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Shortened up-dosing with sublingual immunotherapy drops containing tree allergens is well tolerated and elicits dose-dependent clinical effects during the first pollen season

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ABSTRACT

Background: This study compared a rapid home-based up-dosing schedule for sublingual immunotherapy (SLIT) drops containing tree pollen allergens with two previously established schedules. Furthermore, the clinical effect of the SLIT was investigated with respect to patients' first pollen season under treatment.

Methods: In this open-label, prospective, patient-preference, non-interventional study, local and systemic reactions were compared between three up-dosing groups using a SLIT formulation containing birch, alder, and hazel pollen extracts (ORALVAC® Compact *Bäume*). Clinical improvement after patients' first season under treatment was analysed using symptom scores, ARIA classification, symptom control, and the use of symptomatic medication and was compared with data from the previous, pre-treatment pollen season. As the real-life study design allowed no placebo group, the late-treated patients (co-seasonal) served as a control, and crowd-sourced symptom data from persons with hay fever were used from a free web-based online diary.

Results: In 33 study centres in Germany and Austria, 164 patients were included. The treatment was well tolerated, without difference between the groups during the up-dosing phase. At the end of the assessment, 96.1% rated the tolerability of the treatment as good or very good. Local reactions were mostly mild in severity and no serious adverse events occurred. Symptom scores decreased from the 2016 pollen season to the 2017 pollen season. As for the ARIA classification, 79.0% of patients had persistent, moderate-to-severe rhinitis before treatment, but only 18.6% had the same classification after treatment. In all, 62.4% of patients achieved symptom control, and 34.3% of patients required no symptomatic medication after treatment. The rhinoconjunctivitis score was 34.4% lower for pre-seasonal treatment initiation than for the control group. Crowd-sourced symptom load indices showed that the 2016 season caused slightly more symptoms; however, it is assumed that this difference of 0.3–0.5 (score range 0–10) was of less clinical relevance.

Abbreviations: AE, adverse event; ARIA, Allergic Rhinitis and its Impact on Asthma; IgE, immunoglobulin E; N, number; PHD, Patient's Hay Fever Diary; RCAT, Rhinitis Control Assessment Test; SD, standard deviation; sIgE, specific immunoglobulin E; SLI, symptom load index; SLIT, sublingual immunotherapy; SmPC, Summary of Product Characteristics; TU, therapeutic units; V, visit.

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Conclusion: The treatment administered using the rapid home-based up-dosing schedule was safe and well tolerated. Symptom relief and reduction in medication use were observed during the first pollen season with SLIT.
Trial registration number: NCT03097432 (clinicaltrials.gov).

Background

Allergen immunotherapy is the only potentially curative treatment for immunoglobulin E− (IgE) mediated diseases such as allergic rhinitis, rhinoconjunctivitis, and allergic asthma. It provides long-term relief of symptoms and improves patients' quality of life. It can also prevent new sensitisations and the progression from allergic rhinitis to asthma.[1–3]

With its non-invasive route of administration, sublingual immunotherapy (SLIT) permits home administration and can therefore improve patients' acceptance. However, poor patient adherence remains a challenge. The most common reasons for discontinuing SLIT are intolerable local reactions, lack of efficacy, and inconvenient administration.[4–7] Tablet-based SLIT products with a very short up-dosing phase (within a day)[8,9] are available as well as products with no up-dosing at all.[10,11] In SLIT based on drops, different up-dosing schedules can be planned flexibly by adjusting the number of drops according to the individual needs of the patient.

The SLIT investigated in this study is indicated for birch, alder, and/or hazel pollen–induced allergic rhinitis, rhinoconjunctivitis, or asthma. Previously, two up-dosing schedules have been established (conventional and ultra-rush office-based schedules, Fig. 1).

In this study, we evaluated the rapid home-based up-dosing schedule last included in the German and Austrian summary of product characteristics (SmPC, Fig. 1). This schedule was implemented with the aim of simplifying and facilitating the procedure for both patients and physicians without compromising patients' safety. The aim of the study was to compare the tolerability and safety of the rapid home-based up-dosing schedule with the two established schedules as well as to evaluate the clinical effect of the treatment on the first tree pollen season after treatment initiation.

Materials and methods

Study design

This open-label, prospective, patient-preference, non-interventional study was conducted in Germany and Austria from October 2016 to September 2017. It was given a favourable opinion by the local ethics committees. All patients and/or parents provided informed consent before study inclusion. This trial is listed at clinicaltrials.gov under the identifier NCT03097432.

Adults and children older than 2 years of age could be enrolled at study centres specialised in allergology. The centres were located across Germany and Austria to rule out possible investigator bias in any one centre. The inclusion criterion was the prescription of the investigated tree pollen allergen drops for SLIT ORALVAC® (ORALVAC® Compact *Bäume*, Bencard Allergie GmbH, Munich, Germany/Allergy Therapeutics, Worthing, UK) in patients diagnosed with birch, alder, and/or hazel pollen–induced allergic rhinitis, rhinoconjunctivitis, or asthma. Allocation to one of the three study groups was based on patients' preference rather than randomisation. Patients chose their preferred treatment schedule before they were included in the study. The exclusion criterion was no administration of the investigated tree pollen allergen drops due to contraindications as specified in the SmPC or individual decision.

The study consisted of five visits. Treatment was initiated at the baseline visit (V1). Visit 2 (V2) took place after the up-dosing phase and visit 3 (V3) before the early spring pollen season. Visit 4 (V4) was scheduled by the investigators such that it was to take place during the peak of the pollen season and visit 5 (V5) after the pollen season, after or during treatment depending on the treatment onset and maintenance schedule.

Study endpoints

The primary endpoint was to confirm the tolerability of the rapid home-based up-dosing schedule as well as of the previously established conventional and ultra-rush office-based schedules.

The secondary endpoints were parameters of clinical improvement compared to the previous pollen season (assessed retrospectively at V1 and V5), such as the reduction in symptom scores and symptomatic medication use, improvement in ARIA (Allergic Rhinitis and its Impact on Asthma) classification, as well as the status of symptom control in the 2017 pollen season (assessed prospectively at V4), regardless of up-dosing schedules. The non-interventional study design did not allow a placebo-controlled group; therefore, patients who started SLIT as late as during the onset of the pollen season 2017 (co-seasonal treatment) served as the prospective control group, because the cumulative dose was low at the time of assessment. The prospective comparison of this control group with the pre-seasonal high-dose group could reveal indications of effectiveness.

Considering that the intensity of the pollen season differs from year to year, crowd-sourced symptom data from a free web-based online diary were used to estimate the relevance of differences in the pollen seasons investigated and therefore the contribution of the SLIT to clinical improvement.

Study medication

ORALVAC® Compact *Bäume* (Trees), the tree pollen allergen drops administered in this study, consist of a colourless, aqueous solution containing purified extracts of allergens at a defined concentration (therapeutic units, TU) from birch, alder, and hazel pollen (35%, 30%, and 35%, respectively). Since no internationally harmonised and agreed standards are available allowing comparison of products from different manufacturers, the establishment and use of in-house reference preparations (IHRP) for quality control is required by the European Medicines Agency (EMA) and used as a standard for analysis of batch-to-batch consistency from the National Competent Authorities in Europe.[12,13] In the case of ORALVAC® Compact *Bäume* (Trees), following the IHRP requirement the TU/mL strength of the drug product vaccine is based on the strength of the drug substance relative to that of the diagnostic (skin prick) product, based on the relative amounts of Bet v 1 present (measured by a monoclonal assay). The strengths of the birch, alder, and hazel pollen diagnostic products were originally determined in optimal diagnostic concentration studies. The product is provided in bottles at three different concentrations for the up-dosing period: the solution with the highest concentration of allergen (hereafter referred to as the "maintenance solution"; 7680 TU/mL), the 1:10 dilution of the highest solution (768 TU/mL), and the 1:100 dilution of the highest solution (76.8 TU/mL). One pump delivers 0.07 mL solution.

Administration schedules

In this study, we evaluated three up-dosing schedules: conventional, ultra-rush office-based, and rapid home-based. Two different maintenance options were available for each schedule: the shorter maintenance option with seven pumps daily for 3 months and the longer maintenance option with three pumps daily for 8 months (Fig. 1).

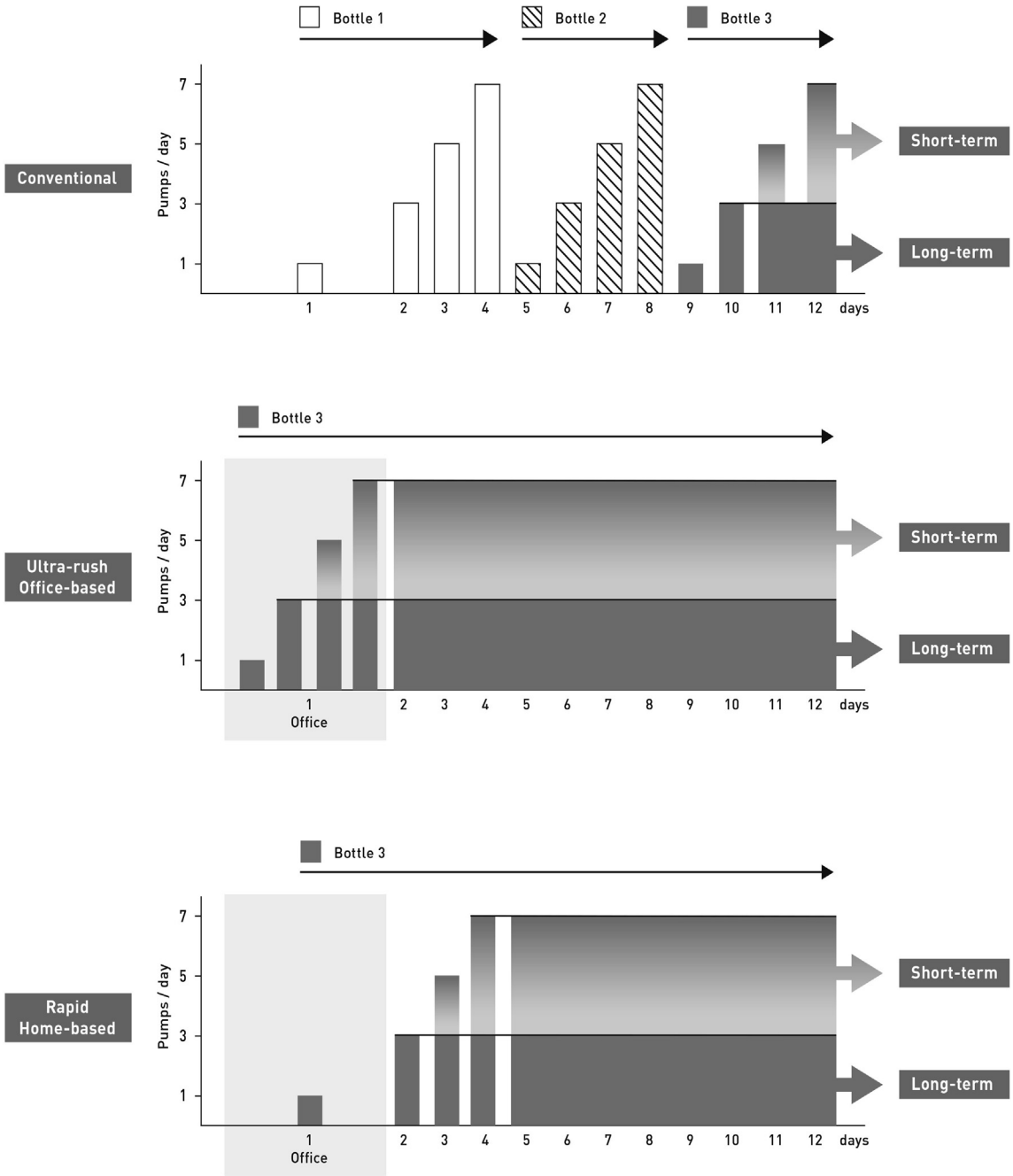

Fig. 1. Up-dosing schedules investigated. (a) The conventional schedule lasts 10–12 days and uses three different bottles with three increasing allergen concentrations to reach the maintenance dose. This schedule permits complete home administration. (b) The ultra-rush office-based schedule consists of two or four administrations. It lasts up to 2 h and must be administered under medical observation. This schedule requires only the highest allergen concentration. (c) The rapid home-based schedule uses the same up-dosing doses as the ultra-rush schedule but are scheduled for 2 to 4 consecutive days. Only the first administration requires medical observation; three subsequent daily administrations are taken at home. Regardless of the up-dosing schedule, the SLIT used in this study can be continued as a short-term treatment with a higher dose (usually seven pumps daily over a period of 3 months per year) or as a long-term treatment with a lower dose (usually three pumps daily over a period of 8 months per year). The investigated up-dosing schedules correspond to the SmPCs for use in Germany and Austria. The SLIT treatment should only be used according to SmPC and in adherence with local legislation and or guidelines.

Tolerability assessment

After each up-dosing administration, patients documented prospectively the occurrence of symptoms and the level of discomfort (no symptoms, mild symptoms, moderate symptoms, severe symptoms) in patient diaries. Local reactions to be assessed were pharyngeal symptoms, which included swelling, itching, and irritation of the mouth, lips, and throat. Systemic reactions were defined as all those other than local symptoms, such as sneezing, runny nose, itching eyes, and respiratory and skin reactions. Systemic respiratory reactions included cough and dyspnoea. Systemic skin reactions were swelling, pruritus, and redness (mouth and throat area excluded). In each patient, the repeated occurrence of an adverse reaction was evaluated as a new reaction.

At V2 (after the up-dosing phase) and at V5 (study completion), patients rated retrospectively the overall tolerability of the treatment as “very good”, “good”, “moderate”, or “poor”.

All adverse events (AEs) and serious adverse events were documented as done in routine practice according to Good Pharmacovigilance

Practice Module VI. For the study, investigators' reports including systemic AEs were graded according to the system by Cox et al.,[14] which was described to be adequate for grading systemic side effects of SLIT.[15] The relation of events to the treatment, the intensity of the AEs, and the grading of systemic AEs were evaluated by the investigator.

Assessment of improvement in clinical parameters

Symptom scores

Nasal symptoms (sneezing, rhinorrhoea, nasal pruritus, and nasal congestion), ocular symptoms (ocular pruritus, redness, and watery eyes), and pulmonary symptoms (dyspnoea and coughing) were assessed retrospectively by the investigator at V1 (previous pollen season of 2016) and V5 (after the 2017 pollen season) with regard to symptom intensity (none, mild, moderate, severe). In addition, rhinitis, conjunctivitis, and asthma symptoms were assessed retrospectively at V1 and V5, as well as prospectively at V4 (during the peak of the 2017 pollen season). Symptom evaluation of rhinitis, conjunctivitis, and asthma was based on the combination of the level of discomfort (no symptoms = 0, mild symptoms = 1, moderate symptoms = 2, and severe symptoms = 3) and the frequency of occurrence (rare = 1, < 4 weeks = 2, ≥ 4 weeks = 3, and always = 4) with a possible range from 1 to 7, respectively, as validated before.[16,17] The rhinoconjunctivitis score was based on the level of discomfort of rhinitis and conjunctivitis symptoms and was rated by the authors on a scale from 0 to 6, with 0–2 points being given for none to mild symptoms and 3–6 for moderate to severe symptoms.

Symptomatic medication

At V1 and V5, patients were asked to retrospectively report the symptomatic medication they had used during the 2016 and 2017 pollen seasons in the categories of oral antihistamines, intranasal corticosteroids, eye drops, inhaled corticosteroids, β_2-adrenergic receptor antagonists, or others. The frequency of use was also assessed (none, seldom, < 4 weeks, ≥ 4 weeks, and always).

ARIA classification of rhinitis

Rhinitis symptoms occurring during the pollen seasons of 2016 and 2017 (assessed retrospectively at V1 and V5) were classified as persistent or intermittent and mild or moderate-severe based on the ARIA classification of rhinitis.[18] The term *persistent rhinitis* is to be used when symptoms last > 4 days/week or > 4 consecutive weeks and *intermittent rhinitis* when symptoms last < 4 days/week or < 4 consecutive weeks. According to this definition and for the purpose of this study, we considered a patient with sensitisations to hazel, alder, and birch pollen, for example, as having *persistent rhinitis*, since the patient could show symptoms as long as from January until mid-April, which is when those trees bloom in Germany and Austria. In addition, a questionnaire was used to assess symptom severity and duration.

Symptom control

The German version of the validated Rhinitis Control Assessment Test (RCAT)[19] was used to determine whether patients' rhinitis symptoms were controlled in the peak of the 2017 pollen season (assessed prospectively at V4). The RCAT is based on six items: nasal congestion, sneezing, watery eyes, sleep disruption, and activity limitation caused by symptoms, as well as patients' self-rating of symptom control. The frequency of each item within a 1-week recall period is assessed on a five-point scale (never = 5, rarely = 4, sometimes = 3, often = 2, and extremely often = 1). A sum of six scores lower than 21 suggests that rhinitis symptoms are not controlled. A total score equal to or higher than 22 means that the patient has achieved symptom control.

Crowd-sourced symptom data and the symptom load index

Prospective crowd-sourced symptom data from a free web-based online diary, the Patient's Hay Fever Diary (PHD, https://www.pollendiary.com/Phd/, accessible via the *Pollen App* on a smartphone or tablet), was used to assess information about symptom intensity during the relevant seasons of the trial. The PHD is currently available in 13 European countries including Germany and Austria. Users fill in a validated questionnaire to record the severity of symptoms affecting the eyes, nose, and lungs as well as to document medication use, from which a total symptom score was calculated. All entries from all active users in Germany were taken into account for the years 2016 and 2017, since the study centres were located across the country for this study. Only the data entries from Vienna were considered, since the only participating Austrian study centre was located in this city. Since the prescribed immunotherapy focused on tree pollen-induced allergic symptoms, the whole period from January until the end of May (Germany)/mid-May (Vienna) was taken into account, consulting the most recent pollen calendars for Germany and Austria.[20] No further data filtering was performed thereafter. The daily symptom scores were transferred directly to symptom load indices (SLIs).[21] Hence, the total symptom scores (including all organs and medication use) were normalised to obtain daily average values of SLI between 0 and 10 for the study period.

Subgroup analyses of the improvement in clinical parameters for the season 2017

Patients who started SLIT late in the 2017 season (co-seasonal treatment, as of 1 April) served as a control group and were compared to those who were treated pre-seasonally. The comparison between the consecutive seasons regarding the reduction in symptom scores, ARIA classification and symptomatic medication was analysed using the retrospective data assessment at V1 and V5. For the prospective comparison between the pre-seasonal and the co-seasonal groups, the percentage of patients who experienced symptom control in the 2017 pollen season and the rhinoconjunctivitis score were analysed using the data obtained during the peak of the 2017 pollen season at V4.

Statistics

The target values regarding the endpoints are mostly presented descriptively. Statistical analyses were performed using IBM SPSS Statistics for Windows (version 23.0, IBM Corp., Armonk, NY, USA). Continuous data were described as mean, standard deviation, minimum, maximum, and number of valid values. A 95% confidence interval was computed if it complemented the analysis in a meaningful way. Categorical data were presented as absolute and percentage frequencies. The differences between the 2016 and 2017 pollen seasons within a group were analysed using the Wilcoxon–Mann–Whitney test, and categorical differences between groups were analysed using the chi-square test; a P value of < 0.05 was considered significant. Effect size analyses were conducted according to Cohen's and Hedges' method, with an effect size < 0.2 meaning no effect, 0.2 to < 0.5 a small, 0.5 to < 0.8 a medium, and ≥ 0.8 a large effect.[22,23] Missing data were not imputed.

Results

Study population

As shown in Fig. 2 and 164 patients were enrolled at 32 study centres in Germany and 1 study centre in Austria (Vienna). Among those, most patients chose the conventional up-dosing schedule (n = 90). Twenty-nine patients opted for the ultra-rush office-based schedule. The rapid, home-based schedule was chosen by 45 patients. There were 104 patients who underwent the lower-dose treatment having an 8-month maintenance phase with a three-pump daily administration (conventional: 68 patients; ultra-rush office-based: 20 patients; rapid home-based: 16 patients). Fifty-four patients were allocated to the high-dose treatment (3-month maintenance phase) with a seven-pump daily administration (conventional: 17 patients; ultra-rush office-based: 8 patients; rapid home-based: 29 patients). In total, 18 patients started the immunotherapy during the pollen season (co-seasonal treatment). Hence, most

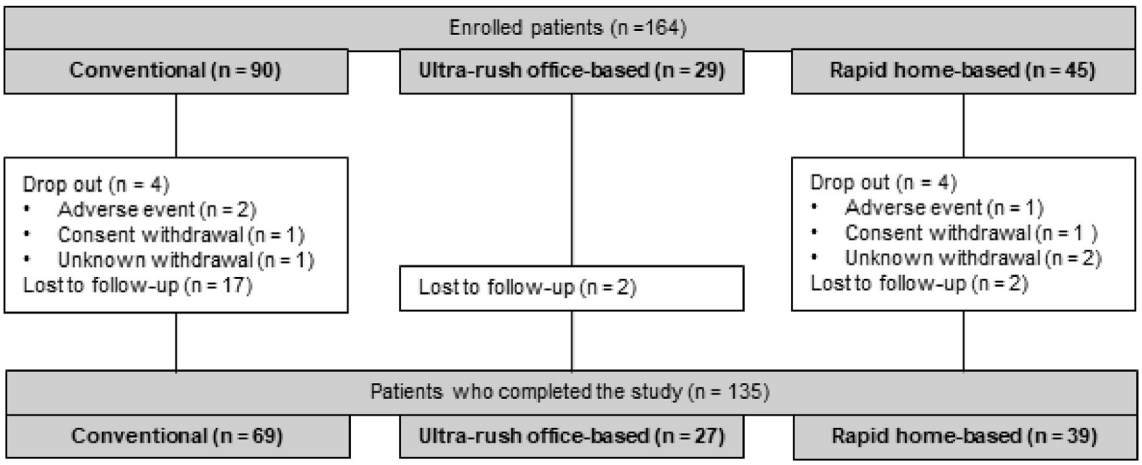

Fig. 2. Study flowchart.

patients (n = 146) were included in the trial before the pollen season began (pre-seasonal treatment).

The mean age of patients was 38.0 years, ranging from 3 to 76 years. For two of the patients the age was unknown. There were more female than male patients in this study (63.8% vs. 36.2%). Age and female/male distribution were similar across all groups. There were more patients with asthma in the ultra-rush office-based group (55.2%) than in the conventional (28.4%) and rapid home-based groups (21.4%). Further patient characteristics of the treatment groups are presented in Table 1.

Tolerability assessed by patients and investigators

At the last study visit, almost all patients (96.1%) assessed their treatment's tolerability as "good" or "very good" (Fig. 3).

Furthermore, we analysed treatment tolerability between up-dosing schedules and subgroups. After up-dosing to the maintenance dose at V2, a similar percentage of patients rated the tolerability as "good" or "very good" in the conventional (91.8%), the ultra-rush office-based (88.9%), and the rapid home-based groups (94.4%). The analysis of the patients' assessments after the pollen season at V5 showed excellent overall tolerability across all subgroups, regardless of treatment initiation and maintenance dose (Fig. 3).

In addition, patients documented the local (pharyngeal) and systemic (skin and respiratory) reactions in a diary on a daily basis during the up-dosing phase.

Local (pharyngeal) reactions

The proportion of patients who did not report any local reaction in the patient diary was comparable between the up-dosing groups during the up-dosing phase: 50.8% in the conventional, 45.5% in the ultra-rush office-based, and 51.9% in the rapid home-based group, whereas the conventional group showed a trend towards a greater intensity of adverse events (AEs) than did the other groups (Fig. 4a).

Systemic (skin and respiratory) reactions

Systemic reactions documented by the patients occurred relatively rarely during the up-dosing phase. In all, 84.7% of patients in the conventional, 72.7% in the ultra-rush office-based and 77.8% in the rapid home-based group did not report any systemic reaction without statistical differences between the groups. Patients in the ultra-rush office-based and the rapid home-based groups did not have any severe reactions (Fig. 4b).

Reports of adverse events

Overall, the applied immunotherapy was well tolerated throughout the different treatment schedules. Altogether, 20 reports of AEs were documented by the investigators, most of them being of mild or moderate intensity; in six reports, the events were systemic reactions, and in only one of these reports the event was classified as severe (Table 2). No serious AE occurred and no case of anaphylaxis was reported.

Table 2 gives an overview of all reports of AEs documented by the investigators for the different up-dosing groups. In the conventional group, six out of eight reports were made for AEs of moderate or severe intensity. Seven reports of AEs were evaluated by the investigator as being probably/possibly or definitely related to the treatment. Of those, one report was for events that were not systemic reactions; in one report the assessment of the investigator was

Table 1
Patient characteristics.

Characteristic	Total	Up-dosing groups		
		Conventional	Ultra-rush office-based	Rapid home-based
Total (n)	164	90	29	45
Age (years), mean ± SD	38.0 ± 16.9	39.9 ± 17.2	38.0 ± 16.7	34.2 ± 16.1
Age (years), minimum	3	5	3	5
Age (years), maximum	76	76	75	73
Female (n; %)	104; 63.8	60; 67.4	18; 62.1	26; 57.8
Male (n; %)	59; 36.2	29; 32.6	11; 37.9	19; 42.2
Asthma patients (n; %)	50; 31.4	25; 28.4	16; 55.2	9; 21.4
Sensitisation to birch pollen (n; %)	133; 81.1	65; 72.2	28; 96.6	40; 88.9
RAST class, mean ± SD	3.42 ± 1.175	3.21 ± 1.193	3.60 ± 1.271	3.58 ± 1.033
Sensitisation to hazel pollen (n; %)	138; 84.1	82; 91.1	20; 69.0	36; 80.0
RAST class, mean ± SD	3.04 ± 1.411	2.89 ± 1.490	4.16 ± 1.451	2.71 ± 1.040
Sensitisation to alder pollen (n; %)	106; 64.6	55; 61.1	15; 51.7	36; 80.0
RAST class, mean ± SD	3.09 ± 1.508	2.76 ± 1.715	4.22 ± 1.758	3.09 ± 0.960

n, number; SD, standard deviation

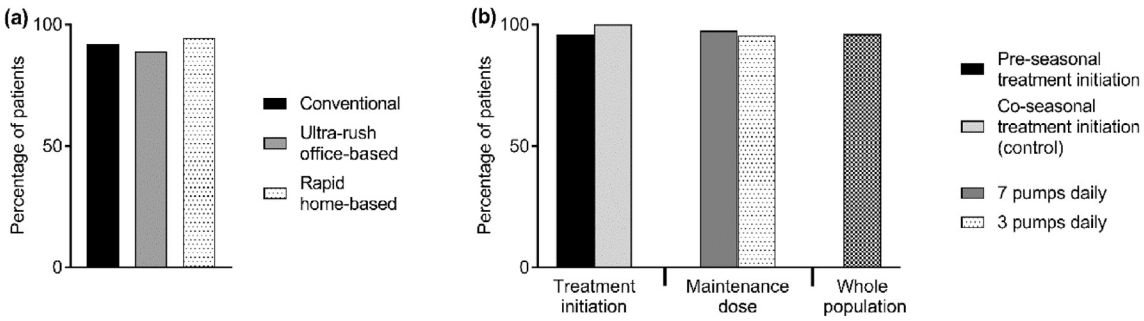

Fig. 3. Patients' assessment of treatment tolerability. Percentage of patients who assessed (a) the tolerability of up-dosing administrations as "good" or "very good" at visit 2 comparing three up-dosing schedules (conventional vs. ultra-rush office-based vs. rapid home-based) and (b) the overall tolerability of the entire treatment as "good" or "very good" at V5 comparing treatment initiation (pre-seasonal vs. co-seasonal) and maintenance dose (three pumps vs. seven pumps).

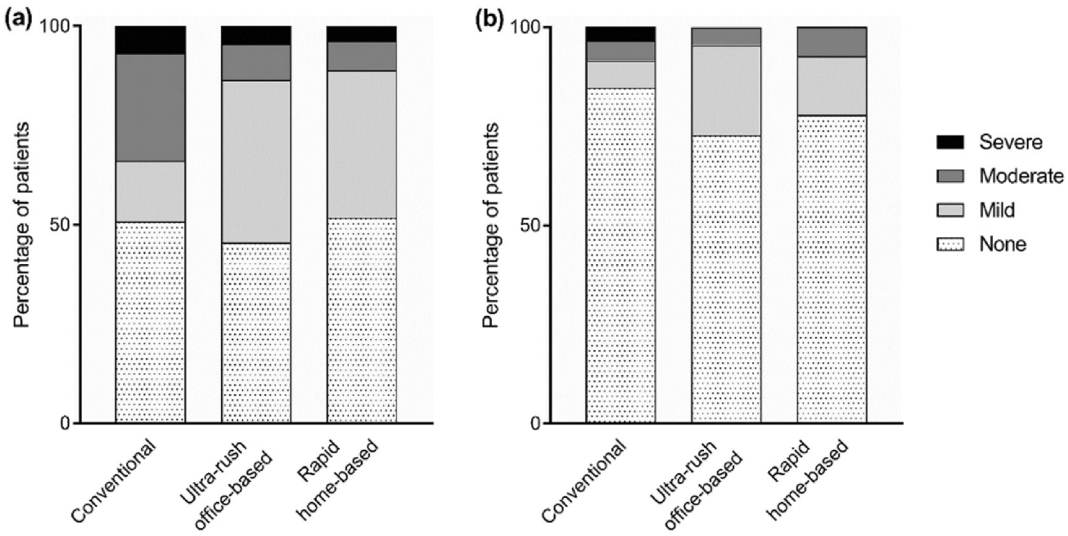

Fig. 4. Tolerability of the up-dosing administrations. Analysis of the percentage of patients who experienced (a) local or (b) systemic reactions during the up-dosing phase comparing the tolerability of the three up-dosing schedules (conventional vs. ultra-rush office-based vs. rapid home-based). Reactions were assessed as mild, moderate or severe by the patients. P values between groups were obtained using the chi-square test, but clinical significance was not shown.

missing, in three reports the events involved grade 1 systemic reactions, and in one report the event was a grade 2 systemic reaction according to the classification developed by Cox et al.[14] In the ultra-rush office-based group, three reports of moderate adverse events were made for reactions induced by the treatment. They were not systemic reactions according to Cox et al.[14] No treatment-related AE was reported by the investigators for the rapid home-based group.

Table 2
Reports of AEs documented by the investigators in the different up-dosing groups.

Up-dosing group		Conventional (8 reports)	Ultra-rush office-based (12 reports)	Rapid home-based (0 reports)
Intensity of AE	Mild	8	9	0
	Moderate	4	3	0
	Severe	2	0	0
Relation of AE to the treatment	Unlikely related	1	3	0
	Possibly related	4	2	0
	Probably related	2	3	0
	Related	1	2	0
Assessment of systemic reactions	Grade 0	1	3	0
	Grade 1	3	2	0
	Grade 2	1	0	0
	Without assessment	1	0	0

Improvement of clinical parameters

The improvement of clinical parameters after treatment with the tree pollen drops in the whole study population was determined by comparing the symptom scores, the ARIA classification, and the use of symptomatic medication between the 2016 pollen season before treatment (assessed retrospectively at V1) and the 2017 pollen season after treatment (assessed retrospectively at V5). The improvement was also determined based on the status of symptom control in the 2017 pollen season and by comparing the rhinoconjunctivitis score between the pre-seasonally treated patients with those starting the treatment late (co-seasonally); both of these parameters were assessed prospectively during the peak of the 2017 pollen season at V4.

Reduction in symptom scores compared to the previous season

Symptom scores were significantly lower after SLIT initiation in 2017 (V5). The mean rhinoconjunctivitis score assessed at V5 for the 2017 season was 42.4% lower than that of the 2016 pollen season as assessed at V1 (Fig. 5a), corresponding to the mean rhinitis, conjunctivitis, and asthma symptom scores with a reduction of 40.5%, 34.2%, and 60.2%, respectively (Fig. 5b).

Reduced symptomatic medication use after SLIT initiation compared to the previous season

Almost all patients (91.2%) reported using symptomatic medications during the 2016 pollen season. The proportion of patients who no longer

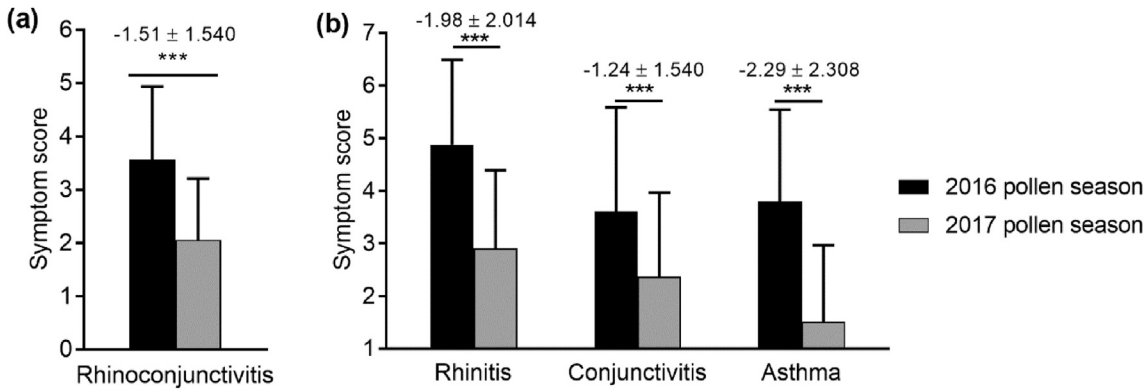

Fig. 5. Reductions in symptom scores. (a) The rhinoconjunctivitis score (0–6 points) and (b) the rhinitis, conjunctivitis, and asthma scores (1–7 points) were assessed retrospectively at visit 1 for the 2016 pollen season and after SLIT initiation at V5 for the 2017 pollen season. The difference between both seasons is shown as mean ± SD. P values between 2016 and 2017 were obtained using the Wilcoxon-Mann-Whitney test: *** indicates $P < 0.001$.

needed symptomatic drugs during the pollen season increased from 8.8% in 2016 to 34.3% in 2017, which means after SLIT initiation. The use of oral antihistamines decreased substantially (Fig. 6).

Reduced rhinitis symptoms according to a modified ARIA classification of rhinitis compared to the previous season

According to the ARIA classification of rhinitis,[18] most patients in this study (79.0%) suffered from persistent, moderate-to-severe rhinitis during the 2016 pollen season. Intermittent, moderate-to-severe rhinitis was observed in 15.3% of patients, whereas intermittent, mild rhinitis was found in 3.8% of patients. From the 2016 pollen season to the 2017 pollen season after SLIT initiation, symptoms in the study cohort improved markedly, such that only 18.6% of the patients presented with persistent, moderate-to-severe rhinitis during the 2017 pollen season (Fig. 7).

Comparison of symptom load index between the consecutive seasons

Since tree pollen load can differ from year to year, the comparison of SLIs between the 2016 and 2017 pollen seasons was considered for this study. The daily average SLIs from January to May are depicted in Fig. 8. In addition, the SLI was calculated for each month and year to obtain information about general symptom severity in the respective months (Table 3). In general, the daily, monthly and seasonal SLIs show a more intense pollen season of the early flowering trees in Germany and Vienna in 2016 than in 2017. The average SLI of the early flowering tree season was 3.97 in 2016 and therefore higher than in the season of 2017 with a value of 3.67 (Table 3). In Vienna, this difference was even more obvious with an average seasonal SLI of 3.69 in the season of 2016 compared to 2017 with an SLI of 3.13. If the monthly SLIs are compared only for March 2017, the SLI was higher than the SLIs of the previous year. In Germany, over 200 entries could be recorded per day in the beginning of the season in January, whereas the highest number of data entries was observed in April 2016 (some days over 4000 users). In Vienna, user entries remained below 10 at the beginning of the season and were also highest in April 2016 (highest day with 345 entries). The detailed monthly SLIs and yearly SLIs are depicted in Table 3. The course of the daily SLIs for Germany and Vienna are displayed in Fig. 8.

Improvement of clinical parameters during the first pollen season under treatment

Upon analysing the results of the RCAT, we observed that rhinitis symptoms were controlled in the 2017 pollen season in 62.4% of patients after SLIT initiation (assessed prospectively at V4). In order to analyse the effect of the SLIT evaluated in the first season of treatment, we compared early (pre-seasonal) treatment with an assumed higher cumulative dose with late (co-seasonal) treatment as a less-treated control group (as a surrogate for a placebo group, which is not allowed in a non-interventional setting). During the peak of the 2017 pollen season, three times more patients who underwent pre-seasonal treatment achieved rhinitis symptom control than did patients who started the

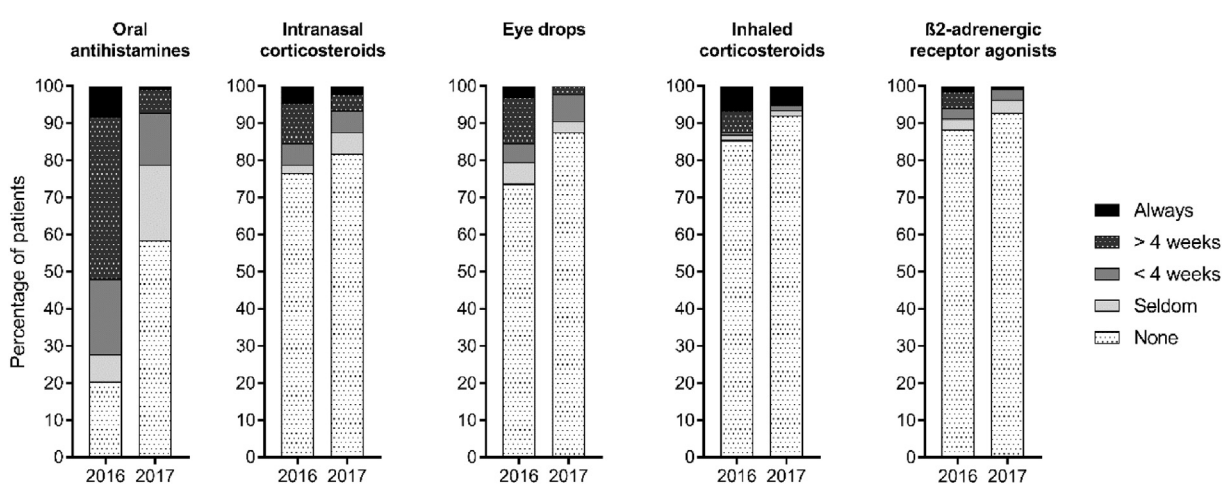

Fig. 6. Reduction in symptomatic medication use. The frequency of the use of different symptomatic medications was assessed retrospectively at V1 for the 2016 pollen season and after SLIT initiation at V5 for the 2017 pollen season.

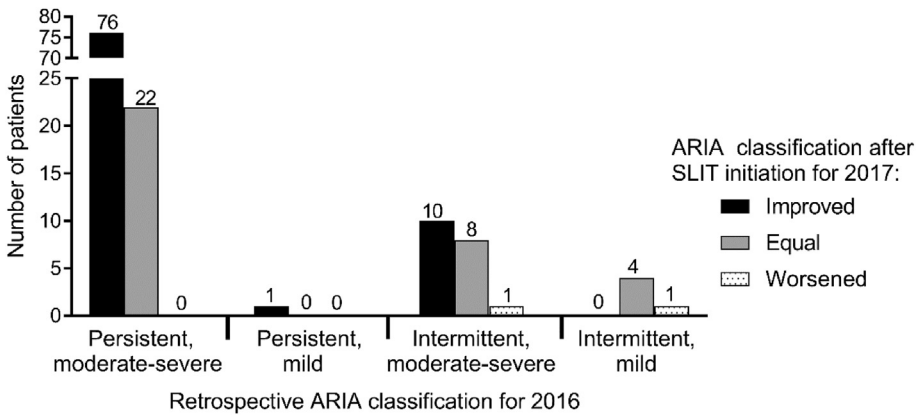

Fig. 7. Improved ARIA (Allergic Rhinitis and its Impact on Asthma) classification of rhinitis. Rhinitis symptoms were assessed and classified as persistent or intermittent as well as mild or moderate-to-severe based on a questionnaire at V1 for the 2016 pollen season and after SLIT initiation at V5 for the 2017 pollen season, retrospectively. The status in 2017 was also assessed and compared to 2016 and rated as improved, equal, or worsened. Data is shown as the number of patients and their respective shift in ARIA classification from 2016 to 2017.

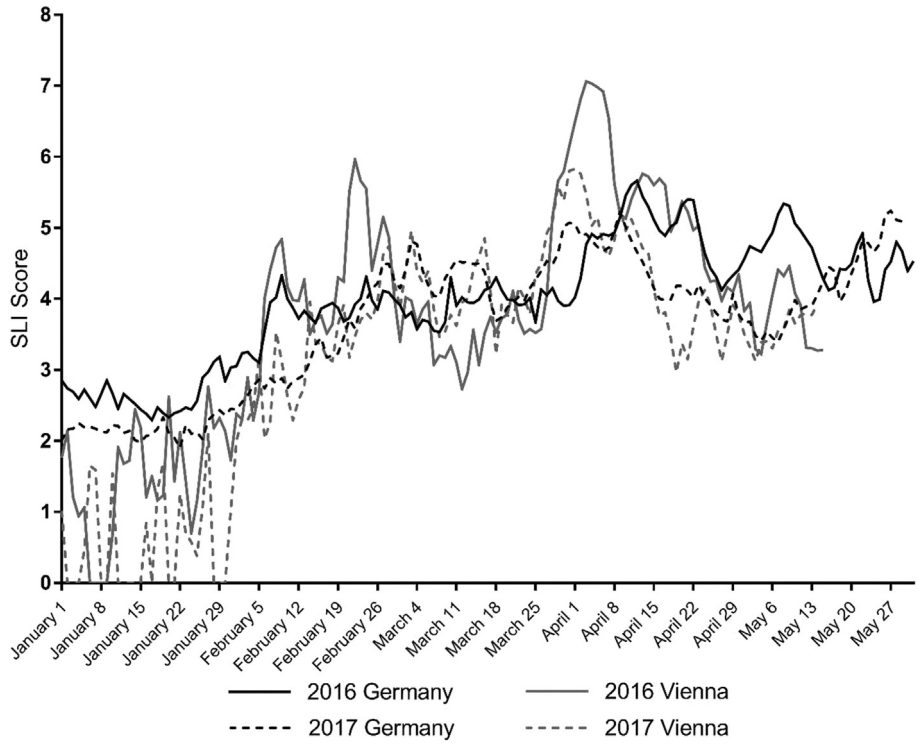

Fig. 8. Comparison of average symptom load index (SLI) values for Germany and Vienna, respectively, from January to May in the years 2016 and 2017, including the total tree season.

treatment during the pollen season (co-seasonal, Fig. 9a). Furthermore, pre-seasonal treatment resulted in a rhinoconjunctivitis score during the peak of the 2017 pollen season that was 34.4% lower than that for co-seasonal treatment (control) (Fig. 9b). Therefore, the pre-seasonal treatment was beneficial with a medium effect (rhinoconjunctivitis $d_{Cohen}/g_{Hedges} = -0.53$), and half of the patients in the pre-seasonal treatment group had moderate-to-severe symptoms (40.0% vs. 78.6%). The proportion of patients who did not need any symptomatic drugs during the peak of the 2017 pollen season (V4) was 36.6% in pre-seasonally treated patients compared to 14.3% in late-treated (co-seasonal) patients.

Table 3
Average symptom load index (SLI) values for Germany and Vienna, respectively, for the months January to May in the years 2016 and 2017, including the total tree season.

Region	Year	Symptom load index (SLI)					
		January	February	March	April	May	Total
Germany	2016	2.63	3.78	3.92	4.89	4.63	3.97
	2017	2.17	3.27	4.30	4.41	4.20	3.67
Vienna	2016	1.46	4.12	3.81	5.44	3.75	3.69
	2017	0.55	3.18	4.22	4.37	3.58	3.13

In parallel to these results, the analysis of the individual symptom scores for rhinitis and conjunctivitis when comparing the 2016 and 2017 pollen seasons showed an obvious symptom reduction for pre-seasonal treatment compared to the control (V1 to V5, Fig. 9c and d). For the rhinitis and conjunctivitis scores, pre-seasonal treatment was beneficial with a medium effect (rhinitis $d_{Cohen}/g_{Hedges} = -0.72$, conjunctivitis $d_{Cohen}/g_{Hedges} = -0.54$). The reduction in the asthma symptom score was not affected by the start of treatment ($d_{Cohen}/g_{Hedges} = 0.01$, small effect).

Discussion

The results of this study showed that the rapid home-based up-dosing schedule using SLIT drops containing tree pollen allergens was

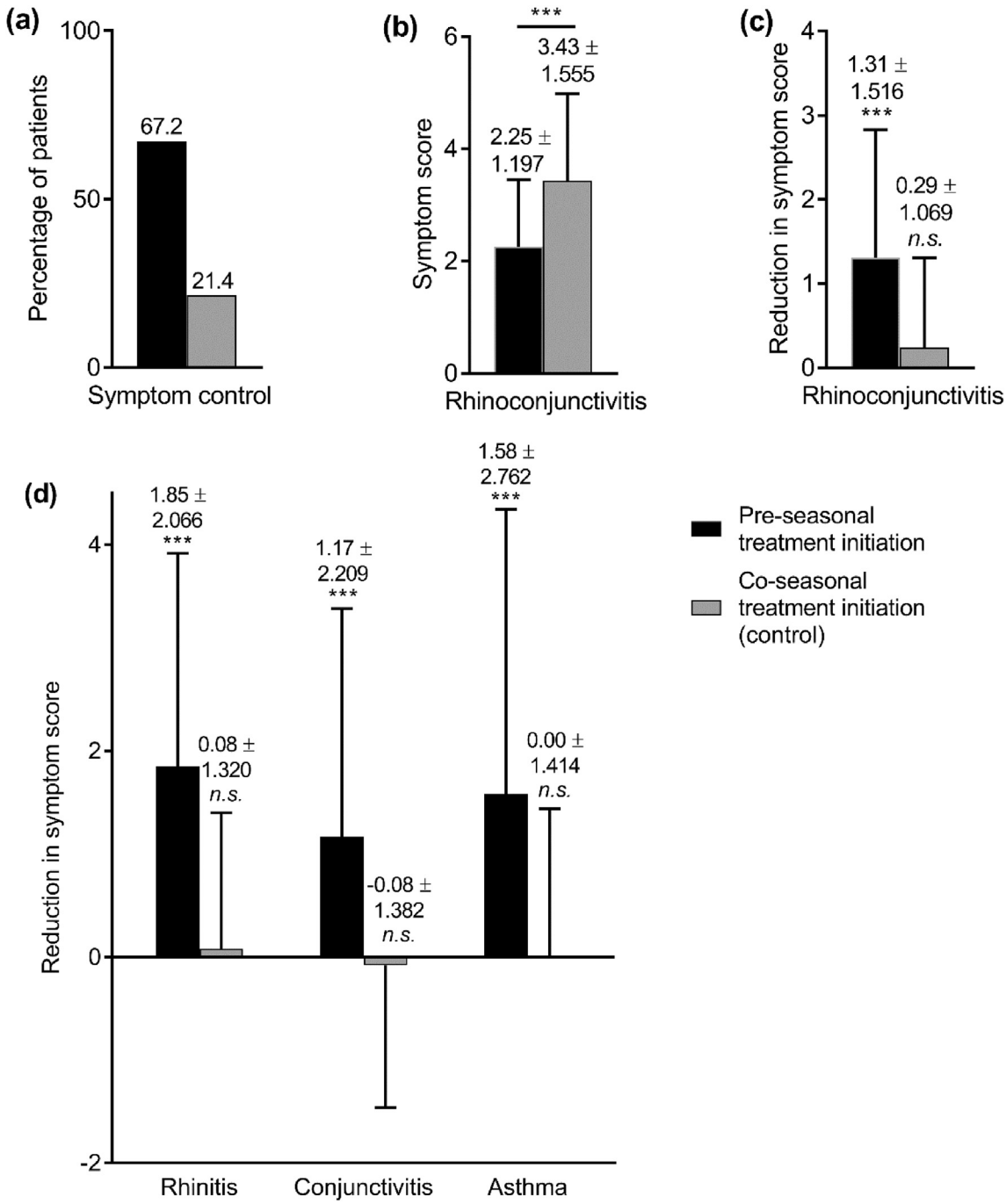

Fig. 9. Impact of treatment start on clinical parameters. Subgroup analysis comparing (a) the rhinitis symptom control during the peak of the 2017 pollen season (assessed prospectively at V4), (b) the rhinoconjunctivitis score during the peak of the 2017 pollen season (assessed prospectively at V4), (c) the reduction in the rhinoconjunctivitis score comparing the 2016 and 2017 pollen seasons (assessed retrospectively at V1 vs V5), and (d) the reduction in mean rhinitis, conjunctivitis, and asthma symptom scores comparing the 2016 and 2017 pollen season (assessed retrospectively at V1 vs V5), with respect to treatment start (pre-seasonal vs. co-seasonal) respectively. In (b), the pre-seasonal and the co-seasonal treatments were compared, while in (c) and (d) the respective treatment was compared to the previous season (2016 vs 2017). P values were obtained using the Wilcoxon-Mann-Whitney test: *** indicates $P < 0.001$, n. s. = not significant.

tolerated equally as well as the two previously established schedules. In the patients' final assessment, 96.1% of all patients rated the tolerability of the SLIT drops as "good" or "very good". Local reactions were mostly mild in severity, and no serious AEs or anaphylaxis occurred. Symptom scores decreased from the 2016 pollen season to the 2017 pollen season. Before undergoing treatment, 79.0% of patients were classified as having persistent, moderate-to-severe rhinitis according to the ARIA classification, but only 18.6% were classified as such after treatment. In all, 62.4% of patients achieved symptom control, and 34.3% of patients required no symptomatic medication after treatment. Pre-seasonal treatment resulted in a rhinoconjunctivitis score during the peak of the 2017 pollen season that was 34.4% lower than that for co-seasonal treatment (control). Although Crowd-sourced SLI showed that the 2016 season caused slightly more symptoms than did the 2017 season, it is assumed that this difference of 0.3–0.5 (score range 0–10) was of less clinical relevance.

Tolerability

Allergen-specific immunotherapy for respiratory allergy has been proven safe with a low incidence of systemic reactions (2.1% in 4363 treated patients), whereby a greater benefit has been reported for modified allergen extracts (allergoids) than for native (unmodified) extracts (odds ratio: 2.7; odds ratio for children: 8.4).[24,25] Divided in application forms, SLIT presents with less than half of systemic reactions compared with subcutaneous immunotherapy (1.1% vs. 2.4%).[24] Diverse studies have investigated rush up-dosing schedules and have reported conflicting results for AEs, with some studies finding such schedules inferior[26–28] while other studies claim them to be non-inferior[29–34] to conventional up-dosing regimens.

Therefore, it is controversial whether up-dosing is necessary in SLIT, and treatment with SLIT tablets does not necessarily call for up-dosing. In the case of the most common SLIT tablets, patients are treated with the maintenance dose from the outset.[35] Another concept is shortened up-dosing that lasts 3 days, which has been used for the five-grass tablet,[36] and 4 days for SLIT tablets with carbamylated allergoids.[37] In our study, we compared three up-dosing schedules to investigate whether the shortened (rapid home-based) up-dosing schedule could be proven with the same tolerability as the previously established schedules. Such a condensed schedule was also used by Passali et al.[9] to optimise the up-dosing schedule for SLIT, finding that up-dosing can be obsolete in the case of allergoids. As described by Ott et al.,[38] an ultra-rush up-dosing schedule for SLIT with drops containing pollen allergens from five grasses was found to be safe and well tolerated, with 69.0% of patients who underwent immunotherapy and similarly 62.7% of those taking placebo experiencing local reactions. Worm et al.[39] conducted a study with sublingual solution of birch pollen over the period of 2 years. The percentage of patients who reported treatment-emergent adverse events was similar between the active and the control groups (70.7% vs. 64.0% in the first year and 46.8% vs. 48.6% in the second year of treatment). The most frequent treatment-emergent AEs were local reactions such as oral pruritus, mouth oedema, and throat irritation. Klimek et al.[40] reported treatment-emergent AEs in 75.7% of patients undergoing SLIT with liquid solutions for birch pollen allergy. Another up-dosing schedule with sublingual drops containing birch pollen was also shown to be tolerable by Pfaar et al.[41] They showed that the majority of adverse reactions were of mild intensity and subsided completely.

Since poor tolerability, especially the occurrence of local reactions, is one of the main factors influencing treatment adherence or treatment discontinuation and finally affecting treatment effectiveness,[42] new treatment schedules focus on improved tolerability and patients' acceptance. The safety and tolerability of the three up-dosing schedules investigated in this study are in line with those reported in the literature. We show that the rapid up-dosing schedule is well tolerated in patients with allergic rhinitis, rhinoconjunctivitis, and allergic asthma. No patients, including those in the two shortened up-dosing arms, had serious adverse reactions. Treatment-related systemic reactions according to Cox et al.[14] were reported by the investigators for only 5 out of 164 patients.

The good tolerability of the treatments was further supported by the patients' evaluation. Although being asked to document adverse reactions on a daily basis during the up-dosing phase, more than three-quarters of patients did not document systemic reactions in the diaries. Most of these systemic reactions were of mild intensity. Half of the patients had local reactions; however, mild reactions predominated. Almost all patients (96.1%) rated the tolerability as "good" or "very good". This number was statistically comparable across all subgroups, although the ultra-rush office-based group rated their treatment scheme slightly less favourably. The number of local and systemic reactions in this group was also higher when compared to the other two groups. However, as the ultra-rush schedule implies the observation by the investigator during the entire up-dosing administration, the highest proportion of patients with asthma was found in this group (more than half of the group) compared to the other two up-dosing groups. Therefore, more reactions were anticipated to occur in these patients, as suggested by the Guidelines on Allergen Immunotherapy drafted by the European Academy of Allergy and Clinical Immunology.[43]

The results allow us to conclude that the investigated SLIT is safe, well tolerated, and accepted by patients independent of the up-dosing schedule.

Clinical improvement

In this study, almost half of patients experienced a reduction in their allergic symptoms from persistent, moderate in the pre-treatment 2016 pollen season to intermittent, mild in the first pollen season under SLIT treatment. In analogy to these observations, results of the RCAT also demonstrate that symptoms decreased from the 2016 pollen season to the 2017 pollen season.

Crowd-sourced symptom data were used in this study to provide additional information on the symptom severity of a season in combination with an immunotherapy trial. Although pollen data (seasonal pollen indices) are usually used to define the severity of a pollen season, recent studies show that the seasonal pollen index and the seasonal SLI do not always correspond.[21,44] Meteorological factors as well as environmental pollution and allergen content[45] have an additional influence on the allergic reaction. Hence, crowd-sourced symptom data may be a more precise tool than pollen data in general for defining the severity of an allergy season.[44] Although the seasonal SLI for Germany and Vienna was higher in 2016 than in 2017, the difference between both years is only about 0.3–0.5 out of averaged values between zero and 10 (Table 3, Fig. 8). As a limitation, it has to be mentioned that the method is not validated for explaining which difference in the SLI reflects clinical relevance so far, and the whole pollen season from January until May was taken into account for this study and not individual seasons, such as the hazel, alder or birch pollen seasons. However, these SLI data with only a minimal difference between the seasons are in line with the finding that the co-seasonal, and therefore, with a lower cumulative dose treated patients did not differ significantly in their symptom scores between both seasons.

The importance of starting immunotherapy early before the onset of the pollen season was reported by one of the first large-scale trials. The authors showed that only patients who started therapy 4 months prior to the onset of the pollen season showed significantly lower scores than those taking placebo. In patients who started the therapy two months before the start of pollen season, the difference versus placebo in this score did not reach statistical significance.[36] This is highlighted by the subgroup analysis in our study that took the patients who were treated late in the study (co-seasonal) as a control group due to the lower cumulative dose administered. Comparison of this control group with the pre-seasonally treated patients with higher cumulative doses revealed a three-fold greater symptom control during the pollen season in early treated patients (pre-seasonal).

An important criterion used to verify the effectiveness of an immunotherapy product is the proportion of treated patients who no longer need symptomatic therapies. The 2-year real-life study with a five-grass pollen tablet by Shah-Hosseini et al.[46] reported that 16.2% of patients in the season preceding the treatment, 48.2% in the first season with treatment, and 57.3% in the second season did not use symptomatic medication. Another study conducted by Pfaar et al.[47] reported a reduction in symptomatic medication use similar to that observed in our study. They investigated a subcutaneous booster immunotherapy for grass pollen allergy and showed that 34.0% of patients were without symptomatic medication in the first season following treatment, whereas this number was 3.8% before treatment. In our study, the percentage of patients who did not need any symptomatic medication increased by over 25% of the whole cohort in 2017 (in total 34.3%) compared to the previous season. Liedtke et al.[19] reported that patients who attained symptom control used significantly less symptomatic medication than did patients with uncontrolled symptoms. Overall, two out of every three patients (62.4%) in our study achieved symptom control and every third

(34.3%) stopped using symptomatic medication during the 2017 pollen season. The 34.4% lower rhinoconjunctivitis score for pre-seasonally treated patients than for the co-seasonal control group confirmed the beneficial effect of the tested SLIT on allergic symptoms already during the first season under treatment.

One of the limitations of this investigation was that it was not a double-blind, randomised, placebo-controlled study. However, the present study with its non-interventional, observational design based on patients' treatment preference may be more representative of a real-world patient population. Another limitation is that symptoms and symptomatic medication use were assessed retrospectively, thus introducing the potential for recall bias. Therefore, where possible, subgroup analyses were conducted prospectively within the 2017 pollen season. Nevertheless, the nearly identical score results across all analysed subgroups support the robustness of the data.

Conclusions

The primary outcome of this study is that all up-dosing schedules of ORALVAC® Compact *Bäume* (Trees), including the shortened ones, are safe, well tolerated and accepted by patients. Therefore, the more patient-friendly and convenient up-dosing methods should prove favourable, given the excellent tolerability and safety of the rapid schedules investigated in this study. In reviewing all beneficial results regarding the symptom scores, RCAT, ARIA classification, and medication use, we conclude that treatment with the investigated SLIT elicits beneficial effects during patients' first pollen season under treatment. Furthermore, the significance of short-term studies investigating allergen-specific immunotherapy could be improved by supporting aerobiological data like crowd-sourced symptom data such as the PHD.

Declarations

Ethics approval and consent to participate

All procedures followed were approved by the local ethics committees and were in accordance with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all individual participants included in the study. This trial is listed at clinicaltrials.gov under the identifier NCT03097432.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request and with permission of Bencard Allergie GmbH.

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Conflicts of interest

RM, SA, KSH, VAD, and MH are employees of CRI - Clinical Research International Ltd. which served as the clinical research organisation for this study.

KBi, MFK, and SG are employees of Bencard Allergie GmbH, Munich, Germany, the sponsor of the study.

NYB, PZ, MB, KBa, and UB have no conflicts of interest to disclose.

Authors' contributions

RM, SA, MFK, and SG designed the study; NYB, SA, PZ, KBi, MH, and SG performed the study supported by the local investigators; RM, NYB, SA, KSH, and VAD analysed the data; MB, KBa, and UB are the developers of the free web-based online diary and analysed and discussed the related data; RM, NYB, SA, VAD, KBi, and SG wrote the paper. All authors have read, discussed and approved the final version of the manuscript.

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