherapeutics, FAES FARMA outside of submitted work and is the Allergy Journal Deputy Editor. Ludger Klimek reports grants and personal fees from Allergopharma, grants and personal fees from Viatris, personal fees from HAL Allergie, personal fees from ALK Abelló, grants and personal fees from LETI Pharma, grants and personal fees from Stallergenes, grants from Quintiles, grants and personal fees from Sanofi, grants from ASIT biotech, grants from Lofarma, personal fees from Allergy Therapeutics, grants from AstraZeneca, grants and personal fees from GSK, grants from Inmunotek, personal fees from Cassella med, personal fees from Novartis, personal fees from Regeneron Pharmaceuticals, personal fees from ROXALL Medizin GmbH, outside the submitted work; and Membership: AeDA; DGHNO; Deutsche Akademie für Allergologie und klinische Immunologie; HNO-BV; GPA; EAACI. Michael Gerstlauer has received research support/study funds for his hospital from the following companies in the last 3 years: Allergopharma, Bencard Allergie, Stallergenes-Greer, Boehringer Ingelheim, Infectopharm. Lecture and consultancy fees have been received from ALK-Abelló, Allergopharma, Bencard Allergie, Leti, Novartis, Sanofi, Stallergenes-Greer in the last 3 years. There are memberships in the following professional societies: GPAU, GPP, EAACI, ERS, DGKJ, AGPAS. Dana Troyke and Kristina Duwensee are employees of Allergopharma GmbH & Co. KG, Reinbek, Germany. Christian Vogelberg has received personal fees for lectures or consultancy from Aimmune Therapeutics, Allergopharma, Allergy Therapeutics, ALK-Abello, AstraZeneca, Bencard Allergie, DBV Technology, LETI Pharma, Novartis Pharma, Orion Pharma, Sanofi Aventis, and Stallergenes-Greer outside of submitted work. There are memberships in the following professional societies: GPAU, GPP, EAACI, AeDA, DGAKI, ERS, DGKJ, APPA.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** all70265-sup-0001-Supinfo.docx.