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REVIEW

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Delivery options for sublingual immunotherapy for allergic rhinoconjunctivitis: clinical considerations for North America*

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Abstract

Background: Sublingual immunotherapy (SLIT) can be delivered via tablets (SLIT-T) or aqueous drops (SLIT-D). SLIT-D dosing recommendations using North American extracts were published in 2015. We review the 2015 recommendations in the context of recent research, and compare and contrast dosing, efficacy, safety, adherence, and cost of SLIT-T and SLIT-D for allergic rhinoconjunctivitis (ARC) in North America.

Methods: Randomized controlled trials (RCT) of SLIT-D and SLIT-T trials were identified by a systematic PubMed search through March 1, 2022.

Results: Dose-finding studies have been conducted for all approved SLIT-T; efficacy in North American populations was demonstrated in 11 RCTs. Approved SLIT-T are uniform internationally. Few dose-finding studies for SLIT-D have been conducted using North American extracts; efficacy was demonstrated in 2 RCTs. Extrapolation of dosing from SLIT-D studies conducted with extracts from other geographic regions is unreliable. Since the 2015 SLIT-D dosing recommendations, no new RCTs of SLIT-D have been conducted with North American extracts, whereas 6 SLIT-T RCTs have since been conducted in North America. Local allergic reactions are the most common adverse events with SLIT-T and SLIT-D, but both can induce systemic allergic reactions. Adherence to SLIT-D and SLIT-T remains a challenge. Patients must pay for SLIT-D directly, whereas SLIT-T is usually covered by insurance.

Conclusion: As part of shared decision-making, patients should be informed about the scientific evidence supporting the use of SLIT-T and SLIT-D for ARC.

Key words: drug administration routes, immunomodulation, rhinitis, immunologic desensitization, anti-allergic agents

Introduction

Allergy immunotherapy (AIT) is one of the many treatment options for allergic rhinoconjunctivitis (ARC) and asthma[1]. AIT improves ARC symptoms and reduces the need for symptom-relieving pharmacotherapies by inducing tolerance to the specific allergen(s)[2]. The developed tolerance can be long-term, lasting years after AIT has been stopped[3-5]. Two methods of AIT administration are in common use, subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). SLIT can be delivered via tablets (SLIT-T) or aqueous drops (SLIT-D)[6]. SLIT can be administered daily at home after a medically supervised first dose, which affords the patient a convenient alternative to office visits required for SCIT. SLIT also generally has a better safety profile than SCIT[7, 8]. There have been no deaths attributed to SLIT, in contrast to SCIT, which very rarely can induce near-fatal and fatal reactions[9].

SLIT-T products are standardized and approved for the treatment of ARC caused by grass, ragweed, house dust mite (HDM), birch (and related trees), and Japanese cedar allergens, depending on the geographic region (Table 1). The HDM SLIT-T is also approved as an add-on treatment for asthma in Europe[10]. There are a few SLIT-D products approved outside of North America,

Table 1. Regulatory-approved SLIT-T and SLIT-D products in the United States, Canada, Germany, Australia, and Japan.

	United States		Canada		Germany		Australia		Japan	
Allergen Source	**SLIT-T**	**SLIT-D**	**SLIT-T**	**SLIT-D**	**SLIT-T**	**SLIT-D**	**SLIT-T**	**SLIT-D**	**SLIT-T**	**SLIT-D**
Pollen										
Short ragweed	+	-	+	-	+	-	-	-	-	-
Northern grasses	+*	-	+*	-	+*	-	+*	-	-	-
Birch	-	-	+†	-	+†	+	-	-	-	-
Alder	-	-	-	-	-	+‡	-	-	-	-
Hazel	-	-	-	-	-	+§	-	-	-	-
Japanese cedar	-	-	-	-	-	-	-	-	+	+
HDM	+	-	+	-	+	-	+	-	+	-

HDM, house dust mite; SLIT-D, sublingual immunotherapy drops; SLIT-T, sublingual immunotherapy tablets. *5-grass mix or timothy grass. †Also approved for the treatment of alder and hazel-related allergic rhinoconjunctivitis. ‡Mixed with birch and hazel. §Mixed with birch and alder.

but none are approved in the US (Table 1). Despite the lack of Food and Drug Administration (FDA) approval, SLIT-D in the US are formulated with allergen extracts that are intended for SCIT administration. Surveys indicate that otolaryngologists in North America tend to use SLIT-D over SLIT-T, in contrast to allergists who tend to use SLIT-T over SLIT-D[11, 12].

A recognized limitation for the use of SLIT-D in North America is a lack of optimized doses with established efficacy and safety based on randomized controlled trials (RCTs)[13, 14]. To address this issue, Leatherman et al. published recommendations for SLIT-D dosing in 2015 based on both available RCTs and expert opinion[13]. The purpose of this review is to critically review the published 2015 recommendations in the context of recent research, and compare and contrast dosing, efficacy, safety, adherence, and cost of SLIT-T and SLIT-D for ARC in North America.

Materials and methods

To identify SLIT-D and SLIT-T RCTs conducted since the recommendations for SLIT-D dosing were published by Leatherman et al. in 2015[13], a systematic search was conducted in PubMed using the terms "allergen immunotherapy AND (rhinoconjunctivitis OR rhinitis) AND (sublingual OR oral OR drops OR aqueous) AND randomized" and were limited to English only articles published between May 1, 2014 and March 1, 2022. Articles that were previously included in the 2015 SLIT-D recommendations[13], those without standard ARC efficacy outcomes data (i.e., combined symptom and medication scores or other efficacy outcomes), those that did not compare active SLIT vs no SLIT treatment (change from baseline was allowed as a comparator for studies with an active control group instead of a placebo control group), those that were secondary analyses of a previously published trial (long-term follow-up results were allowed), and those that were not RCTs were excluded. The search terms resulted in 185 publications, which after initial title and abstract review, were narrowed down to 75 relevant publications for review of the full publication. After review for exclusion criteria, 13 publications were excluded because they were secondary analyses, 9 were excluded because they did not include efficacy outcomes, 8 were not RCTs, and 3 were not SLIT trials. Therefore, a total of 42 SLIT-D and SLIT-T RCTs based on the selection and exclusion criteria were ultimately identified. Characteristics and outcomes of these 42 trials are described in Supplemental Table 1. Non-systematic literature searches were conducted to obtain supplemental information about SLIT dosing, efficacy, safety, and adherence.

Discussion

Dosing

The efficacy and safety of AIT is dependent on dose and duration[15-18]. Repeated doses do not accumulate, meaning repeated ineffective doses do not result in an effective dose over time[15, 19, 20]. For SLIT-T, freeze-dried and compressed formulations have been shown to differ in the kinetics and quantity of major allergen released, which may impact efficacy and safety[21-23]. Therefore, allergen-specific and formulation-specific dose-finding studies are essential to determine the optimal dose of SLIT products. In the 2015 dosing recommendations, the authors recognized that there were few large dose-finding studies of SLIT-D for consideration[13]. Effective SLIT-D doses were difficult to determine because doses that were effective in some studies were not effective in others and because of differences in extract formulations (i.e., aqueous or alum-absorbed). Neither timing nor duration for SLIT-D are clearly defined[24]. Nevertheless, Leatherman et al. provided a range of SLIT-D dosing recommendations using best available evidence from the available RCTs and expert opinion (Table 2)[13].

One of the limitations of the 2015 SLIT-D dosing recommendati-

Table 2. Recommended SLIT-D dosing (10-mL treatment vial). Reproduced with permission from Leatherman et al., 2015[13].

Allergen	Published dosing range (μg/day)	Recommended daily dose range (μ/day)	Labeled potency used for calculations	Amount of concentrate to add for vial mixing in mL (range)
House dust mite				
Dermatophagoides pteronyssinus	0.32–47	16 (10–28)	10,000 AU/mL	5 (3–9)[a]
Dermatophagoides farinae	0.07–121	16 (10–28)	10,000 AU/mL	5 (3–9)[a]
Standardized extract: grass				
Timothy grass	15–30	15-30	100,000 BAU/mL	1 (1–2)
Bermuda grass	5–40	18	100,000 BAU/mL	2.5 (1–5)
Standardized extract: weed				
Ragweed	12–124	15–50	1:20 wt/vol or 100,000 AU/mL	2 (2-5)
Cat, hair	n/a	n/a	10,000 BAU/mL	6 (4-8)
Dog, nonstandardized	n/a	n/a	1:20 wt/vol	2 (2–4)[b]
Nonstandardized extract				
Pollen, other	5–40	18	1:20 wt/vol	2 (2–4)[b,c]
Mold/fungi, cockroach	n/a	n/a	1:20 wt/vol	2 (2–4)[b,c]

AU, allergy units; BAU, bioequivalent allergy unit; n/a, not available; SLIT, sublingual immunotherapy. [a] If treating with both dust mites, consider adding one-half of the recommended dose for each because of significant cross-reactivity. [b] Based on 1:20 wt/vol concentrate solution. [c] Nonstandardized antigen dosing based on 30 times recommended monthly SCIT dosing (0.5 mL of 1:100 to 1:200 wt/vol solution), because microgram content was not available for the nonstandardized pollens.

ons was that the majority of the studies examined for guidance were not conducted in North America[13]. Although there have been several successful trials with SLIT-D products in Europe and Asia and data from these trials are important, the allergen extracts used in those trials are unavailable to North American healthcare providers. Comparison of efficacy and safety studies with extracts manufactured in other regions of the world versus those manufactured in North America is unreliable because of differences in extract protein content, major allergen content, and relative potencies[25]. To further confuse the issue, potency, an indicator of both major allergen content and overall biologic activity, can be labeled in many different ways depending on the manufacturer (e.g., allergy units, bioequivalent allergy units [BAU], index of reactivity [IR], etc.). In North America, a limited number of standardized extracts have met potency specifications against standards generated by the manufacturing companies' and are labeled in units associated with biologic activity based on skin test reactions (not based on clinical efficacy measures). Over 95% of the SCIT extracts available in North America are not standardized and have therefore not been evaluated for potency or allergen content. Standardized aqueous extracts available in the US are listed in Table 3. Non-standardized extracts are labeled by weight/volume or protein nitrogen units. These units do not describe the amount of active ingredient and, therefore, do not provide a measure of potency or allergen content. Moreover, the quantity of the allergens administered with SLIT-D extracts in Europe and in US SCIT extracts can also differ substantially depending on the manufacturer[25, 26]. Thus, one cannot simply extrapolate data from European or Asian SLIT-D studies to the sublingual use of North American SCIT extracts. Since the 2015 SLIT-D dosing recommendations, only 6 new studies have been conducted in North America, all of which were with SLIT-T (Supplemental Table 1)[18, 27-31]. No new RCTs of SLIT-D using North American extracts have been conducted to update or expand upon the prior recommendations.

Another limitation of the 2015 SLIT-D dosing recommendations was the overlap in effective and non-effective doses (e.g., micrograms per month) reported in the studies examined. This led to a need to provide a broad range of recommended dosing for some allergens (Table 2)[13]. It is known that a 3-fold difference may separate an effective dose from an ineffective dose[15, 32]. A 2018 survey of allergists in practice showed that a large variation in SLIT-D doses are used[33]. Aside from the 2015 SLIT-D dosing recommendations, healthcare providers may also use other methods to determine SCIT-D dosing. In general, higher doses than those used in SCIT are necessary[24], and a daily SLIT-D dose equivalent to a monthly maintenance SCIT dose has been suggested, at least for grass[34]. One resource for otolaryngic allergy practice simply suggests adding 1 mL of each extract concentrate when preparing a maintenance vial[24]. Because there are no clinical trial data, it is unknown if the doses derived

Table 3. Standardized allergen extracts available in the United States.

Extract allergen category	Specific allergens in extract
Grasses	Northern grasses, e.g., timothy grass, perennial rye, Orchard, Kentucky blue (June), redtop, meadow fescue, sweet vernal
	Bermuda grass
House dust mite	*Dermatophagoides farinae*
	Dermatophagoides pteronyssinus
Weeds	Short ragweed
Pet	Cat hair

using these methods are clinically efficacious and whether the microgram content is an appropriate measure linked to efficacy. The use of modified quantitative testing (MQT) has been suggested to help plan the starting dose for SLIT-D[24], although there is little evidence to support this practice. Based on clinical trials with SCIT, intradermal dilutional testing to determine dosing is not recommended[35-37].

There is less ambiguity in the dosing for SLIT-T because randomized, double-blind, placebo-controlled (RDBPC) dose-finding studies have been conducted for all of the SLIT-T approved in North America[15, 16, 19, 38]. The approved SLIT-T are uniform internationally. For the five-grass SLIT-T, the daily maintenance dose in adults and children is 300 IR[39]. The five-grass SLIT-T is typically given pre- and co-seasonally. For the Timothy grass SLIT-T, the daily maintenance dose in North America is 2800 BAU, for the ragweed SLIT-T is 12 Amb a 1-Units, for the HDM SLIT-T is 12 SQ-HDM, and for the tree SLIT-T is 12 SQ-Bet[40-43]. SQ is a standardization method based on potency, major allergen content, and complexity of the allergen extract (characterization of major and minor allergens)[42]. In North America, the Timothy grass, ragweed, and tree SLIT-T are typically given pre- and co-seasonally, and HDM SLIT-T is typically given year-round. However, all SLIT-T are permitted to be initiated at any time of the year and may be administered year-round. Year-round use of Timothy grass SLIT-T is becoming more common.

The effective allergen content measured in micrograms for SLIT-D should not be assumed to be equivalent across different SLIT-D preparations, or to the effective allergen content in a SLIT-T product and vice versa[14]. This principle is demonstrated by comparing the only successful large RDBPC trial of SLIT-D conducted in North America, where the major allergen dose was approximately 50 μg Amb a 1 in 94% of the subjects[44], whereas the approved dose for the ragweed SLIT-T is 12 μg Amb a 1[40]. Thus, the same microgram of allergen that is effective in a SLIT-T product cannot be assumed to be effective for SLIT-D.

A perceived advantage of SLIT-D is that it allows for mixture of allergens, which is common practice for SCIT in North America. However, for both SCIT and SLIT-D, there is limited data on efficacy and safety of allergen mixtures[45] and Leatherman et al. were not able to make an evidenced-based recommendation on multiallergen SLIT-D mixes[13]. No additional studies of SLIT-D mixtures using North American extracts have been conducted since the 2015 dosing recommendations. Therefore, there is little evidence to support that multiallergen SLIT-D mixtures are efficacious. The American Academy of Allergy, Asthma & Immunology (AAAAI)/American College of Allergy, Asthma & Immunology (ACAAI) AIT Task Force Practice Parameters and the Canadian Society of Allergy and Clinical Immunology recommend that for SCIT, one pollen extract within a highly cross-reactive group be selected which can provide cross-protection for all allergens within the group[46, 47]. The AAAAI/ACAAI AIT Task Force does not currently endorse SLIT-D[14].

In all of the pivotal RDBPC trials of SLIT-T, the majority of the patients were polysensitized to more than one allergen but were only treated with one SLIT-T[15, 30, 48-52]. There have been 2 studies on the safety of co-administering multiple tablets and 2 studies on co-administering SLIT-T with SLIT-D[53-56]. In the dual SLIT-T studies, a sequential dosing schedule was followed (4 weeks with each tablet alone in 1 study and 2 weeks with each tablet alone in 1 study)[53, 55]. Ultimately the tablets were co-administered within 5 minutes of each other. Combinations evaluated were grass + ragweed SLIT-T and HDM + Japanese cedar SLIT-T[53, 55]. There do not seem to be any additional safety concerns when the SLIT-T are co-administered. To date, there are no data on the efficacy of co-administered SLIT-T.

Efficacy

The vast majority of the SLIT studies have been conducted outside of North America. As discussed above, extrapolation of data from European (or other regions) SLIT-D products to SLIT-D preparations of US extracts cannot be made based on allergen content alone. To date, there have been 13 SLIT-T (11 were Phase 3 or 4) and 7 SLIT-D (1 was Phase 3) RDBPC efficacy trials conducted in North America[15, 18, 20, 27-31, 44, 48-52, 57-62]. Of these, 9 of the 13 SLIT-T trials were field trials that demonstrated significant improvement in symptoms and a reduction in symptom-relieving medication use compared with placebo (standard of care which allowed for symptom-relieving medication use) as measured by a combined symptom and medication score[15, 27, 29, 30, 48-52]. One grass SLIT-T field trial did not show a significant improvement from placebo in the primary endpoint (daily symptom score)[60]. The remaining 3 SLIT-T trials were environmental exposure chamber (EEC) trials, two of which were dose-finding trials for the tree SLIT-T and the HDM SLIT-T that demonstrated significant improvement in symptoms after allergen challenge versus placebo[18, 31]. The third SLIT-T EEC trial investigated the potential

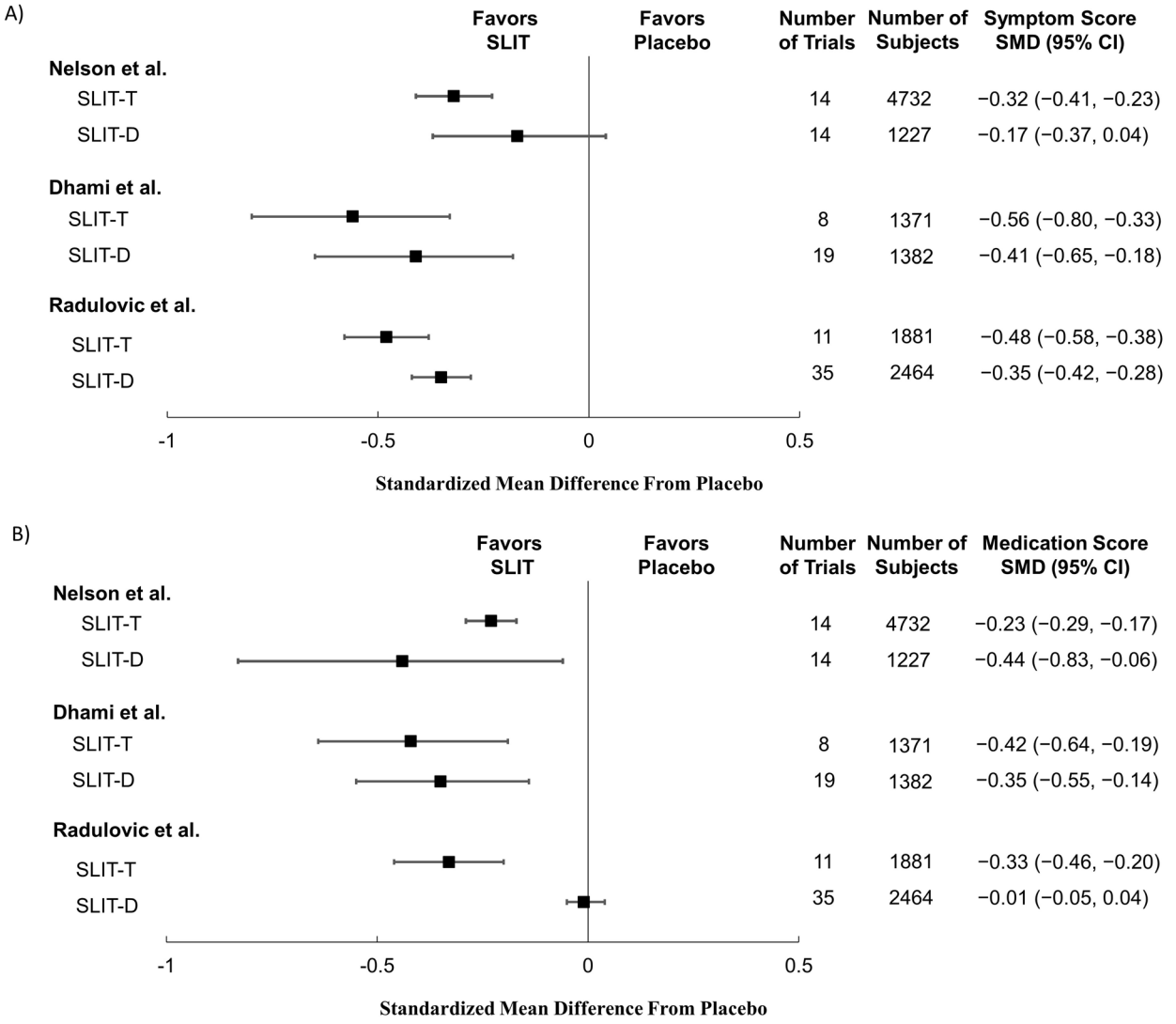

Figure 1. Comparison of the improvements versus placebo in A) symptoms and B) symptom-relieving medication use between SLIT-T and SLIT-D in published meta-analyses(63-65). SMD, standardized mean difference.

bystander effect of grass SLIT-T treatment after birch challenge and found no significant bystander effect on birch-induced symptoms (no confirmatory grass challenge was conducted)[28]. Only 2 of the 7 trials of SLIT-D using US extracts demonstrated a significant improvement in symptom and medication scores compared with placebo[44, 62].

Three meta-analyses have compared the standardized mean difference in symptom and medication scores from placebo between SLIT-T and SLIT-D studies, including studies conducted outside North America[63-65]. In all 3 of the analyses, SLIT-T had a numerically greater standardized mean difference in symptom score than SLIT-D (SLIT-T vs SLIT-D: −0.32 vs −0.17; −0.56 vs −0.41; and −0.48 vs −0.35; Figure 1A). In 2 of the analyses, SLIT-T had a numerically greater standardized mean difference in symptom-relieving medication use score than SLIT-D (SLIT-T vs SLIT-D: −0.42 vs −0.35; −0.33 vs −0.01), and in the third analysis SLIT-D had a greater standardized mean difference (SLIT-T vs SLIT-D: −0.23 vs −0.44; Figure 1B). A fourth meta-analysis compared median score differences and found that the improvements in symptoms from placebo were greater for SLIT-T than SLIT-D (SLIT-T vs SLIT-D: −0.43 vs −0.11) and reductions in medication use were similar between the two groups (SLIT-T vs SLIT-D: −0.30 vs −0.28)[66].

There have been no trials directly comparing SLIT-T versus SLIT-D. One post hoc analysis compared the pooled results of a 5-grass SLIT-T RCT with a 5-grass SLIT-D RCT and found that both treatments significantly improved the combined symptom and medication score, with no significant difference between SLIT-T and SLIT-D (p=0.104)[67]. It should be noted that the trials were not powered to evaluate non-inferiority between SLIT-T and

Table 4. Cost of monthly supply of SLIT-T and SLIT-D in the United States. SLIT-D daily doses are those recommended by Leatherman et al.[13].

SLIT product	Manufacturer cash cost for monthly supply†	Cost for monthly supply with manufacturer coupon or average bulk discount
Grass		
Grass SLIT-T	$309	$25-$100‡
5-grass SLIT-T	$450	$15-$100§
SLIT-D, 15-30 μg/day *		
10 mL supply	$23-$46	$10-$21
50 mL supply	$15-$31	$7-$14
Ragweed		
SLIT-T	$309	$25-$100‡
SLIT-D, 15-50 μg/day *		
10 mL supply	$46-$148	$21-$68
50 mL supply	$26-$86	$12-$39
House dust mite		
SLIT-T	$309	$25-$100‡
SLIT-D, 32 μg/day *		
10 mL supply	$237	$102
50 mL supply	$189	$81

SLIT-D, sublingual immunotherapy drops; SLIT-T, sublingual immunotherapy tablet. *Cost to the prescriber to obtain a monthly supply of the dose recommended by Leatherman et al. (Grass, 15-30 μg/day; Ragweed, 15-50 μg/day; HDM, *D. pteronyssinus* plus *D. farinae* each 16 μg/day)[13]. Cost to the patient will vary depending on individual prescriber practices and other factors. † In 2020 US dollars. ‡ Coupon offer is for commercially insured patients and the cost with coupon depends on commercial insurance coverage and the pharmacy network (e.g., covered or no covered in-network specialty pharmacy [$25], covered retail pharmacy [$50] or not covered retail pharmacy [$100]). Available at: https://www.alksavings.com/#/app/layout/home, §$15 for commercially insured patients and up to $100 savings for uninsured patients. Available at: https://www.oralair.com/copaysavings

SLIT-D. Moreover, the grass SLIT-D RCT used in the pooled analysis did not allow symptom-relieving medication use and thus had a "true placebo", whereas the 5-grass SLIT-T RCT allowed symptom-relieving medication use in the placebo group. This highlights the fact that interpretation of the efficacy of SLIT, and AIT trials in general, can be complicated by a substantial placebo effect and the allowed use of symptom-relieving medication. The placebo effect in allergy medication and AIT trials is well-known. A meta-analysis of AIT trials demonstrated that up to 68% of the total treatment effect of SLIT in adults was attributed to a placebo effect[68]. Such a large placebo effect in ARC trials is partially because the primary outcome typically includes a subjective reporting of symptom scoring by the patient, which is susceptible to psychological mechanisms[69]. Another contributor to the placebo effect in AIT trials is the allowed use of symptom-relieving medications. The use of symptom-relieving medications in the placebo group potentially lowers (improves) the symptom score of the placebo group, which decreases the ability to detect a true difference in scores between active treatment and placebo (basement effect). To help offset the impact of symptom-relieving medication use in AIT trials, the recommended primary outcome is a combined score of symptom and medication use[70], and results are often presented as percentage improvement relative to placebo. Such an analysis takes into account 'real world' conditions for patients for whom these medications are widely available.

Disease modification and sustained effect

In contrast to symptom-relieving pharmacotherapy, AIT changes the immunologic mechanisms that drive ARC symptoms and therefore has the potential to have sustained effects after treatment is stopped[71]. Two large RDBPC 5-year trials demonstrated that 3 years of year-round timothy grass SLIT-T treatment resulted in significantly improved symptoms and symptom-relieving medication use compared with placebo 2 years after the end of treatment[3, 72]. Thus, the timothy grass SLIT-T is recognized by the US FDA as having a sustained effect and met the criteria set by the European Medicines Association for a disease-modifying effect[41, 73]. These studies show that 3 years of timothy grass SLIT-T treatment appears to be required to achieve the sustained effect. The five-grass SLIT-T has demonstrated clinical benefits for up to 2 years after 3 years of pre- and co-seasonal treatment in a RDBPC trial[74]; however, the results were not sufficiently robust for the tablet to be recognized by regulatory authorities as having a sustained effect or as a disease-modifying treatment. One RDBPC trial of the Japanese cedar SLIT-T has demonstrated a sustained and disease modifying effect for up to 2 years after 3 years of treatment[17, 75, 76]. Trials evaluating a sustained and disease-modifying effect with the HDM, ragweed, and tree SLIT-T have not yet been conducted.

There have been 2 RDBPC trials of SLIT-D (both used European extracts) that evaluated a sustained effect. One trial demonstrated a significant improvement in symptom score compared with placebo 1 year after completing 3 years of co-seasonal five-grass SLIT-D treatment, but improvement in the combined symptom and medication score did not reach significance for the 1-year follow-up[77]. The second trial demonstrated a sustained effect from placebo 1 year after completing 32 weeks of *Artemisia annua* SLIT-D[78]. In a prospective, randomized, open-controlled trial of HDM SLIT-D, patients received treatment for 3, 4, or 5 years[79]. A sustained significant improvement in the combined symptom and medication score compared with placebo was

observed every year for 6 years after treatment discontinuation in patients who received 3 years of treatment and for 7 years for patients who received 4 or 5 years of treatment. Another RCT of HDM SLIT-D found that 1 or 2 years of treatment resulted in a sustained improvement in symptom scores 1 year after treatment discontinuation[80]. In addition, a retrospective study of patients receiving 1, 2, 3, or 4 years of HDM SLIT-D demonstrated that a sustained improvement in symptom scores compared with placebo was observed for up to 8 years after treatment discontinuation in patients who received 4 years of treatment, but the duration of sustained effect decreased in proportion to the other years of treatment duration[81].

The RDBPC trials of SLIT-T that included North American populations indicate that treatment induces a significant increase from baseline in allergen specific IgG4, specific IgE, and IgE-blocking antibodies compared with placebo[15, 27, 29, 30, 48, 49, 51, 52, 60]. Significant increases from baseline in allergen specific IgG4 and specific IgE were also demonstrated in 4 of the 7 SLIT-D trials conducted in North America[20, 44, 57, 58]. One trial of HDM SLIT-D noted a significant increase from baseline in allergen-specific IgG4, but not specific IgE[59]. A trial of dual HDM and timothy grass SLIT-D demonstrated a significant increase in allergen-specific IgG4 but a significant decrease in specific IgE compared with placebo[62]. In the trial of cat SLIT-D, there was no significant increase from baseline in either allergen-specific IgG4 or specific IgE[61].

Prevention of asthma and new sensitizations

The potential prevention of asthma is a key motivation for use of AIT in children. One large, RDBPC 5-year trial of grass SLIT-T in children found that the SLIT-T significantly reduced the proportion of patients with asthma symptoms or asthma medication use compared with placebo (16% vs 20%, p=0.036)[72]. Four open-label, controlled trials have demonstrated that treatment with either HDM or pollen SLIT-D with European extracts significantly reduces the proportion of patients that develop asthma or prevents decreases in forced expiratory volume in 1 second (FEV1)[82-85].

Prevention of development of new allergen sensitizations is another potential motivator for AIT use, but a meta-analysis of 18 AIT studies published in 2017 found that there is little high quality evidence to support such an outcome[86]. Of the 18 studies, 6 were with SLIT (1 SLIT-T and 5 SLIT-D). Only the SLIT-T trial was a RDBPC trial[3]. After long-term follow-up 2 years after ending a 3-year treatment period with grass SLIT-T, there was no difference in new sensitizations between treatment and placebo, although this trial was conducted in adults and most were already multisensitized at baseline[3]. The 5 SLIT-D trials were all open-label, with conflicting results on the prevention of sensitizations[79, 82, 84, 85, 87]. Since the 2017 SLIT meta-analysis was published, an open-label RCT demonstrated that a significantly lower percentage of children receiving HDM SLIT-T developed new sensitizations after 1 year compared with controls (4% vs 27%, respectively)[88]. Another open-label, non-randomized trial of HDM SLIT-D demonstrated that after 5 years of treatment, 58% of patients in the control group, 13% in a standard SLIT-D group, and 8% in an adjuvanted (e.g., adjuvant added to improve the antigenic effect) SLIT-D group developed new sensitizations[83].

Safety/tolerability

SLIT in either tablet or drop form is generally considered a safer treatment than SCIT[7, 8]. The most common AEs with SLIT-T and SLIT-D are local allergic reactions such as oral pruritus, throat irritation, ear pruritus, and mouth edema[89-91]. With SLIT-T, the local allergic reactions have been demonstrated to be mostly mild-to-moderate, last approximately 30 minutes to 1 hour, and typically abate or disappear after 2 weeks of treatment[89]. The duration and recurrence of AEs for SLIT-D are less well characterized.

Systemic allergic reactions

Both SLIT-T and SLIT-D carry the risk of inducing systemic allergic reactions, including anaphylaxis. Surveillance data from a survey in the US found a systemic allergic reaction rate of 1.4% for SLIT-D between the years of 2012 and 2013[92]. No equivalent data for SLIT-T are yet available, although a review of SLIT-T trials found that epinephrine was administered to 0.2% of subjects for SLIT-T treatment-related events[93]. Rarely, severe systemic allergic reactions can occur, especially after the first dose of administration[92]. The prescribing information for all the SLIT-T state that the first dose should be administered under the supervision of physicians experienced with severe allergic reactions and that the patient should be observed for 30 minutes after the first dose[39-42]. In the US, the FDA recommends that self-injectable epinephrine be prescribed along with SLIT-T, although this recommendation is controversial because of the low risk of anaphylaxis with SLIT-T in relation to the high cost of autoinjectors[94]. No other country has a similar recommendation.

Asthma

Uncontrolled asthma is a risk factor for life-threatening reactions for SCIT and appears to be a risk factor for severe reactions to SLIT[92]. In early SLIT trials, even mild asthma was an exclusion criteria, but trials in the last decade have included subjects with mild to moderate persistent asthma. Pooled analyses of SLIT-T trials indicate that there is no difference in the safety profile of subjects with controlled mild and moderate persistent asthma compared with no asthma[89, 90]. The HDM SLIT-T is also approved as an add-on treatment for asthma in Europe[10].

Eosinophilic esophagitis

There is a direct relationship between eosinophilic esophagitis

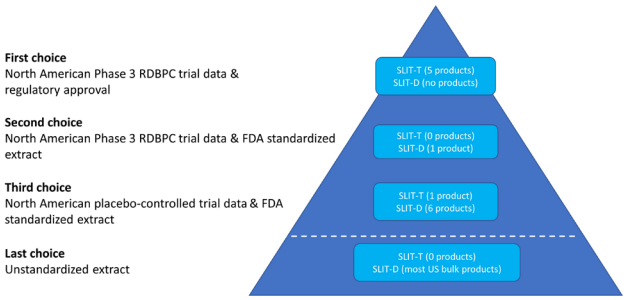

Figure 2. Suggested algorithm for selecting a sublingual immunotherapy product in North America. There are no SCIT products approved based on Phase 1-3 trials by regulatory agencies in North America. FDA, US Food and Drug Administration; RDBPC, randomized, double-blind, placebo-controlled.

(EoE) and food allergy oral immunotherapy[95]. There are also reported cases of EoE associated with SLIT-T and SLIT-D[90, 96, 97], but it is unknown if there is a direct relationship between EoE and SLIT for aeroallergens and the mechanism is unclear. Because of differences in contact with the lower esophagus, there may be differences between SLIT-T (immediate absorption in the mouth) and SLIT-D (swallowed) in relation to EoE. A history of EoE is currently a contraindication for SLIT-T.

Cost

Cost is a common reason patients discontinue SLIT[98, 99]. Commercial insurance coverage for SLIT-T in the US is approximately 75% and the tablets are covered under Medicare[100]. Manufacturers of SLIT-T offer coupons on their websites to offset the cost to patients and can range from $15 (€14) to $100 (€92) depending on commercial insurance coverage and the pharmacy network (Table 4). In contrast, SLIT-D are not covered by commercial insurance because of lack of FDA approval. The cost to the prescriber for SLIT-D is dependent on the dose used and the specific allergen (Table 4). The out-of-pocket cost to the patient for SLIT-D will vary depending on individual prescriber practices and other factors.

Adherence

Daily treatments, particularly long-term treatments, have notoriously poor adherence rates[101]. As with all daily long-term treatments, adherence to SLIT remains a challenge and many patients do not complete the recommended 3 years of treatment[102, 103]. Although adherence to SLIT in general has been evaluated in many studies, adherence to SLIT-T and SLIT-D specifically is not always distinguished and no study has directly compared adherence between the two.

Selection of SLIT Products

The choice of AIT treatments should be based on scientific evidence. Evidence based medicine is the standard for any medical condition to provide effective and safe treatment, in a cost-efficient manner. With the exception of SLIT-T, most SCIT and SLIT-D therapies have been implemented and marketed without being evaluated in large, RDBPC clinical trials. Nevertheless, because of historical reasons, SCIT and SLIT-D are used widely in North America and Europe. Multiple RDBPC trials have been conducted for SLIT-T and have undergone regulatory review before being approved in many countries worldwide. European AIT guidelines for ARC recommend that only AIT treatments with documented efficacy should be prescribed, with the exception of AIT for rare allergens[104]. It is recognized that a "class effect" of SCIT or SLIT treatments for a particular allergen cannot be assumed based on clinical evidence for other individual treatments[105]. To illustrate the current and unsatisfying clinical reality, a suggested algorithm on how to select a SLIT treatment in North America based on an evidence-based approach is shown in Figure 2. The most preferred treatment would have clinical evidence based on North American Phase 3 RDBPC trials that had undergone regulatory review and approval according to today's standards of Good Manufacturing Practice and Good Clinical Practice. If such an AIT treatment is not available, one could choose a treatment with a US manufactured FDA standardized extract that is supported by North American Phase 3 RDBPC trials. Only one FDA standardized extract (short ragweed) has been evaluated in a Phase 3 clinical efficacy and safety SLIT-D trial[44]. The trial outcome was positive, but the trial did not lead to FDA approval. A few bulk extracts (e.g., dog, cat, timothy grass, and HDM) have been evaluated in small US SCIT and SLIT-D trials and shown evidence of effect[62, 106, 107]. However, such evidence has not yet been replicated in Phase 3 trials and have not led to regulatory approval. Most US allergen extracts are not standardized but remain licensed for diagnostic use and have been grandfathered in to be used for SCIT despite the absence of formal studies.

Conclusion

Since the 2015 SLIT-D dosing recommendations, no new evidence has emerged to update SLIT-D dosing or efficacy for North America. As part of the shared decision-making process, patients should be made aware that SLIT-T are approved by regulatory agencies and have been well-studied in clinical trials, whereas SLIT-D in North America lacks comparably strong clinical evidence and are not approved by regulatory agencies. Well-designed clinical trials are needed to address the knowledge gaps in SLIT-D dosing, efficacy, and safety using North American allergen extracts.

Abbreviations

ACAAI, American College of Allergy, Asthma & Immunology; AAAAI, American Academy of Allergy, Asthma & Immunology;

AIT, allergy immunotherapy; ARC, allergic rhinoconjunctivitis; BAU, bioequivalent allergy units; EEC, environmental exposure chamber; EoE, eosinophilic esophagitis; FDA, US Food and Drug Administration; FEV1, forced expiratory volume in 1 second; HDM, house dust mite; IR, index of reactivity; MQT, modified quantitative testing; RCT, randomized controlled trials; RDBPC, randomized, double-blind, placebo-controlled; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SLIT-D, sublingual immunotherapy drops; SLIT-T, sublingual immunotherapy tablets

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Authorship contribution

KL contributed conceptualization, reviewing and editing. JMP contributed conceptualization, reviewing & editing. SEL contributed conceptualization, reviewing and editing. KR contributed conceptualization, reviewing and editing. HN contributed conceptualization, reviewing and editing.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Conflict of interest

K. Lam is a speaker for Optinose. S.E. Lee has received clinical trial funding and participated in advisory boards for AstraZeneca, Genzyme, GlaxoSmithKline, Genentech, and Sanofi Regeneron. J.M. Pinto is a speaker for Optinose and Sanofi-Regeneron; he has served on advisory boards or in consulting arrangements for GlaxoSmithKline, Astellas, Connect Pharma, AstraZeneca, Genentech, and ALK-Abello. H. Nolte and K. Rance are employees of ALK, Bedminster, NJ, USA

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This manuscript contains supplementary material

SUPPLEMENTARY MATERIAL

Supplemental Table 1. Randomized SLIT allergic rhinoconjunctivitis trials conducted since publication of SLIT dosing guidelines by Leatherman et al in 2015[1].

Reference	Study Phase (N Randomized)	Country or Region	Formulation	Allergen	Daily Maintenance Dose	Primary Efficacy Endpoint	Primary Endpoint Met?
Bozek et al, 2014[2]	Not specified (N=78)	Poland	Drops	Grass	240 IR (5 days/week); cumulative dose 225 μg Phl p 5	Mean weekly nasal symptom score after 3 years	Yes (p=0.008 active vs placebo)
Scadding et al, 2017[3]	Not specified (N=106)	UK	Tablets	Grass	2800 BAU; 15 μg Phl p 5	TNSS after allergen challenge at year 3 (1 year after treatment discontinuation)	No (p=0.75 active vs placebo)
Jerzynska et al, 2016[4]	Not specified (N=100)	Poland	Tablets	Grass	300 IR; 20-25 μg of the group 5 major allergens	TCS, symptom score, and medication score at month 5	Yes (p<0.05 vs no SLIT control group for TCS; not significant for symptom score or medication score alone)
Mösges et al, 2017[5]	Phase 2 (N=158)	Germany	Carbamylated monomeric allergoid tablets	Grass	300 UA, 600 UA, 1000 UA, and 2000 UA*	Proportion of subjects per group with a change in the response threshold needed to induce a positive conjunctival provocation test response at screening and week 12; improvement in 60% of patients was considered clinically meaningful	Yes (>60% of patients had clinically meaningful improvement in all 4 groups)
Valovirta et al, 2018[6]	Not specified (N=812)	Europe	Tablets	Grass	2800 BAU; 15 μg Phl p 5	Time to onset of asthma	No (p=0.667 vs placebo)
Ellis et al, 2018[7]	Phase 4 (N=93)	Canada	Tablets	Grass	2800 BAU; 15 μg Phl p 5	Change from baseline in TNSS after birch pollen challenge	No (p=0.83 vs placebo)
Pfaar et al, 2019[8]	Phase 3 (N=406)	Europe	Drops	Birch	40,000 AUN/mL; 0.4 mg/mL Bet v 1	TCS after 3 to 6 months	Yes (p<0.0001 vs placebo)
Pfaar et al, 2016[9]	Phase 2 (N=269)	Europe	Drops	Birch	3333, 10,000, 20,000, or 40,000 AUN/mL; 10,000 AUN/mL = 46.7 μg Bet v 1	Change from baseline in symptom score following a titrated nasal provocation test at month 5	Yes (p=0.008 for 20,000 AUN/mL and p<0.001 for 40,000 AUN/mL vs placebo)
Biedermann et al, 2019[10]	Phase 3 (N=634)	Europe	Tablets	Birch	12 SQ-Bet†; approximately 60 μg Bet v 1	TCS during birch pollen season	Yes (p<0.0001 vs placebo)
Couroux et al, 2019[11]	Phase 2 (N=219)	Canada	Tablets	Birch	2, 7, or 12 SQ-Bet; 12 SQ-Bet = approximately 60 μg Bet v 1	Total symptom score after birch pollen challenge at week 24	Yes (p=0.03 for 7 SQ-Bet and p=0.02 for 12 SQ-Bet vs placebo)
Mäkelä et al, 2018[12]	Phase 2 (N=637)	Europe	Tablets	Birch	0.5, 1, 2, 4, 7, or 12 SQ-Bet; 12 SQ-Bet = approximately 60 μg Bet v 1	Total symptom score during birch pollen season	Yes (p=0.02 for the 7 SQ-Bet dose vs placebo)
Nony et al, 2015[13]	Phase 2 (N=455)	Europe and Russia	Tablets	Birch	12.5, 25, or 50 μg Bet v 1	Adjusted TCS	Yes (p=0.02 for all doses vs placebo)

Reference	Study Phase (N Randomized)	Country or Region	Formulation	Allergen	Daily Maintenance Dose	Primary Efficacy Endpoint	Primary Endpoint Met?
Okamoto et al, 2015[14]	Phase 3 (N=531)	Japan	Drops	Japanese Cedar	2,000 JAU/mL‡; 10,000 JAU/mL = approximately 7.3-21 μg/mL Cry j 1	TCS during peak symptoms in the 2nd season	Yes (p<0.0001 vs placebo)
Gotoh et al, 2019[15]	Phase 2/3 (N=1042)	Japan	Tablets	Japanese Cedar	2,000, 5,000, or 10,000 JAU/mL‡; 10,000 JAU/mL = approximately 7.3-21 μg/mL Cry j 1	TCS during peak season	Yes (p<0.001 for all doses vs placebo)
Yonekura et al, 2019[16]§	Phase 2/3 (N=1042)	Japan	Tablets	Japanese Cedar	5,000 JAU/mL‡; 10,000 JAU/mL = approximately 7.3-21 μg/mL Cry j 1	TCS during the 3rd peak season	Yes (p<0.0001 vs placebo)
Yonekura et al, 2021¶	Phase 2/3 (N=1042)	Japan	Tablets	Japanese Cedar	5,000 JAU/mL‡; 10,000 JAU/mL = 12.5 μg/mL Cry j 1	TCS during the 5th peak season (2 years after treatment end)	Yes (p<0.001 vs placebo)
Guo et al, 2017[17]	Not specified (N=48)	China	Drops	HDM	Not specified	TNSS and individual symptom scores during the 11th and 12th month of treatment	Yes (p<0.05 vs placebo)
Karakoc-Aydiner et al, 2015[18]#	Not specified (N=48)	Europe	Drops	HDM	4 μg Der p and 4 μg Der f 1	TNSS at year 3	Yes (p=0.01 vs controls)
Lin et al, 2016[19]	Not specified (N=500)	China	Drops	HDM	3 drops/day at 333 μg/mL *D. farinae* for patients <14 years old and 2 drops/day at 1000 μg/mL *D. farinae* for patients >14 years old	TNSS change from baseline at years 1, 2, and 3	Yes (p<0.01 vs baseline)
Potter et al, 2015[20]	Not specified (N=60)	South Africa	Drops	HDM	300 IR 3 days a week	Total symptom score at year 2	No (p>0.05 vs placebo)
Shao et al, 2014[21]	Not specified (N=264)	China	Drops	HDM	0.15 mL at 333 μg/mL *D. farinae*	TNSS at 1 year	Yes (p<0.01 vs control)
Vesna et al, 2016[22]	Not specified (N=61)	Serbia	Drops	HDM	15 drops of 1000 PNU/mL *D. pteronyssinus* extract (approximately 19.9 μg/mL of allergen) twice weekly	TCS over the last month of 1 year of treatment	Yes (p<0.05 vs control)
Wang et al, 2017[23]	Not specified (N=68)	China	Drops	HDM	333 μg/mL *D. farinae* (number of drops per day not specified)	TNSS change from baseline at 1 year	Yes (p<0.05 vs baseline)
Xian et al, 2020[24]	Not specified (N=67)	China	Drops	HDM	200 STU 3 days a week; 200 STU = 0.8/0.8 μg Der p 1/Der f 1	TNSS change from baseline at month 12	Yes (p=0.045 vs placebo)
Yin et al, 2016[25]	Not specified (N=156)	China	Drops	HDM	333 μg/mL, 3 drops for patients ≤12 years old, 1000 μg/mL, 3 drops for patients >12 years old	TNSS vs placebo at 12 months	Yes (p=0.032 vs placebo)
Chen et al, 2020a[26]	Not specified (N=150)	China	Drops	HDM	333 μg/mL *D. farinae* (number of drops per day not specified)	DSS and DMS during the last 2 weeks of 3 years of treatment	Yes (p<0.001 vs placebo)
Chen et al, 2020b[27]	Not specified (N=86)	China	Drops	HDM	2 drops/day at 1000 μg/mL *D. farinae*	TCS at months 6, 12, and 24	Yes (p<0.05 vs placebo at month 24 only)
Demoly et al, 2016[28]	Phase 3 (N=992)	Europe	Tablets	HDM	6 or 12 SQ-HDM;	TCS during the last 8 weeks of 1 year of treatment	Yes (p=0.004 vs placebo for both doses)
Hüser et al, 2017[29]	Phase 2 (N=131)	Germany	Tablets	HDM	300, 1000, 2000, or 3000 UA/day*; 1000 UA=2.7 μg group 1 HDM allergen and 3000 UA=8.1 μg group 1 HDM allergen	Change from baseline in allergic severity at day 84 based on reaction to the conjunctival provocation tests	No (p<0.10 vs placebo for all doses)
Masuyama et al, 2018[30]	Phase 3 (N=458)	Japan	Tablets	HDM	10,000 JAU (aka 6 SQ-HDM); 100,000 JAU=22.2 -66.7 μg/mL Der f 1 and Der p 1 combined	TCS during the last 8 weeks of 1 year of treatment	Yes (p<0.001 vs placebo)

Reference	Study Phase (N Randomized)	Country or Region	Formulation	Allergen	Daily Maintenance Dose	Primary Efficacy Endpoint	Primary Endpoint Met?
Nolte et al, 2016[31]	Phase 3 (N=1,482)	US and Canada	Tablets	HDM	12 SQ-HDM; 12 SQ-HDM contains approximately 15 μg Der p 1 and Der f 1 combined and 15 μg Der p 2 and Der f 2 combined	TCS during the last 8 weeks of 1 year of treatment	Yes (p<0.001 vs placebo)
Nolte et al, 2015[32]	Phase 2 (N=124)	Austria	Tablets	HDM	6 SQ-HDM or 12 SQ-HDM; 12 SQ-HDM contains approximately 15 μg Der p 1 and Der f 1 combined and 15 μg Der p 2 and Der f 2 combined	TNSS at week 24 exposure challenge	Yes (p≤0.03 vs placebo for both doses)
Okamoto et al, 2019[33]	Phase 3 (N=438)	Japan	Tablets	HDM	300IR	Adjusted TCS during the last 4 weeks of 1 year of treatment	Yes (p<0.001 vs placebo)
Okamoto, et al, 2017[34]	Phase 3 (N=968)	Japan	Tablets	HDM	300IR or 500IR	Adjusted TCS during the last 8 weeks of 1 year of treatment	Yes (p<0.001 vs placebo for both doses)
Okubo et al, 2017[35]	Phase 3 (N=946)	Japan	Tablets	HDM	10,000 JAU (aka 6 SQ-HDM) or 20,000 JAU (aka (12 SQ-HDM); 12 SQ-HDM contains approximately 15 μg Der p 1 and Der f 1 combined and 15 μg Der p 2 and Der f 2 combined	TCS during the last 8 weeks of 1 year of treatment	Yes (p<0.001 vs placebo for both doses)
Roux et al, 2016[36]	Phase 2 (N=355)	Canada	Tablets	HDM	100IR, 300IR, or 500IR; 500IR=22-23 μg Der p 1 and 99-102 μg Der f 1	Change from baseline in area under the curve of the TNSS at 6-month exposure challenge	Yes (p=0.04 vs placebo for the 500IR dose)
Demoly et al, 2021[37]	Phase 3 (N=1607)	Canada, US, and Europe	Tablets	HDM	300IR	TCS during the last 4 weeks of 1 year of treatment	Yes (p<0.001 vs placebo)
Baba et al, 2021[38]	Not specified (N=332)	India	Tablets	HDM	2800 BAU of Der f, Der p and Blomia in different ratios	TNSS and Asthma Control Test score averaged over 1 week each after 1, 2, and 3 years of treatment and	Yes (p<0.001 for TNSS and p=0.006 for Asthma Control Test vs baseline for all 3 years)
Lou et al, 2020[39]	Not specified (N=71)	China	Drops	*Artemisia annua*	Maximum 16,000 BU/mL	TNSS during peak season	Yes (p<0.001)
Caruso et al, 2018[40]	Not specified (N=26)	Italy	Drops	*Parietaria officinalis*	300IR	Individual symptom scores at month 12	Yes (p≤0.008 vs placebo)
Katotomichelakis et al, 2015[41]	Not specified (N=138)	Europe	Drops	Varied by individual	300IR/mL 8 applications 3 times a week or 10,000 AUN/mL 5 drops daily	Change from baseline in total symptom score	Yes (p<0.001 vs baseline)
Nolte et al, 2020[42]	Phase 3 (N=1025)	Canada, US, and Europe	Tablets	Ragweed	12 Amb a 1-Unit	TCS during peak season	Yes (p<0.001 vs placebo)

AUN, allergy units native; BAU, bioequivalent allergen units; DMS, daily medication score; DSS, daily symptom score; HDM, house dust mite; IR, index of reactivity; STU, standard therapeutic unit; TCS, total combined symptom and medication score; TNSS, total nasal symptom score.

*UA, units of allergy, describes the allergenic potency, 1 UA corresponds to 1/40 of the mean provocation dosage of the comparable unmodified allergen determined by nasal provocation testing in allergy patients. †SQ is a measure of the biological allergen activity based equally on the major allergen content and total allergenic activity. ‡JAU is a unique titer unit based on standardized allergen extract, developed by the Japanese Society of Allergology. §3-year follow-up from trial first reported by Gotoh et al.(15). ¶5-year follow-up from trial first reported by Gotoh et al.(15). #3-year follow-up from trial first reported by Eifan et al.(43).

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