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A 300 IR 5-grass pollen sublingual immunotherapy tablet-specific systematic review and meta-analysis confirms its clinical benefits for patients with allergic rhinoconjunctivitis with or without asthma

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ABSTRACT

Background: In the realm of allergen immunotherapy (AIT), the quality of evidence varies across different products, making it unjustifiable to extend overall conclusions to all AIT products, as highlighted by WAO and EAACI.

Objective: To confirm the efficacy of the 300 IR 5-grass pollen sublingual AIT (SLIT)-tablet through a specific meta-analysis of randomized controlled trials (RCTs) involving patients with allergic rhino-conjunctivitis (ARC) with/without mild/intermittent asthma.

Methods: Data from published RCTs on the 300 IR 5-grass SLIT-tablet were gathered from electronic databases (MEDLINE, ISI Web of Science, LILACS, the Cochrane Library and ClinicalTrial.gov) and manual searches up to November 2023. Populations, treatments, and outcome data were combined. Efficacy was assessed based on symptom score (SS) and medication score (MS), measured as standardized mean difference (SMD) or mean difference (MD).

Results: Results from 5 RCTs comprising 1468 patients revealed a significant reduction in SS (SMD, −0.36; 95%confidence interval [CI], −0.52 to −0.19; $P < 0.05$) and MS (SMD, −0.29; 95% CI, −0.40 to −0.19; $P < 0.05$) compared to placebo. The difference of −0.36 SMD for SS corresponds to a MD of −1.26 SS points, greater than the minimal important difference. Subgroup analysis did not show differences in efficacy according to age, asthma status, and geographic location of the study (USA, Canada, Europe, Russia). No safety issues were reported.

Conclusion: This product-specific meta-analysis reinforces the evidence of clinical benefits associated with the 300 IR 5-grass SLIT-tablet, suggesting its appropriateness as a therapeutic choice for patients with ARC, irrespective of concurrent asthma, and exhibiting a favorable safety profile.

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INTRODUCTION

Allergen immunotherapy (AIT) is a commonly employed treatment approach for moderate-to-severe allergic rhinitis induced by airborne allergens. AIT can be administered through subcutaneous (SCIT) or sublingual (SLIT) routes.[1]

The efficacy and safety of AIT have been established through randomized controlled trials (RCTs) and meta-analyses that incorporate both randomized and nonrandomized studies (NRS).[2–7] However, meta-analyses have revealed significant heterogeneity between individual studies, both RCTs and NRS, due to inconsistencies in their findings. This diversity in results may stem from variations in evidence quality, studied populations, implemented protocols, and trial durations. Additionally, it may also reflect potential differences in the efficacy of specific AIT products, which could impact the precision of the meta-analysis's overall conclusions. Considering these varying factors, the World Allergy Organization (WAO) and the European Academy of Allergy and Clinical Immunology (EAACI) have advocated for conducting product-specific meta-analyses for AIT. They emphasized that claims of efficacy based on a "class effect" and lacking supportive evidence for individual products (through the design and execution of rigorous clinical trials), are inappropriate.[1,8] Consequently, the last German, Austrian, and Swiss guideline has adopted a product-specific approach.[9]

The 300 IR 5-grass pollen SLIT-tablet is now one of the most utilized marketed products for grass allergy, especially in Europe.[10] Evidence indicated its safety and efficacy in managing symptoms and reducing the need for symptom-relieving medication in individuals experiencing allergic rhinoconjunctivitis (ARC) triggered by grass pollen, with or without mild intermittent asthma.[11–16]

The aim of this focused systematic review and meta-analysis of RCTs was to assess more precisely the efficacy and safety of the 300 IR 5-grass SLIT-tablet in patients with ARC with or without mild intermittent asthma and evaluate the overall evidence certainty.

METHODS

Search strategy and selection criteria

We conducted and reported this systematic review and meta-analysis following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA),[17] Grading of Recommendations, Assessment, Development and Evaluation (GRADE),[18,19] and Cochrane guidelines.[20]

This study is registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols, INPLASY (registration number 202430066).

From inception to November 15, 2023, we systematically searched PubMed/MEDLINE, the Cochrane Library, the ISI Web of Science and the ClinicalTrial.gov databases for published and unpublished RCTs evaluating the efficacy of the 300 IR 5-grass pollen SLIT-tablet (Oralair®, Stallergenes Greer, Antony, France) in patients with ARC.

A full list of the search terms is available in the protocol and the appendix (Supplemental Table 1).

Studies were included in the meta-analysis if: 1) they were RCTs assessing efficacy and safety of 300 IR 5-grass SLIT-tablet vs. placebo in patients with moderate or severe rhino-conjunctivitis to grass pollen with or without mild intermittent allergic asthma; 2) there was a pre-seasonal treatment duration of 4 months (16 weeks); 3) they assessed the efficacy of 300 IR 5-grass SLIT-tablet; 4) they used symptom score (SS) and medication score (MS) or daily combined symptom and medication score (DCS) as primary outcome measures of treatment effect.

We excluded studies not published as full papers or not reporting on the primary outcomes. We

imposed no language constraints throughout our search process. Extensively, we examined the reference lists and articles citing the studies included, along with recent reviews or meta-analyses, to identify any further pertinent studies. In addition, we asked the study sponsor to assist in compiling a comprehensive list of RCTs investigating the efficacy of the 300 IR 5-grass SLIT-tablet for ARC to supplement our data collection.

Data collection

We conducted a comprehensive search of titles and abstracts, examined full-text articles, extracted data, and evaluated risk of bias and study quality independently and in duplicate (DDB, GP), employing a standardized pre-piloted form (https://www.rayyan.ai).[21] Discrepancies were resolved through consensus adjudication. We gathered information on study characteristics, setting, eligibility criteria, study population, intervention, and outcomes.

Outcomes

In line with the established approach for AIT, we prioritized outcomes deemed significant for patients with ARC and considered indicative of treatment efficacy and safety.[8] The critical/meaningful outcomes included: symptom severity assessed via symptom score (SS); reduction in the use of drugs aimed at symptom relief, measured by medication score (MS); a scoring system integrating both SS and MS, the daily combined score (DCS); and adverse events (AEs).

Data analysis

We pooled summary measures using DerSimonian and Laird random-effects model.[22] We combined continuous outcomes (SS, MS, DCS) across studies using standardized mean difference (SMD) or mean difference (MD) whether the scores were measured on different scales or the same scale. The relevant standard deviations which were not reported in the VO53.06 study publication were kindly provided by Stallergenes Greer.

We evaluated the between-study heterogeneity utilizing the χ^2 test (with a significance threshold set at $p = 0.10$) and measured it using the I^2 statistic, which quantifies the proportion of variability attributable to heterogeneity rather than sampling errors.[23] Sources of heterogeneity were investigated by removing potential outlier studies and conducting predetermined subgroup analyses and sensitivity analyses. The selection of subgroup-defining characteristics was driven by clinical and methodological considerations. To test the robustness of the findings, sensitivity analyses were carried out using a fixed-effect meta-analysis.

Heterogeneity was further explored by performing an influential analysis in which outlier studies were excluded until homogeneity was attained. This method permitted the examination of the impact of studies identified as deviating significantly in either results or methodology. Outliers were determined by the Baujat plot, which illustrates each study's contribution to the overall Q-test statistic for heterogeneity on the horizontal axis against the study's influence on the vertical axis, defined as the standardized squared difference between the overall estimate with and without the respective study included in the model.[24]

Subsequently, each study was individually excluded to ascertain that no single study unduly influenced the significance of any result (robust analysis). Publication bias was assessed through funnel plot inspection, Egger's linear regression test, Begg's rank test, and fail-safe calculation, a method to estimate whether publication bias could be safely disregarded.[25,26] A fail-safe number indicates the number of insignificant, unpublished (or missing) studies needed to be added to the meta-analysis to nullify an overall statistically significant result. A large fail-safe number relative to the observed studies instills confidence in the summary conclusions.[27]

We did all the analyses in Review Manager (RevMan 5.0),[28] ProMeta 3.0 softwares,[29] and R (RFoundation) using Metafor statistical package (accessed January 2024).[30]

Risk of bias and certainty of evidence

We assessed the risk of bias (RoB) of RCTs using the version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2).[20]

The certainty (quality) of evidence was evaluated using the GRADE approach.[19]

We used GRADEpro GDT (available from gradepro.org) to create the summary of finding tables.[31]

RESULTS

Our bibliographic search identified a total of 92 records. Following initial screening and categorization, we evaluated 18 studies and ultimately incorporated 5 RCTs into this systematic review and meta-analysis (refer to Fig. 1).[11-15] Some of these RCTs included patients treated with tablets at different allergen doses or with a pre-seasonal treatment lasting less than 4 months. Considering the 5-grass SLIT-tablet is approved at a 300 IR daily dose for maintenance and should be initiated about 4 months before the expected onset of the pollen season as indicated, we extracted only the data of interest from these studies as specified in the methods (pre-seasonal treatment of about 4 months, 300 IR tablet arm). One study (VO53.06) was a long-term study with pre-co-seasonal treatment for 3 consecutive years and 2 post-treatment years.[15,16] Finally, a total of 1468 analyzable patients (708 in the active and 760 in the placebo arm) were included in the meta-analysis, after exclusion of patients treated with different SLIT doses or with a pre-seasonal treatment <4 months.

The characteristics of the 5 qualifying studies used for meta-analysis are summarized in Table 1.

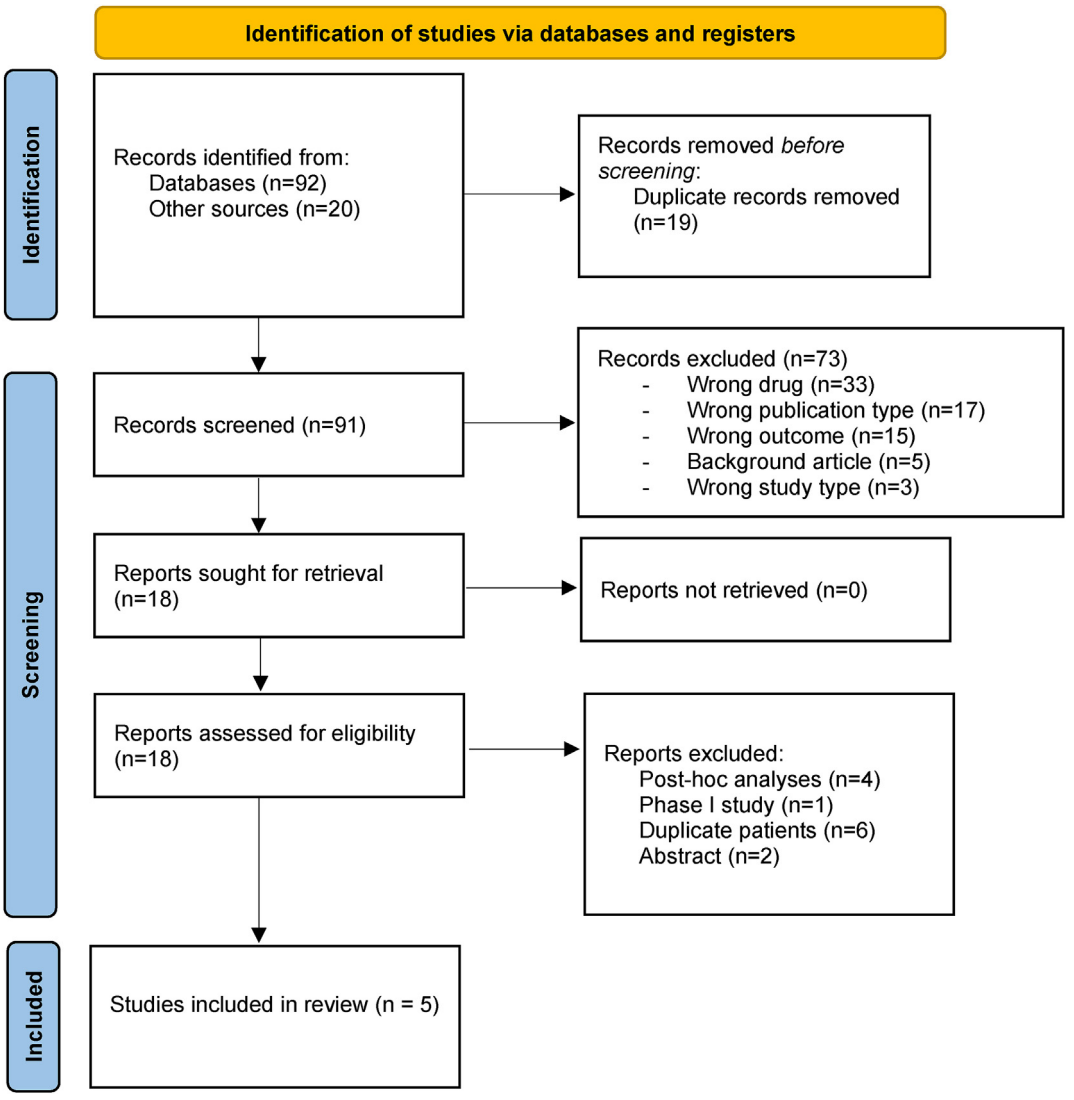

Fig. 1 Flow chart of the literature search

Source (study code)	Country (centers)	Intent-to-Treat vs. Placebo Participants	Male sex (%)	Age, Mean (Range), y	Asthma, %	Poly-Sensitization, %	Severity of ARC	Treatment Duration (Preseason + Grass Pollen Season), wks.
Didier, 2007 (VO34.04)	10 countries in Europe (n = 42)	155 vs. 156 randomized, 133 vs. 146 completed, 136 vs. 148 analyzed	56.9	28.9 (18–45)	10	54.5	Moderate or severe	16 + 4
Wahn, 2009 (VO52.06)	5 countries in Europe (n = 29)	139 vs. 139 randomized, 131 vs. 135 completed, 131 vs. 135 analyzed	64.3	10.9 (4–17)	21.4	59	Moderate or severe	16 + 6
Cox, 2012 (VO61.08USA)	United States (n = 51)	233 vs. 240 randomized, 207 vs. 223 completed, 208 vs. 228 analyzed	46.6	37.2 (18–65)	20.1	78	Severe	18 + 6
Horak 2009[§] (VO56.07A)	Austria (n = 1)	45 vs. 44 randomized, 42 vs. 40 completed, 45 vs. 44 analyzed	41.6	27.3 (18–50)	n.r.	n.r.	Moderate or severe	16
Long-term study								
Didier 2011 (VO53.06)	10 countries in Europe, Canada, and Russia (n = 45)	207 vs. 219 randomized, 1st year 189 vs. 204 completed, 188 vs. 205 analyzed 3rd year 148 vs. 163 completed, 149 vs. 165 analyzed	62.2	30.5 (18–49)	15.3	60.6	Severe	16 + 7 (1st year) 16 + 8 (2nd year) 16 + 8 (3rd year)

Table 1. Patients and study characteristics among trials in meta-analysis. *ARC, allergic rhinoconjunctivitis; n.r., not reported; wks, weeks. [§]The Horak study was conducted in an allergen challenge chamber*

Four RCTs were multicenter studies, carried out in different European countries, Canada, Russia or in the United States.[11–13,15] There was only 1 single center study, the Horak et al study (VO56.07A), based on data collected in an allergen challenge chamber in Austria.[14] The study completion rate ranged from 89.7%[11] to 95.7%.[12] The sample size of the studies included in the meta-analysis varied from 278 to 473 patients,[12,13] excluding the VO56.07A study (n = 89 patients).[14] One study was conducted in children (VO52.06, mean age 10.9 years),[12] and the others in adults (mean of the mean age of patients from the individual adult studies, 31.0 ± 4.4 years). The proportion of patients with asthma ranged from 10% to 21.4%. Most patients were polysensitized to allergens different from grass (range: 54.5%–78%).

In all studies, except the VO56.07A study (in which the patients were treated for 4 months outside of the pollen season),[14] the pre-seasonal treatment lasted approximately 16 weeks, and the co-seasonal treatment length varied from 4 to 6 weeks according to the duration of the pollen season.

The risk of bias was estimated as low in all RCTs (Supplemental Fig. 1).

Efficacy based on symptom score

The effect of the 300 IR 5-grass SLIT-tablet on SS is showed in Fig. 2. Apart from the VO56.07A study conducted outside the pollen season, the primary evaluation period was the first pollen period for single season studies and the third pollen period for the long-term study VO53.06. However, for both single season and long-term RCTs the data from the first pollen period after the start of treatment were included in this analysis, even though the efficacy assessment during the first pollen period was not the primary outcome of the long-term study.[15] All the RCTs showed a reduction in SS during the pollen period compared to the placebo (Fig. 2A). The pooled SMD for the treatment effect was −0.36 (95%CI, −0.52 to −0.19; $P < 0.0001$), indicating a statistically significant difference between the 5-grass SLIT-tablet and placebo. A moderate degree of heterogeneity between the results of individual studies was reported (Q = 8.83; df = 4; $P < 0.07$; $I^2 = 58\%$) (Fig. 2A).[18,23]

Two studies mainly contributed to the heterogeneity: the VO53.06 study (Year 1) and the VO56.07A study (Supplemental Fig. 2).[14,15] The exclusion of the VO53.06 Year 1 study, which was not the primary assessment period, permitted the use of mean difference (MD) to assess the treatment effect instead of SMD, as this study used the LS mean to report the data instead of arithmetic mean as in the other RCTs (Fig. 2B).[15] The pooled MD for the treatment effect was −1.26 SS points (95%CI, −1.64 to −0.89; $P < 0.00001$), indicating a statistically significant benefit of 5-grass SLIT-tablet compared to placebo with no heterogeneity (Q = 2.98; df = 3; $P < 0.39$; $I^2 = 0\%$) (Fig. 2B).

Also, the exclusion of the VO56.07A study, which was conducted in an artificial setting, did not change the results, confirming the clinically meaningful effect of 300 IR tablets compared to placebo (MD, −1.16; 95%CI, −1.56 to −0.76; $P < 0.00001$; test for heterogeneity: Q = 0.86; df = 2; $P < 0.65$; $I^2 = 0\%$).[14]

Fixed-effects methods showed results equal to or comparable with the random-effects meta-analysis confirming the robustness of the data (Table 2).

The visual inspection of funnel plots, rank and regression tests, and the fail-safe number did not show substantial evidence of publication bias (Supplemental Fig. 3).

Subgroup analyses by age, geographical area in which the study was performed (Europe *vs.* USA), and asthma status did not show any significant difference between subgroups (Table 2). Influential analysis confirmed the robustness of the results after the exclusion of each study in turn (Supplemental Fig. 4).

Efficacy based on medication score

Fig. 2C shows data on medication score. All the studies showed a statistically significant difference between treatment and placebo. The pooled SMD was −0.29 (95%CI, −0.40 to −0.19; $P < 0.0001$), suggesting a clear benefit with the 300 IR 5-grass SLIT-tablet, with no evidence of between-study heterogeneity (Q = 1.54; df = 3; $P < 0.67$; $I^2 = 0\%$). Similar results were observed when the fixed-effects model was used to pool the data

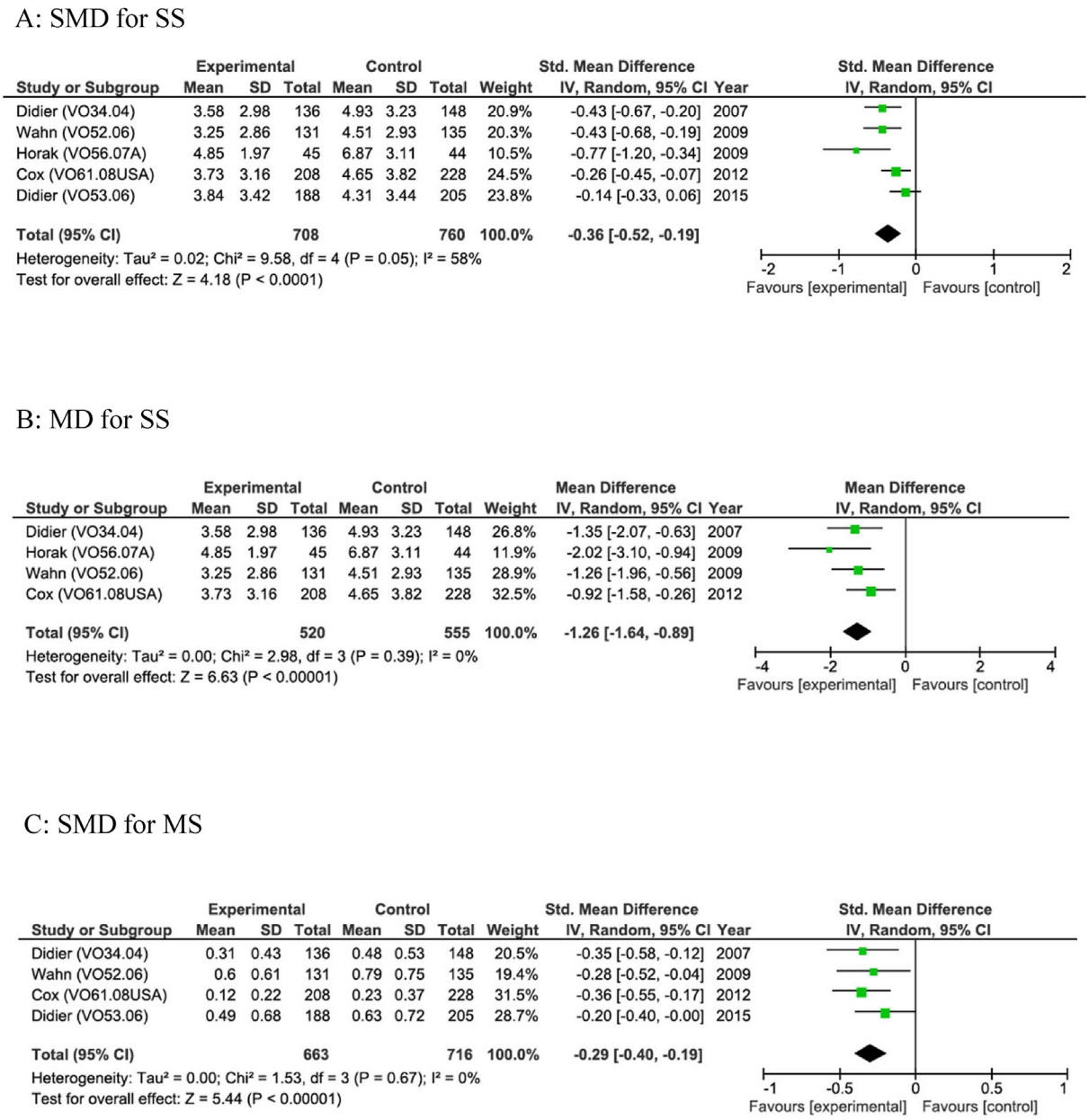

Fig. 2 Meta-analysis of the efficacy of 300 IR 5-grass pollen SLIT tablet vs. placebo for seasonal allergic rhinoconjunctivitis. MD, mean difference; MS, medication score; SD, standard deviation; SMD, standardized mean difference; ss, symptom score

(SMD, −0.29; 95%CI, −0.40 to −0.19; $P < 0.0001$), as there is no heterogeneity ($I^2 = 0\%$) (Table 2). There was no evidence of publication bias (Supplemental Fig. 3). Table 2 shows the results of subgroup analysis by age, geographical site, and proportion of patients with asthma. Like SS, there was no difference between the subgroups. Influential analysis confirmed the robustness of the results (Supplemental Fig. 4).

Long-term efficacy based on daily combined score

Supplemental Fig. 5 shows the differences in daily combined score (DCS) between the 300 IR 5-grass SLIT-tablet and placebo at 2 different time points, third treatment year and second post-treatment year of the long-term study VO53.06, respectively.[16] In both cases there was a statistically

A. Symptom score
1. Fixed effects model

Studies	Participants 300 IR tablet *vs.* placebo	Point estimate	95%CI	*P*
5 studies[26-30]	708 *vs.* 760	−0.32	−0.42, −0.22	<0.00001
4 studies[26-29]	520 *vs.* 555	−1.27	−1.64, −0.89	<0.00001
3 studies[26-28]	475 *vs.* 511	−1.16	−1.56, −0.76	<0.00001
2. Subgroup analysis under the random-effects model				
Subgroups	Participants 300 IR tablets *vs.* placebo	Point estimate	95%CI	*P*
Adults[26,28-30] Children[27]	577 *vs.* 625 131 *vs.* 135	−0.34 −0.43	−0.55, −0.14 −0.68, −0.19	<0.001 0.0005
Europe[26,27,29,30] USA[28]	500 *vs.* 532 208 *vs.* 228	−0.40 −0.26	−0.62, −0.17 −0.45, −0.07	<0.0005 0.007
Asthma (>20%)[27,28] Asthma (<20%)[26,30]	339 *vs.* 363 324 *vs.* 353	−0.33 −0.28	−0.50, −0.16 −0.57, −0.01	<0.0001 0.06
B. Medication score 1. Fixed effects model				
Studies	Participants 300 IR tablets *vs.* placebo	Point estimate	95%CI	*P*
4 studies[26-28,30]	663 *vs.* 716	−0.29	−0.40, −0.19	<0.0001
2. Subgroup analysis under the random-effects model				
Subgroups	Participants 300 IR tablet *vs.* placebo	Point estimate	95%CI	*P*
Adults[26,28,30] Children[27]	532 *vs.* 581 131 *vs.* 135	−0.30 −0.28	−0.42, −0.18 −0.52, −0.04	<0.00001 0.02
Europe[26,27,30] USA[28]	455 *vs.* 488 208 *vs.* 228	−0.27 −0.36	−0.39, −0.14 −0.55, −0.17	<0.0001 0.0002
Asthma (>20%)[27,28] Asthma (<20%)[26,30]	339 *vs.* 363 324 *vs.* 353	−0.33 −0.26	−0.48, 0.18 −0.41, −0.11	<0.0001 0.0007

Table 2. Sensitivity analysis based on fixed effects model, and subgroup analyses for SS and MS

significant difference in the active treatment arm compared to placebo.

Evidence certainty

The overall certainty of the evidence for the main outcomes (SS, MS) was judged as high for both SS and MS due to the low risk of bias of the individual RCTs, low risk of publication bias and low degree of inconsistency, precision, and indirectness (Table 3).

Safety

The number of patients with treatment-emergent adverse events (TEAE) and the number

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	placebo	Relativ (95% CI)	Absolute (95% CI)		
Symptom score (follow-up: mean 1 years; assessed with: MD; scale from: 0 to 10)												
5	randomized trials	not serious	not serious	not serious	not serious	none	708	760	-	SMD **0.36 SD lower** (0.52 lower to 0.19 lower)	⨁⨁⨁⨁ High	CRITICAL
Medication score (follow-up: mean 1 years; assessed with: SMD)												
4	randomized trials	not serious	not serious	not serious	not serious	none	663	716	-	SMD **0.29 SD lower** (0.4 lower to 0.19 lower)	⨁⨁⨁⨁ High	CRITICAL

Table 3. GRADE evidence profile. ***CI:*** *confidence interval;* ***SMD:*** *standardized mean difference*

of discontinuations due to TEAE was greater in the 300 IR group, but TEAEs were mostly mild (Table 4).

DISCUSSION

This focused meta-analysis of RCTs including a total of 1468 patients (708 in the active treatment arm, 760 in the placebo arm) with allergic rhinoconjunctivitis to grass pollen, with or without mild intermittent controlled asthma provides high certainty evidence that the 300 IR 5-grass SLIT-tablet is safe and effective in reducing symptoms and the use of medication aimed at allergy symptoms relief compared to placebo (i.e., patients taking only symptom-relieving medications), with no effect according to age or asthma status and no difference between patients treated in Europe, Russia or the United States. The largest effect was observed in the Horak et al study, based on the results in an allergen challenge chamber, which are not influenced by the exposure to other pollens present during the grass pollen season, such as parietaria or olive.[14] In addition, since symptom-relieving medications were not permitted during the treatment period in this study, in contrast to other RCTs, the observed effect can be seen as a true effect of the 300 IR 5-grass SLIT-tablet compared with placebo. Influential analysis and sensitivity analysis based on fixed-effects model confirmed the robustness of the findings.

The average benefit reported was not solely statistically significant but also clinically meaningful with a difference between the 300 IR tablet and placebo of 1.26 SS points. This result is above the estimated minimal clinically important difference (MCID) of 1 SS point,[32] and appears to be greater than the pooled estimate of the 2 marketed SLIT tablets for grass allergy (1-grass and 5-grass pollen) which was previously assessed as equal to 0.83 SS points.[2] It should be noted that the present meta-analysis used more strict inclusion criteria reflecting the indication of the 300 IR 5-grass pollen SLIT-tablet as approved.

Data from the long-term VO53.06 study covering 3 treatment years and follow-up show that the effect is sustained over 3 years of treatment and maintained for at least 2 years after treatment cessation.[15,16]

Study	Didier 2007 (VO34.04)		Wahn 2009 (VO52.06)		Horak 2009 (VO56.07A)		Cox 2012 (VO61.08USA)		Didier 2011[a] (VO53.06)		Total		*P*
	Placebo (n = 156)	300 IR (n = 155)	Placebo (n = 139)	300 IR (n = 139)	Placebo (n = 44)	300 IR (n = 45)	Placebo (n = 240)	300 IR (n = 233)	Placebo (n = 219)	300 IR (n = 207)	Placebo (n = 798)	300 IR (n = 779)	
Patients with TEAE N (%)	76 (48.7)	97 (62.6)	114 (82)	118 (84.9)	14 (31.8)	27 (60.0)	54 (22.5)	128 (54.9)	174 (79.5)	183 (88.4)	432 (54.1)	553 (71.0)	<0.0009
Discontinuation due to AE N (%)	0 (0)	8 (5.1)	2 (1.4)	7 (5)	2 (4.5)	1 (2.2)	2 (0.8)	15 (6.4)	2 (0.9)	13 (6.3)	8 (1)	44 (5.6)	<0.00001

Table 4. Adverse events. [a]*1st year; TEAE, treatment emergent adverse events*

No safety issues were reported despite a greater number of total adverse events with the 300 IR 5-grass tablet compared to placebo. However, those adverse events were mostly mild and tended to disappear over time as notably shown in the long-term VO53.06 study where TEAEs decreased in number and intensity over the 3 treatment years.[11–16,33] There was some difference in terms of withdrawals for adverse events, which were greater in the active treatment arm, as expected.

These safety results were comparable to the other marketed 1-grass SLIT tablet,[2] and other grass SLIT liquid formulations.[3]

Strengths & limitations

The analysis's strengths stem from several key aspects: a sizable participant cohort, facilitating robust assessment of treatment effects; uniformly well-powered individual studies; consistent implementation of treatment protocols and allergen dosages across all studies; minimal risk of publication bias, posing little threat to final outcomes; negligible heterogeneity, reduced to null levels following exclusion of the influential study, indicating potential for enhanced consistency and reliability when concentrating on a singular product; low individual study bias risk and high certainty of evidence. Subgroup analyses showed no difference according to age and asthma status or studies performed in the US and in different European countries and Russia. This suggests the findings are applicable to different patient populations, minimizing concerns regarding indirectness and generalization of the results to the overall population. According to the GRADE approach this low risk of indirectness strengthens the certainty of evidence based on RCTs, making confirmatory data from NRS unnecessary in systematic reviews to inform health recommendations.[34] Nonetheless, several real-world studies conducted with the 300 IR 5-grass SLIT-tablet in different countries and with different methodologies (more than 7500 patients exposed) confirmed the short and long-term benefits of this product in patients of all age groups with grass pollen-induced ARC with or without mild intermittent controlled asthma.[35–45] Of note, among the included studies, there is also a long-term RCT providing data over 3 years of AIT plus 2 years of follow-up after the end of treatment.[15,16] This evidence, which is not

commonly provided by RCTs for practical reasons, confirms the efficacy of the 300-IR 5-grass pollen SLIT-tablet over time, and its good tolerability profile, resulting in a low discontinuation rate. Lastly, differing from prior meta-analyses, this meta-analysis encompassed RCTs employing the identical 18-point SS scale and assessment technique (excluding the VO53.06 study[16]). Consequently, we were able to present outcomes in SS units (mean differences), offering a more straightforward interpretation compared to standardized mean differences (SMDs).

A limitation could be the apparently small number of studies assessing the outcome: 4 RCTs with an assessment after a pre- and co-seasonal treatment (1 of these also assessing the efficacy in the following seasons), and 1 RCT conducted in an allergen challenge chamber. However, the small degree of heterogeneity among the results of individual studies, showing a remarkably consistent results, and the big sample size, leading to a pooled analysis of more than 1450 patients (708 in the active treatment arm, 760 in the placebo arm), suggest that the results are robust and unlikely to be substantially changed by new study results.

CONCLUSIONS

We performed a meta-analysis focusing on a single AIT product as recommended by WAO and EAACI in order to confirm its specific efficacy and safety. The results showed that the 300 IR 5-grass pollen SLIT-tablet is effective in achieving clinically meaningful improvements in rhinoconjunctivitis symptoms and reducing the use of symptom-relieving medications compared with placebo. The efficacy is unaffected by age, asthma and geographic location included making the findings generalizable. The effect size is comparable to, if not greater than seen with other immunotherapy products, with low rates of AEs and withdrawals due to AE or reasons other than AE, suggesting a good tolerability profile and patient compliance with the product.

Abbreviations

AE: adverse event; AIT: allergen immunotherapy; ARC: allergic rhinoconjunctivitis; BAU: biological arbitrary unit; CI: confidence interval; DCS: daily combined score; EAACI: European Academy of Allergy and Clinical Immunology; IR: index of reactivity; MCID: minimal clinically important difference; MD: mean difference; MS: medication score; NRS: nonrandomized studies; RCT: randomized controlled trial; RoB: risk of bias; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy; SMD: standardized mean difference; SS: symptom score; TEAE: treatment-emergent adverse event; WAO: World Allergy Organization

Availability of data and materials

Data are available from the corresponding author on reasonable request.

Author's contributions

DDB and GWC developed the concept of this work. DDB and GP did the article search, assessed the articles, and extracted the data. DDB did all the analyses. DDB wrote the first manuscript draft, which was revised by GWC, GP, MO, SD, SS and JCS.

Ethics statement

This study is registered at the International Platform of Registered Systematic Review and Meta-analysis Protocols, INPLASY (number 202430066). There was no testing of human subjects. The present meta-analysis is based on published data from clinical trials, all of them having their respective ethics evaluation and approvals.

Author's consent for publication

All authors approved the final version of this manuscript for publication.

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Declaration of competing interest

DDB reports having received fees from Stallergenes Greer. GP reports having received support for attending meetings and/or travel from Stallergenes Greer and Sanofi Regeneron, and fees for participation on a Data Safety Monitoring Board or Advisory Board from Stallergenes Greer, AstraZeneca and GlaxoSmithKline. MO and SD report no competing interests. JCS and SS are employees of Stallergenes Greer. GWC reports having received consulting fees, and/or payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events (to him or his institution Humanitas Research Hospital, Milan, Italy), and/or support for attending meetings and/or travel, and/or participation on a Data Safety Monitoring Board or Advisory Board, from Stallergenes Greer, Hal Allergy, Menarini, AstraZeneca, GlaxoSmithKline, Chiesi, OmPharma, Sanofi Regeneron, Faes, Sanofi Aventis.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100985.

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REFERENCES

1. Bachert C, Larché M, Bonini S, et al. Allergen immunotherapy on the way to product-based evaluation–a WAO statement. *World Allergy Organ J*. 2015;8(1):29. https://doi.org/10.1186/s40413-015-0078-8. eCollection 2015.
2. Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of grass pollen allergen sublingual immunotherapy tablets for seasonal allergic rhinoconjunctivitis: a systematic review and meta-analysis. *JAMA Intern Med*. 2015;175(8):1301–1309. https://doi.org/10.1001/jamainternmed.2015.2840.
3. Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a meta-analysis-based comparison. *J Allergy Clin Immunol*. 2012;130(5):1097–1107.e2. https://doi.org/10.1016/j.jaci.2012.08.012.
4. Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev*. 2010;(12), CD002893. https://doi.org/10.1002/14651858.CD002893.pub2.
5. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev*. 2007;(1), CD001936. https://doi.org/10.1002/14651858.CD001936.pub2.
6. Dretzke J, Meadows A, Novielli N, Huissoon A, Fry-Smith A, Meads C. Subcutaneous and sublingual immunotherapy for seasonal allergic rhinitis: a systematic review and indirect comparison. *J Allergy Clin Immunol*. 2013;131(5):1361–1366. https://doi.org/10.1016/j.jaci.2013.02.013.
7. Nelson H, Cartier S, Allen-Ramey F, Lawton S, Calderon MA. Network meta-analysis shows commercialized subcutaneous and sublingual grass products have comparable efficacy. *J Allergy Clin Immunol Pract*. 2015;3(2):256–266.e3. https://doi.org/10.1016/j.jaip.2014.09.018.
8. Roberts G, Pfaar O, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. *Allergy*. 2018;73(4):765–798. https://doi.org/10.1111/all.13317.
9. Pfaar O, Ankermann T, Augustin M, et al. Guideline on allergen immunotherapy in IgE-mediated allergic diseases. *Allergol Select*. 2022;6:167–232. https://doi.org/10.5414/ALX02331E.
10. Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. *Ann Allergy Asthma Immunol*. 2009;103(6):451–459. https://doi.org/10.1016/S1081-1206(10)60259-1.
11. Didier A, Malling HJ, Worm M, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2007;120(6):1338–1345. https://doi.org/10.1016/j.jaci.2007.07.046.
12. Wahn U, Tabar A, Kuna P, et al, SLIT Study Group. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2009;123(1):160–166.e3. https://doi.org/10.1016/j.jaci.2008.10.009.
13. Cox LS, Casale TB, Nayak AS, et al. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE. *J Allergy Clin Immunol*. 2012;130(6):1327–13234.e1. https://doi.org/10.1016/j.jaci.2012.08.032.
14. Horak F, Zieglmayer P, Zieglmayer R, et al. Early onset of action of a 5-grass-pollen 300-IR sublingual immunotherapy tablet evaluated in an allergen challenge chamber. *J Allergy Clin Immunol*. 2009;124(3):471–477. https://doi.org/10.1016/j.jaci.2009.06.006, 477.e1.
15. Didier A, Worm M, Horak F, et al. Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis. *J Allergy Clin Immunol*. 2011;128(3):559–566. https://doi.org/10.1016/j.jaci.2011.06.022.
16. Didier A, Malling HJ, Worm M, Horak F, Sussman GL. Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score. *Clin Transl Allergy*. 2015;5:12. https://doi.org/10.1186/s13601-015-0057-8.
17. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372, n71. https://doi.org/10.1136/bmj.n71.
18. Schünemann H, Brożek J, Guyatt G, Oxman A, GRADE handbook. Grading of recommendations, assessment, development and evaluation (GRADE) Working Group. https://gdt.gradepro.org/app/handbook/handbook.html; 2013. Accessed April 8, 2024.
19. The GRADE Working Group. 2004-2024, 2024. https://www.gradeworkinggroup.org/. Accessed 20 January 2024.
20. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane; 2023. Version 6.4 (updated August 2023). Available from: www.training.cochrane.org/handbook. Accessed January 20, 2024.
21. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev*. 2016;5:210. https://doi.org/10.1186/s13643-016-0384-4.

22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Contr Clin Trials*. 1986;7(3):177–188. https://doi.org/10.1016/0197-2456(86)90046-2.
23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–1558. https://doi.org/10.1002/sim.1186.
24. Baujat B, Mahé C, Pignon J-P, Hill C. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. *Stat Med*. 2002;21(18):2641–2652. https://doi.org/10.1002/sim.1221.
25. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634. https://doi.org/10.1136/bmj.315.7109.629.
26. Lin L, Chu H. Quantifying publication bias in meta-analysis. *Biometrics*. 2018;74(3):785–794. https://doi.org/10.1111/biom.12817.
27. Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane; 2023 (updated August 2023). Available from: version 6.4. www.training.cochrane.org/handbook. Accessed January 20, 2024.
28. Review Manager (RevMan) [Computer program]. *Version 5.0*. London, United Kingdom: The Cochrane Collaboration; 2012.
29. ProMeta [Computer software]. Version 3.0. Internovi, Cesena, Italy.
30. Wiechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Software*. 2010;36(3):1–48. https://doi.org/10.18637/jss.
31. Gradepro GDT. *GRADEpro guideline development tool [software]. McMaster university and evidence prime*; 2021. Available from: gradepro.org . Accessed January 20, 2024.
32. Devillier P, Chassany O, Vicaut E, et al. The minimally important difference in the Rhinoconjunctivitis Total Symptom Score in grass-pollen-induced allergic rhinoconjunctivitis. *Allergy*. 2014;69(12):1689–1695. https://doi.org/10.1111/all.12518.
33. Casale TB, Cox LS, Wahn U, Golden DBK, Bons B, Didier A. Safety review of 5-grass pollen tablet from pooled data of clinical trials. *J Allergy Clin Immunol Pract*. 2017;5(6):1717–1727. https://doi.org/10.1016/j.jaip.2017.04.020.
34. Cuello-Garcia CA, Santesso N, Morgan RL, et al. GRADE guidance 24 optimizing the integration of randomized and non-randomized studies of interventions in evidence syntheses and health guidelines. *J Clin Epidemiol*. 2022;142:200–208. https://doi.org/10.1016/j.jclinepi.2021.11.026.
35. Pastorello EA, Losappio L, Milani S, et al. 5-grass pollen tablets achieve disease control in patients with seasonal allergic rhinitis unresponsive to drugs: a real-life study. *J Asthma Allergy*. 2013;6:127–133. https://doi.org/10.2147/JAA.S53801.
36. Shah-Hosseini K, Krudewig EM, Hadler M, et al. Management of grass pollen allergy with 5-grass pollen tablet: results of a 2-year real-life study. *Adv Ther*. 2017;34:1382–1397. https://doi.org/10.1007/s12325-017-0535-6.
37. Pfaar O, Richter HG, Klimek L, et al. Sublingual immunotherapy with a five-grass pollen tablet in adult patients with allergic rhinitis: an open, prospective, noninterventional, multicenter study. *BioMed Res Int*. 2015;2015, 584291. https://doi.org/10.1155/2015/584291.
38. Eberle P, Brueck H, Gall R, et al. An observational, real-life safety study of a 5-grass pollen sublingual tablet in children and adolescents. *Pediatr Allergy Immunol*. 2014;25:760–766. https://doi.org/10.1111/pai.12298.
39. Gerstlauer M, Szepfalusi Z, Golden D, Geng B, de Blic J. Real-life safety of 5-grass pollen tablet in 5-to-9-year-old children with allergic rhinoconjunctivitis. *Ann Allergy Asthma Immunol*. 2019;123:70–80. https://doi.org/10.1016/j.anai.2019.04.011.
40. Antolin-Amerigo D, Tabar IA, Del mar Fernández-Nieto M, et al. Satisfaction and quality of life of allergic patients following sublingual five-grass pollen tablet immunotherapy in Spain. *Drugs Context*. 2017;6, 212309. https://doi.org/10.7573/dic.212309.
41. Klein TM, Hadler M, Augustin M, Blome C. Patient needs and benefits of sublingual immunotherapy for grass pollen-induced allergic rhinitis: an observational study. *Immunotherapy*. 2021;13:1193–1204. https://doi.org/10.2217/imt-2021-0161.
42. Schafer U, Kienle-Gogolok A, Hadler M, Karagiannis E, Schnitzer S. Treatment satisfaction during sublingual immunotherapy with a five-grass pollen tablet for allergic rhinoconjunctivitis: a prospective, non-interventional study. *Drugs Real World Outcomes*. 2017;4:109–117. https://doi.org/10.1007/s40801-017-0109-6.
43. Van Nunen S, Burk MB, Burton PK, et al. 5-grass-pollen SLIT effectiveness in seasonal allergic rhinitis: impact of sensitization to subtropical grass pollen. *World Allergy Org. J*. 2022;15(2), 100632. https://doi.org/10.1016/j.waojou.2022.100632.
44. Devillier P, Wahn U, Zielen S, Heinrich J. Grass pollen sublingual immunotherapy tablets provide long-term relief of grass pollen-associated allergic rhinitis and reduce the risk of asthma: findings from a retrospective, real-world database subanalysis. *Expet Rev Clin Immunol*. 2017;13:1199–1206. https://doi.org/10.1080/1744666X.2017.1398082.
45. Devillier P, Molimard M, Ansolabehere X, et al. Immunotherapy with grass pollen tablets reduces medication dispensing for allergic rhinitis and asthma: a retrospective database study in France. *Allergy*. 2019;74:1317–1326. https://doi.org/10.1111/all.13705.