



Sublingual immunotherapy tablets as a disease-modifying add-on treatment option to pharmacotherapy for allergic rhinitis and asthma

Stephen Brunton, Harold S. Nelson, David I. Bernstein, Simon Lawton, Susan Lu & Hendrik Nolte

To cite this article: Stephen Brunton, Harold S. Nelson, David I. Bernstein, Simon Lawton, Susan Lu & Hendrik Nolte (2017): Sublingual immunotherapy tablets as a disease-modifying add-on treatment option to pharmacotherapy for allergic rhinitis and asthma, Postgraduate Medicine, DOI: [10.1080/00325481.2017.1308208](https://doi.org/10.1080/00325481.2017.1308208)

To link to this article: <http://dx.doi.org/10.1080/00325481.2017.1308208>

 View supplementary material 

 Accepted author version posted online: 22 Mar 2017.
Published online: 27 Mar 2017.

 Submit your article to this journal 

 Article views: 56

 View related articles 

 View Crossmark data 

CLINICAL FOCUS: CLINICAL IMMUNOLOGY & INFECTIOUS DISEASES
REVIEW



Sublingual immunotherapy tablets as a disease-modifying add-on treatment option to pharmacotherapy for allergic rhinitis and asthma

Stephen Brunton^a, Harold S. Nelson^b, David I. Bernstein^c, Simon Lawton^d, Susan Lu^e and Hendrik Nolte^e

^aPrimary Care Respiratory Group, Lake View Terrace, CA, USA; ^bDepartment of Medicine, National Jewish Health, Denver, CO, USA; ^cBernstein Clinical Research Center and Department of Medicine and Environmental Health, University of Cincinnati, Cincinnati, OH, USA; ^dALK-Abelló, Hørsholm, Denmark; ^eMerck & Co., Inc., Kenilworth, NJ, USA

ABSTRACT

Allergic rhinitis (AR) with or without conjunctivitis (AR/C) is associated with a significant health and economic burden, and is often accompanied by asthma. Pharmacotherapies are the mainstay treatment options for AR and asthma, but guidelines also recommend allergy immunotherapy (AIT). Unlike pharmacotherapies, AIT has the ability to modify the underlying immunologic mechanisms of AR and asthma with the potential for long-term benefits after treatment is discontinued. Immunotherapy may also prevent progression of AR/C to asthma. Sublingual immunotherapy (SLIT)-tablets are a self-administered alternative to subcutaneous immunotherapy that provide the benefits of AIT without the cost and inconvenience of frequent office visits or the discomfort of injections. SLIT-tablets are also an option that can be utilized by primary care clinicians. Pharmacotherapies are generally effective in mild disease although a number of patients remain uncontrolled. SLIT-tablets have proven efficacy for AR in adults, children, and poly-sensitized allergic patients. Indirect comparisons indicate that SLIT-tablets have superior or comparable efficacy compared with traditional pharmacotherapies for seasonal AR, and superior efficacy for perennial AR. House dust mite (HDM) SLIT-tablets have also demonstrated clinically relevant benefits for asthma, with significant observed reductions in daily inhaled corticosteroid use, risk of asthma exacerbations, and asthma symptoms. SLIT-tablets are well tolerated, with minimal risk of systemic allergic reactions. The most common treatment-related adverse events are oral site reactions such as oral pruritus and throat irritation. Based on the favorable efficacy and safety profile, as well as the convenience of at-home oral administration and disease-modifying effects, SLIT-tablets should be considered as an alternative or add-on treatment to pharmacotherapy for AR/C, and as an add-on treatment for HDM allergic asthma.

ARTICLE HISTORY

Received 23 December 2016
Accepted 15 March 2017

KEYWORDS

Allergic rhinitis;
antihistamines; asthma;
intranasal corticosteroids;
sublingual immunotherapy;
tablets

1. Introduction

Allergic rhinitis (AR) with or without conjunctivitis affects ≥ 500 million people worldwide and carries a significant health and economic burden [1]. The symptoms of AR decrease health-related quality of life, with patients and caregivers often reporting a negative impact on work and school productivity, daily activities, and sleep [2,3]. Approximately 40–45% of patients with AR report that the discomfort of AR symptoms cannot be ignored or tolerated without relief [2].

Up to 40% of patients with AR also have asthma, and most patients with asthma also have AR [1]. Flare-ups of AR can be associated with asthma exacerbations, some of which may be serious. Patients with asthma and AR are approximately two-fold more likely to have an asthma-related hospitalization compared to patients with asthma alone [4,5]. Both conditions are characterized by inflammation of the airway, either the upper airway in the case of AR, or the lower airway in the case of asthma. The patterns of inflammation are similar, with accumulations of mast cells, eosinophils, basophils, and T cells in the respective airways [6]. The high incidence of AR

and asthma comorbidity, along with the similar pathogenic inflammatory mechanisms, has led to the 'one airway' theory connecting the two conditions [6]. Thus, it has been proposed that anti-inflammatory AR medications could also have an impact on asthma. Some studies of intranasal corticosteroids (INCS) for the treatment of AR have partially borne out this theory, demonstrating a reduction in asthma symptoms and bronchial hyperreactivity [7–9], whereas more recent studies show no impact on asthma control [10,11].

Allergy immunotherapy (AIT) is a prescribed therapy that has systemic effects and alters the underlying immunologic mechanisms that cause AR and allergic asthma by inducing tolerance to the relevant allergen [12]. AR guidelines recommend AIT for patients with seasonal or house dust mite (HDM) AR who do not want to be on constant or long-term pharmacotherapy, or in whom pharmacotherapy is insufficient or not well tolerated [1]. Asthma guidelines recommend AIT for patients for whom there is a clear relationship between asthma symptoms and exposure to an allergen to which the patient is sensitized, and in patients with exacerbations

despite taking Step 3 or Step 4 therapy [13,14]. Despite these recommendations, AIT is underutilized, with only about 16–22% of patients with AR having ever received AIT [15,16]. The purpose of this review is to examine the evidence supporting SLIT-tablets as an add-on or alternative treatment option to pharmacotherapy for AR with or without conjunctivitis, and as an add-on treatment for HDM allergic asthma.

2. Pharmacotherapy for AR and asthma

Treatment guidelines recommend antihistamines, INCS, decongestants, and leukotriene receptor antagonists as pharmacotherapy treatments for AR [1]. Treatment with pharmacotherapies is generally as needed, or daily, and many of the pharmacotherapies for AR are available over the counter. Approximately 50–75% of patients treat their AR with over-the-counter antihistamines and decongestants [15,17]. In surveys of such patients, 27% of adults and 40% of children reported being ‘very satisfied’ with over-the-counter treatments and 48% felt better over-the-counter medications were needed to manage symptoms [2,17]. Meta-analyses of AR pharmacotherapies have found that INCS are more efficacious than antihistamines and leukotriene receptor antagonists, and treatment guidelines recommend INCS as first-line treatment for moderate-to-severe AR [1,18–21]. However, there is a minority of patients whose AR remains uncontrolled with INCS; two-thirds of surveyed patients indicated that INCS relieves most of their AR symptoms, and only one-third of patients reported being very satisfied with INCS treatment [2].

The main recommended pharmacotherapy treatments for asthma are beta₂-agonists (short- and long acting), inhaled corticosteroids (ICSs), and combined ICS/beta₂-agonists [13,14]. Most asthma pharmacotherapy treatments are used as needed or daily [13]. The large, international, multicenter Gaining Optimal Asthma Control trial found that the majority of patients with asthma were able to achieve disease control, although 20–40% of patients remained uncontrolled despite guideline-recommended pharmacotherapy [22].

Pharmacotherapies for AR and asthma treat symptoms and inflammation with a relatively quick onset of action. Antihistamines and decongestants can relieve symptoms within minutes and INCS have an onset of action of approximately 12 h and maximum effect within weeks [1,23]. Asthma pharmacotherapies can provide immediate symptom relief in the case of beta₂-agonists, whereas the effects of ICS are gradual over the course of weeks [13,24]. However, none of the pharmacotherapies have disease-modifying effects.

3. Allergy immunotherapy (AIT)

AIT is delivered either subcutaneously (SCIT) or sublingually (SLIT). SCIT is generally administered weekly, biweekly, or monthly under medical supervision in a physician’s office, whereas SLIT is generally administered daily at home via drop or tablet formulations. For SLIT-tablets, the home administration is after the first dose has been administered under medical supervision of a physician with experience in the diagnosis and treatment of allergic diseases. In North America, SLIT drops are an off-label use of extracts intended

for SCIT [25]. Such off-label use is problematic as there is little evidence to support the efficacy of such practice and the effective dose has not been established. Of the handful of clinical trials with SLIT drops that have been conducted in North America [26–32], only 2 trials demonstrated a significant improvement in AR symptoms [28,32]. To date, there are no US Food and Drug Administration (FDA)-approved SLIT drop products. In contrast, SLIT-tablets are well-characterized, standardized products. Many clinical trials conducted in countries worldwide have demonstrated the efficacy of SLIT-tablets for AR and asthma [33–48]. Two SLIT-tablets are currently approved in Europe, the USA, and Canada for grass AR. These tablets are the timothy grass SLIT-tablet (GRASTEK®/GRAZAX®, Merck & Co., Inc., Kenilworth, NJ, USA/ALK, Hørsholm, Denmark) for patients aged 5+ years, and the 5-grass (sweet vernal, orchard, perennial rye, timothy, and Kentucky blue grass) SLIT-tablet (ORALAIR®, Stallergenes S.A., Antony, France/Greer Laboratories, Inc., Lenoir, NC, USA) for patients aged 5+ years in Europe and 10+ years in the USA [49,50]. One SLIT-tablet is approved in the USA and Canada for ragweed AR (RAGWITEK®, Merck & Co., Inc., Kenilworth, NJ, USA /ALK) for patients aged 18+ years. SLIT-tablets for HDM (ODACTRA®/ACARIZAX®/MITICURE®, Merck & Co., Inc., Kenilworth, NJ, USA/ALK/Torii Pharmaceutical Co., Ltd., Tokyo, Japan) are approved in the USA, Europe, Australia, and Japan for treatment of AR, and also for allergic asthma in Europe and Australia.

Most physicians in North America are less familiar with SLIT and more familiar with SCIT, the traditional ‘allergy shots.’ There is little data available regarding the efficacy of SLIT vs. SCIT. Five small ($N \leq 71$ patients) head-to-head, double-blind, placebo-controlled trials have directly compared the efficacy of SLIT with SCIT; 4 trials were for seasonal AR and one was for HDM [51–55]. In two of the five trials, AR symptoms were significantly improved and AR rescue medication use was significantly decreased vs. placebo after 1 year of treatment with both SCIT and SLIT [52,53]. In two of the trials, AR symptoms after 1 year of treatment or after nasal allergen challenge were significantly reduced vs. control by SCIT, but not SLIT [51,55]. In the fifth trial, 1 year of SCIT and SLIT both improved AR symptoms, but no statistical analysis or rescue medication use was reported [54]. In the four trials that conducted statistical analyses, no significant differences in symptom scores were found between SCIT and SLIT. Efficacy of SLIT vs. SCIT has also been indirectly compared in several meta-analyses of double-blind, placebo-controlled trials. A meta-analysis conducted in 2012 found that improvements in grass AR symptoms based on the standardized mean difference (SMD) were SCIT>SLIT-tablets>SLIT-drops [56], and a meta-analysis published in 2013 found a trend toward greater improvement in AR symptoms and rescue medication use with SCIT over SLIT [57]. The most recent meta-analysis, which includes the recent large SLIT-tablet trials, was published in 2015 and focused on commercially available SCIT, SLIT-tablets, and SLIT-drops for grass AR [58]. Improvements in AR symptoms vs. placebo based on SMD were grass SLIT-tablet = SCIT>SLIT-drops, with no significant differences between treatments (Figure 1). There are no definitive head-to-head trials comparing the efficacy of SLIT vs. SCIT.

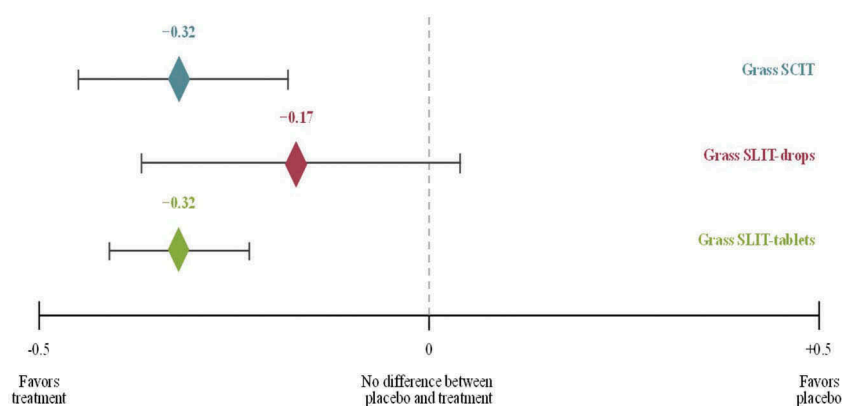


Figure 1. Comparative efficacy of allergic rhinitis symptom scores based on standardized mean differences from placebo ($\pm 95\%$ CI) among grass SCIT, SLIT-drops, and SLIT-tablets. SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy. Adapted with permission from Nelson et al [58]; reproduced with permission as modified by Dahl et al. [59].

In general, SLIT is considered to be safer than SCIT because SCIT has been associated with fatal systemic allergic reactions [60–62], whereas no fatal reactions have been reported with SLIT [63]. The majority of adverse events with SCIT are injection site reactions, and the majority of adverse events with SLIT are local oral-pharyngeal reactions (e.g. oral pruritus, throat irritation). Both therapies carry the risk of systemic allergic reactions and anaphylaxis. Cases of anaphylaxis are estimated to be 1 per 33,300 injections of SCIT, and 1 per 100 million administrations of SLIT [63].

A disadvantage of AIT (both SCIT and SLIT) compared with pharmacotherapy is the long-term commitment needed to complete a full course of treatment (3+ years) [64]. However, this disadvantage needs to be balanced with the sustained symptom relief and decreased dependence on pharmacotherapy. Another disadvantage is the relatively slow onset of action (4–8 weeks) [65–67]. Cost to patients due to inadequate or no AIT insurance coverage may be a deterrent to initiating AIT, or result in discontinuing treatment early [68]. Furthermore, in the USA patients receiving SLIT-tablets are required to be prescribed an epinephrine autoinjector, which can cost up to \$500. Epinephrine autoinjectors are not co-prescribed outside of the USA as the risk of serious anaphylaxis after the first tablet administration is considered very low. A compilation of the SLIT-tablets (timothy grass, ragweed, and HDM) revealed an epinephrine administration rate of 1.80 administrations per 100,000 SLIT-tablets [69]. However, numerous studies have demonstrated that over the course of several years AIT is more cost-effective than pharmacotherapy (reviewed in [70]). Some of the drivers of the cost-savings with AIT appear to be decreased AR pharmacotherapy use, decreased asthma medication use, and decreased asthma-related healthcare.

4. Efficacy of pharmacotherapy vs. SLIT-tablet for AR

The need for alternatives to pharmacotherapy for AR is underscored by results of a survey of healthcare practitioners, in which the primary reason for prescribing AIT was identified as ‘other therapies don’t work.’ [71] However, there is no direct

comparison of the efficacy of pharmacotherapy vs. SLIT for AR as no head-to-head trials have been conducted. Indirect comparisons between pharmacotherapies and SLIT are hindered by substantial differences in trial designs. Most notably, in SLIT trials (and other formulations of AIT), AR rescue medication use is allowed in all treatment groups, including placebo. Thus, the improvements in symptoms/rescue medication use in SLIT trials are not compared with a true placebo, but to a placebo plus background rescue medication (antihistamines, nasal steroids). Therefore, an observed treatment effect size of approximately 20% with SLIT is actually more impressive, considering meta-analyses of pharmacotherapy trials have reported an estimated treatment effect vs. placebo of 5% for leukotriene antagonists, 7–9% for antihistamines, and 17–26% for INCS [20,72]. Regulatory guidelines published in 2000 and later recommend the primary end point for AIT reflect both symptom severity and rescue medication use, as opposed to pharmacotherapy trials where the impact on symptoms alone is primarily the measure of efficacy. Another major trial design difference is trial duration, which is approximately 2 peak-season weeks with pharmacotherapy vs. several weeks or months with SLIT. In addition, pharmacotherapy trials generally use a subject population with a minimum symptom threshold at baseline prior to randomization and initiation of study treatments, which enriches for highly symptomatic patients. In contrast, seasonal SLIT trials begin several weeks before the onset of seasonal symptoms and patients are qualified for inclusion based on clinical history, skin prick testing, and serum-specific IgE levels. Despite these caveats, attempts have been made to indirectly compare the effect of pharmacotherapy vs. SLIT-tablets for AR using meta-analyses. Devillier et al. [18] compared treatments for grass AR and found the symptom effect size vs. placebo was 23.6% with grass SLIT-tablets, 23.5% with INCS, 15.0% with oral antihistamines, and 6.5% with a leukotriene receptor antagonist. Durham et al. [21] compared treatments for seasonal and perennial AR and found the nasal symptom effect size vs. placebo for seasonal AR was 22.2% with an INCS, 17.1% with a ragweed SLIT-tablet, 16.3% with a timothy grass SLIT-tablet, 8.5% with an oral antihistamine, and 5.4% with a leukotriene receptor antagonist (Table 1). For perennial AR, the nasal symptom effect size

Table 1. Symptom treatment effect size for SLIT-tablets and pharmacotherapies for SAR and PAR.

Treatment	Number of trials	Total number of subjects	Difference in mean: active treatment from placebo (95% CI)	Relative difference from placebo, % ^a
Timothy grass SLIT-tablet	6	3094	−0.46 (−0.60, −0.32)	−16.3 ^b
Ragweed SLIT-tablet	2	658	−0.57 (−0.87, −0.26)	−17.1 ^c
HDM SLIT-tablet	2	1768	−0.57 (−0.83, −0.31)	−16.1 ^d
Leukotriene receptor antagonist				
SAR	5	3584	−0.40 (−0.54, −0.26)	−5.4
PAR	2	3215	−0.25 (−0.39, −0.12)	−3.7
Oral antihistamine				
SAR	6	1916	−0.59 (−0.79, −0.40)	−8.5
PAR	3	2539	−0.31 (−0.49, −0.13)	−4.8
Intranasal corticosteroid				
SAR	4	958	−1.44 (−1.74, −1.15)	−22.2
PAR	4	1182	−0.58 (−0.77, −0.39)	−11.2

Data from Durham et al. [21]; compiled with permission.

HDM: house dust mite; PAR: perennial allergic rhinitis; SAR: seasonal allergic rhinitis; SLIT: sublingual immunotherapy.

^aCalculated as [(active treatment−placebo)/placebo] × 100%.

^bRelative % improvement in rhinoconjunctivitis daily rescue medication score ranged from 27% to 38% in the trials.

^cRelative % improvement in rhinoconjunctivitis daily rescue medication score was 38% and 46% in the two trials.

^dRelative % improvement in rhinitis daily rescue medication score in the 2 trials was 18% and 21%.

vs. placebo was 16.1% with a HDM SLIT-tablet, 11.2% with an INCS, 4.8% with an oral antihistamine, and 3.7% with a leukotriene receptor antagonist (Table 1). Together these data indicate that SLIT-tablets are comparable to INCS and more effective than antihistamines and leukotriene receptor antagonists in reducing seasonal AR symptoms. SLIT-tablets also appear to be more effective than pharmacotherapies for perennial AR. SLIT-tablets have the additional benefit of long-term and disease-modifying potential [73,74].

No head-to-head trials have been conducted to examine the efficacy of pharmacotherapy vs. SLIT-tablets for treatment of asthma. Two AR trials demonstrated a significant improvement in asthma symptoms as secondary/exploratory endpoints with grass SLIT-tablet treatment versus placebo [35,45]. In addition, several clinically relevant benefits for asthma have been demonstrated with HDM SLIT-tablets. In a trial of subjects with mild-to-moderate asthma controlled by ICS, 1 year of treatment with HDM SLIT-tablet resulted in an 81 mcg/day greater ICS reduction compared with placebo [44]. ICS use was reduced even more in the subgroup of patients with partially controlled asthma, with a 327 mcg/day greater ICS reduction compared with placebo [75]. A trial of up to 18 months of HDM SLIT-tablet treatment in asthmatic subjects not well controlled by ICS demonstrated a 34% reduction in the risk of moderate or severe asthma exacerbation vs. placebo (full analysis set; hazard ratio = 0.66 [95% CI, 0.47–0.93]; $P = 0.02$) [47]. Furthermore, in a trial of HDM SLIT-tablet in subjects with AR with or without asthma, up to 1 year of treatment improved asthma symptom scores by 19% vs.

placebo in the overall trial population, and by 25% in the subjects with a history of asthma [76]. Thus, HDM SLIT-tablet beneficially affects ICS use, asthma exacerbations, and asthma symptoms.

The effects on symptoms and inflammation for AR and asthma with pharmacotherapy are temporary, whereas AIT modifies the immune system, resulting in disease modification and a long-term effect [77]. Two long-term trials with SLIT-tablets have been conducted. A 5-year study with daily timothy grass SLIT-tablet demonstrated a significant beneficial effect on AR symptom scores up to 2 years after ending a 3-year treatment period [74]. This study led to an indication of timothy grass SLIT-tablet as a disease-modifying treatment in Europe, and recognition by the FDA as having a sustained effect [59]. A 5-year study with a 5-grass SLIT-tablet administered pre-and co-seasonally demonstrated a significant combined symptom/medication score compared with placebo up to 2 years after a 3-year treatment period [73], but based on EU and FDA criteria, the tablet did not receive an indication as disease modifying or recognition as having a sustained effect [59]. It is still uncertain if intermittent SLIT will lead to preventive or long-lasting effects.

5. Safety of pharmacotherapy for AR and asthma vs. SLIT-tablet

5.1. Safety of pharmacotherapy for AR

Pharmacotherapies for AR are generally well tolerated with few side effects (Table 2). The first-generation antihistamines have well-known sedating effects which have been attenuated in second- and third-generation antihistamines [78]. Oral, and to a lesser extent intranasal, decongestants can have stimulatory effects such as insomnia, nervousness, restlessness, tre-

Table 2. Common side effects for allergic rhinitis and asthma pharmacotherapies.

Pharmacotherapy	Common side effects
Allergic rhinitis	
Oral H ₁ antihistamines (second and third generation) [78]	Mild sedation, headache
Intranasal H ₁ antihistamines [78]	Bitter taste, nasal discomfort
Intranasal corticosteroids [2,81]	Draining into esophagus, epistaxis, throat irritation, nasal dryness, nasal burning
Leukotriene receptor antagonists [80,82]	Very well tolerated, no side effects with frequency greater than placebo
Oral decongestants [1,79]	Insomnia, restlessness, nervousness, palpitations, hypertension, agitation, tremor, headache, dry mucous membranes, urinary retention, exacerbation of glaucoma or thyrotoxicosis
Intranasal decongestants [1,79]	Same as oral formulations but to a lesser extent
Asthma	
Beta-agonists [82]	Headache, throat irritation, stimulatory effects including nervousness, tachycardia, and tremor
Inhaled corticosteroids [82]	Oral candidiasis, rhinitis, cough, sore throat, hoarseness, headache, upper respiratory tract infection
Leukotriene receptor antagonists	See in allergic rhinitis section above

mor, etc. [1,79]. Cardiac-related events including hypertension and palpitations can also occur [1,79]. Intranasal decongestants should be used for less than 10 days to avoid rebound congestion [1]. The leukotriene receptor antagonists appear to be very well tolerated, with no adverse events occurring at frequencies greater than that of placebo [13,80]. Of the AR pharmacotherapies, the INCS have the most notable side effects. In a large survey of patients with AR, 17% of adults and 10% of children/adolescents discontinued use of INCS because of side effects; these side effects were retrograde drainage into the esophagus, followed by bad taste, drying feeling, spray volume uncomfortable, drowsiness, burning, headache, and nose bleeds [2]. Nose bleeds are a concern with INCS use among prescribers, but the incidence is low (3–7%) and most episodes are transient and mild [81]. Systemic effects with INCS are also possible, and there is an FDA-mandated class warning on all INCS products regarding possible effects on growth velocity and the hypothalamic-pituitary-adrenal (HPA) axis function in children [79]. However, the majority of studies in children have found very little, if any, effects on HPA axis function or growth [79].

5.2. Safety of pharmacotherapy for asthma

Specific common side effects of beta-agonists are headache and throat irritation, as well as stimulatory effects including nervousness, tachycardia, and tremor [13,83]. Long-acting beta-agonists (LABAs) as monotherapy may increase the risk of asthma-related death [84], but this increased risk remains to be definitively confirmed. As a precaution, the FDA requires a class warning that LABA therapy without use of a controller medication is contraindicated in asthma, that LABAs should not be used in patients whose asthma is adequately controlled on low- or medium-dose ICS, that, if possible, LABAs should be discontinued once asthma control is achieved and maintained, and that children requiring the addition of a LABA to an ICS should use a combination product to ensure adherence to both medications [82].

The most common side effects with ICS are application site related, including oral candidiasis, rhinitis, cough, sore throat, and hoarseness [13,82]. The same class warning regarding effects on the HPA axis and growth velocity that apply to INCS apply to ICS; several studies with ICS have shown a small, but significant reduction in growth velocity vs. placebo (reviewed in Loke et al. [85]). Furthermore, ICS use is associated with an increased risk of cataract development [82].

5.3. Safety of SLIT-tablets

The most common side effects for timothy grass SLIT-tablets are mild-to-moderate oral site reactions (i.e. oral pruritus, throat irritation, ear pruritus, mucosa swelling; Table 3) [86]. The oral site reactions generally have an onset with the first dose of the SLIT-tablet and recur for less than 14 days [87]. The duration of the reactions is approximately 30–60 min [87]. Similar safety profiles to that of timothy grass SLIT-tablets have been reported for 5-grass, ragweed, and HDM SLIT-tablets [33,36,76,88]. Oral site reactions typically do not require any treatment and are more of a tolerability issue

Table 3. Common side effects for timothy grass SLIT-tablets. Treatment-related AEs in $\geq 3\%$ of adult subjects.

Treatment-related AEs, % of Patients	Adults		Children	
	Timothy grass SLIT-tablet N = 1669	Placebo N = 1645	Timothy grass SLIT-tablet N = 447	Placebo N = 434
Oral pruritus	26.7	3.5	24.4	2.1
Throat irritation	22.6	2.8	21.3	2.5
Ear pruritus	12.5	1.1	7.2	0.5
Mouth edema	11.1	0.8	9.8	0.2
Oral paresthesia	9.8	2.0	5.4	1.2
Tongue pruritus	5.7	0.5	9.2	0.9
Lip swelling	4.0	0.2	7.2	0.5
Pharyngeal edema	3.4	0.1	2.9	0
Eye pruritus	3.0	1.8	3.4	2.1

Data from the Grastek company briefing, 2014 [91].

AE: adverse event; SLIT: sublingual immunotherapy.

than a serious safety concern. However, systemic allergic reactions are possible with SLIT-tablets. To date, none of the reported systemic allergic reactions in the clinical trials associated with SLIT-tablets have been life threatening or serious. Across the clinical development program of timothy grass, ragweed, and SQ HDM SLIT-tablets, representing 8152 patients treated with approved doses, there have been 11 (0.1%) reported systemic allergic reactions (Table 4). Epinephrine was administered for SLIT-tablet-related events at a rate of 1.80 administrations per 100,000 SLIT-tablets [69]. Analysis of the post-marketing safety database (N = 112,330) for the 5-grass SLIT-tablet found 12 events considered possibly consistent with anaphylaxis for an event rate of 0.011%; epinephrine was administered for 2 of these events [89]. Prescribing information in the USA recommends that SLIT-tablets should not be prescribed to patients with a history of severe systemic allergic reaction or any severe local reaction to SLIT, although such history is not a contradiction in Europe [49,50,90].

6. Prescribing of SLIT-tablets

Tolerance induced by AIT takes several weeks to develop. The US prescribing information for the timothy grass and ragweed SLIT-tablets recommend treatment initiation at least 12 weeks before the start of the respective pollen season, whereas initiation of the 5-grass SLIT-tablet is recommended to be 4 months before the start of grass pollen season [49,50,90]. Thus, patients need to be evaluated for potential SLIT-tablet treatment months before regional pollen seasons (See supplemental Figure 1), which may be challenging as patients often do not seek treatment until symptoms appear. In contrast, HDM SLIT-tablets are initiated at any time of year and patients can expect to begin to have relief of HDM allergy symptoms within 2–3 months of starting [93]. Healthcare providers may be reluctant to start AIT during the pollen season due to concerns about an increased risk of severe or serious systemic allergic reactions. However, a recent systematic review has demonstrated that there does not appear to be an increase in adverse events of concern when AIT is initiated during the pollen season [94]. If pollen SLIT-tablets are initiated during pollen season, patients should be advised that improvement in symptoms and medication use may not be readily apparent

Table 4. Systemic allergic reactions associated with timothy grass, ragweed, or HDM SLIT-tablets.

Symptoms/signs of reaction	Intensity	Day of onset	Treatment	Discontinued trial
Timothy grass SLIT-tablets [91]				
Swelling of lips, oral itch, and dysphagia	Moderate	1	Epinephrine, cetirizine	Yes
Chest discomfort, dysphagia, dysphonia, oral pharyngeal itch, swelling and irritation, rash	Mild	1	Epinephrine, loratadine, prednisone	Yes
Oral itch, sneezing, rhinorrhea, and throat irritation	Mild	1	Epinephrine, loratadine	No
Lip swelling, dysphagia, and intermittent cough	Moderate	1	Epinephrine	Yes
Light-headedness, headache, sleepiness, ear itch	Mild	1	None	No
Light headedness, oral itch	Mild	1	None	No
Burning sensation under tongue and ear, rhinorrhea, throat irritation	Mild	2	None	No
Chest tightness, dyspnea	Moderate	42	None	Yes
Lower lip edema, redness on corners of mouth and chin, epigastric discomfort, dizziness	Moderate	2	None	Yes
Ragweed SLIT-tablets [92]				
Oral symptoms, throat swelling, dyspnea, nausea, light headedness	Severe	6	Epinephrine, diphenhydramine, prednisone, ranitidine	Yes
HDM SLIT-tablets [76]				
Itchy palms, facial flushing, dyspnea, pre-syncope, throat swelling	Moderate	1	Epinephrine, desloratadine, pseudoephedrine	Yes

HDM: house dust mite; SLIT: sublingual immunotherapy.

during the initiating season. Being able to initiate year-round regardless of seasonal exposure is particularly relevant when treating HDM allergies. Subgroup analyses of completed clinical trials have not shown a safety signal due to other allergies when treating or initiating with HDM SLIT-tablets throughout the year [95].

Many patients are sensitized to multiple allergens, which could warrant SLIT-tablet treatment for more than one allergen if relevant symptoms are present. An open-label safety trial found that simultaneous treatment with timothy grass and ragweed SLIT-tablets was well tolerated following a sequential single SLIT-tablet approach (i.e. one SLIT-tablet for 2 weeks, followed by one SLIT-tablet in the morning and the other SLIT-tablet in the evening for

2 weeks, culminating in simultaneous treatment of the SLIT-tablets) [42].

Because of the risk of severe or serious local or systemic allergic reactions, the first dose of SLIT-tablet should be administered under the supervision of a physician experienced in the diagnosis and treatment of allergic diseases, followed by at least a 30 min observation period [49,50,90]. Patients should be educated on how to recognize a systemic allergic reaction and told to seek immediate medical care if they experience a severe allergic reaction. In the USA, a prescription for an epinephrine auto-injector needs to accompany the prescription for SLIT-tablets and patients should be educated on its appropriate use.

7. Profile of a SLIT-tablet patient

Although traditionally AIT is reserved for patients with severe allergies, according to guidelines AIT should be considered for patients who are positive for specific IgE against clinically relevant allergens and who have corresponding allergic rhinoconjunctivitis symptoms [64]. Another factor that should be taken into consideration for initiating AIT is the need to improve health-related quality of life (i.e. sleep quality, work/school productivity) associated with AR symptoms. Also, patients who do not respond well to pharmacotherapy or who have troublesome side effects with pharmacotherapy may be good AIT candidates. SLIT-tablets may be particularly beneficial for children. Not only are SLIT-tablets efficacious in the pediatric population [34,35,48], but the ability of AIT to potentially reduce the risk of developing asthma and/or other allergen sensitizations is appealing [96–98]. SLIT-tablets provide the benefits of AIT without the inconvenience of time-consuming frequent office visits for children and caregivers and without the fear and discomfort of injections, both of which may deter children and their caregivers from traditional SCIT.

In the USA, AIT practice with SCIT generally consists of multiple allergens to which the patient is sensitized [99]. Thus, there was some concern that SLIT-tablets for a single allergen would not be effective in patients who were multi-sensitized. In a pooled analysis of timothy grass SLIT-tablets, the improvement in grass combined symptom/medication score was 28% in monosensitized subjects and 26% in multi-sensitized subjects [100]. Therefore, it appears the concerns regarding lack of efficacy in multisensitized patients was unwarranted.

As with any long-term treatment, adherence and persistence is key to AIT efficacy. The ability of a patient to be compliant to daily SLIT-tablet treatment should be determined before prescribing. Furthermore, the presence and severity of asthma needs to be evaluated before prescribing grass or ragweed SLIT-tablets. If asthma is present, it should be stable and well controlled. In the USA, the safety of HDM, grass, or ragweed SLIT-tablets has not been established in patients with severe, unstable, uncontrolled asthma, and the presence of such a condition is a contraindication. HDM SLIT-tablets in Europe are indicated for patients with HDM allergic asthma that is not well controlled with ICS, that is associated with

mild-to-severe HDM AR, and where the patients' asthma status has been carefully evaluated.

8. Conclusions

SLIT-tablets have favorable efficacy when compared to pharmacotherapies for AR, and HDM SLIT-tablets can provide clinically relevant benefits for asthma patients. The safety profile of SLIT-tablets is favorable; the at-home oral administration provides a safe and convenient alternative to traditional SCIT. As such, SLIT-tablets should be considered as an alternative or add-on treatment to pharmacotherapy for AR with or without conjunctivitis, and as an add-on treatment for HDM allergic asthma.

Geolocation information

North America, Europe, Japan, Australia.

Funding

This manuscript was funded by Merck.

Declaration of interest

S Brunton has served on advisory boards for Merck & Co., Inc., Kenilworth, NJ, USA and Teva, and is on the speakers bureau for Teva. HS Nelson has served on advisory boards for Merck & Co., Inc., Kenilworth, NJ, USA, and Circassia, and received grants/research support from Circassia. DI Bernstein has served on advisory boards for Merck & Co., Inc., Kenilworth, NJ, USA, and Circassia, and received grants/research support from Merck & Co., Inc., Stallergenes, and Greer, and is a member of the Immunotherapy committee for AAAAI/ACAAI. S Lawton and H Nolte are employees of ALK, Hørsholm, Denmark. S Lu is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and H. Nolte was an employee of Merck & Co., Inc., Kenilworth, NJ, USA at the time of this work. Medical writing and editorial assistance was provided by Erin P. Scott, PhD, and Benjamin Scott, PhD, of Scott Medical Communications, LLC. This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

- Bousquet J, Khaltav N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63:8–160.
- Katellaris CH, Lai CK, Rhee CS, et al. Nasal allergies in the Asian-Pacific population: results from the allergies in Asia-Pacific survey. *Am J Rhinol Allergy*. 2011;25(Suppl 1):S3–S15.
- Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of allergic rhinitis: results from the pediatric allergies in America survey. *J Allergy Clin Immunol*. 2009;124:S43–S70.
- Price D, Zhang Q, Kocevar VS, et al. Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults. *Clin Exp Allergy*. 2005;35:282–287.
- Thomas M, Kocevar VS, Zhang Q, et al. Asthma-related health care resource use among asthmatic children with and without concomitant allergic rhinitis. *Pediatrics*. 2005;115:129–134.
- Jeffery PK, Haahtela T. Allergic rhinitis and asthma: inflammation in a one-airway condition. *BMC Pulm Med*. 2006;6(Suppl 1):S5.
- Corren J, Adinoff AD, Buchmeier AD, et al. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol*. 1992;90:250–256.
- Foresi A, Pelucchi A, Gherson G, et al. Once daily intranasal fluticasone propionate (200 micrograms) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. *J Allergy Clin Immunol*. 1996;98:274–282.
- Watson WT, Becker AB, Simons FE. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. *J Allergy Clin Immunol*. 1993;91:97–101.
- Nathan RA, Yancey SW, Waitkus-Edwards K, et al. Fluticasone propionate nasal spray is superior to montelukast for allergic rhinitis while neither affects overall asthma control. *Chest*. 2005;128:1910–1920.
- Dahl R, Nielsen LP, Kips J, et al. Intranasal and inhaled fluticasone propionate for pollen-induced rhinitis and asthma. *Allergy*. 2005;60:875–881.
- Moingeon P, Mascarell L. Induction of tolerance via the sublingual route: mechanisms and applications. *Clin Dev Immunol*. 2012;2012:623474.
- National Heart, Lung, and Blood Institute Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. 2007. Available from: <http://www.nhlbi.nih.gov/guidelines/asthma/>.
- Global strategy for asthma management and prevention, Global Initiative for Asthma (GINA). 2017. Available from: <http://www.ginasthma.org/>.
- Blaiss MS, Dykewicz MS, Skoner DP, et al. Diagnosis and treatment of nasal and ocular allergies: the allergies, immunotherapy, and rhinoconjunctivitis (AIRS) surveys. *Ann Allergy Asthma Immunol*. 2014;112:322–8 e1.
- Schmitt J, Stadler E, Kuster D, et al. Medical care and treatment of allergic rhinitis: a population-based cohort study based on routine healthcare utilization data. *Allergy*. 2016;71:850–858.
- Fromer LM, Blaiss MS, Jacob-Nara JA, et al. Current Allergic Rhinitis Experiences Survey (CARES): consumers' awareness, attitudes and practices. *Allergy Asthma Proc*. 2014;35:307–315.
- Devillier P, Dreyfus JF, Demoly P, et al. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. *BMC Med*. 2014;12:71.
- Matricardi PM, Kuna P, Panetta V, et al. Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: a comparison based on meta-analyses. *J Allergy Clin Immunol*. 2011;128(791–9):e6.
- Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med*. 2004;116:338–344.
- Durham SR, Creticos PS, Nelson HS, et al. Treatment effect of sublingual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: pooled analyses. *J Allergy Clin Immunol*. 2016;138:1081–1088.
- Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? the Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med*. 2004;170:836–844.
- Simons FE, Simons KJ. Histamine and H1-antihistamines: celebrating a century of progress. *J Allergy Clin Immunol*. 2011;128:1139–50.e4.
- Phillips K, Osborne J, Lewis S, et al. Time course of action of two inhaled corticosteroids, fluticasone propionate and budesonide. *Thorax*. 2004;59:26–30.
- Nelson HS. Allergen immunotherapy: what's new, what's next? *Expert Rev Clin Immunol*. 2015;11:959–961.
- Amar SM, Harbeck RJ, Sills M, et al. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus

- combination in a multiallergen extract. *J Allergy Clin Immunol.* **2009**;124(150–6):e1–5.
27. Bush RK, Swenson C, Fahlberg B, et al. House dust mite sublingual immunotherapy: results of a US trial. *J Allergy Clin Immunol.* **2011**;127:974–81 e1–7.
 28. Creticos P, Esch R, Couroux P, et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. *J Allergy Clin Immunol.* **2013**;133:751–758.
 29. Esch RE, Bush RK, Peden D, et al. Sublingual-oral administration of standardized allergenic extracts: phase 1 safety and dosing results. *Ann Allergy Asthma Immunol.* **2008**;100:475–481.
 30. Nelson HS, Oppenheimer J, Vatsia GA, et al. A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. *J Allergy Clin Immunol.* **1993**;92:229–236.
 31. Skoner D, Gentile D, Bush R, et al. Sublingual immunotherapy in patients with allergic rhinoconjunctivitis caused by ragweed pollen. *J Allergy Clin Immunol.* **2010**;125:660–666.
 32. Swamy RS, Reshamwala N, Hunter T, et al. Epigenetic modifications and improved regulatory T-cell function in subjects undergoing dual sublingual immunotherapy. *J Allergy Clin Immunol.* **2012**;130:215–24 e7.
 33. Bergmann KC, Demoly P, Worm M, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol.* **2014**;133:1608–14.e6.
 34. Blaiss M, Maloney J, Nolte H, et al. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol.* **2011**;127:64–71 e4.
 35. Bufer A, Eberle P, Franke-Beckmann E, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol.* **2009**;123:167–73 e7.
 36. 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**;130:1327–1334.
 37. Creticos PS, Maloney J, Bernstein DI, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. *J Allergy Clin Immunol.* **2013**;131:1342–9 e6.
 38. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol.* **2006**;118:434–440.
 39. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy.* **2006**;61:185–190.
 40. 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**;120:1338–1345.
 41. Durham SR, Yang WH, Pedersen MR, et al. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol.* **2006**;117:802–809.
 42. Maloney J, Berman G, Gagnon R, et al. Sequential treatment initiation with timothy grass and ragweed sublingual immunotherapy tablets followed by simultaneous treatment is well tolerated. *J Allergy Clin Immunol Pract.* **2016**;4:301–9 e2.
 43. Maloney J, Bernstein DI, Nelson H, et al. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial. *Ann Allergy Asthma Immunol.* **2014**;112:146–53.e2.
 44. Mosbech H, Deckelmann R, de Blay F, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: A randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol.* **2014**;134:568–75.e7.
 45. Nelson HS, Nolte H, Creticos P, et al. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol.* **2011**;127:72–80 e2.
 46. Nolte H, Hebert J, Berman G, et al. Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults. *Ann Allergy Asthma Immunol.* **2013**;110:450–6 e4.
 47. Virchow JC, Backer V, Kuna P, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: a randomized clinical trial. *JAMA.* **2016**;315:1715–1725.
 48. Wahn U, Tabar A, Kuna P, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol.* **2009**;123:160–6 e3.
 49. Grastek (Timothy grass pollen allergen extract tablet for sublingual use). Full Prescribing Information, Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA, **2014**.
 50. Oralair (Sweet vernal, orchard, perennial rye, timothy, and kentucky blue grass mixed pollens allergen extract tablet for sublingual use). Full Prescribing Information, Stallergenes S.A., Antony, France, **2014**.
 51. Aasbjerg K, Backer V, Lund G, et al. Immunological comparison of allergen immunotherapy tablet treatment and subcutaneous immunotherapy against grass allergy. *Clin Exp Allergy.* **2014**;44:417–428.
 52. Khinchi MS, Poulsen LK, Carat F, et al. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy.* **2004**;59:45–53.
 53. Quirino T, Iemoli E, Siciliani E, et al. Sublingual versus injective immunotherapy in grass pollen allergic patients: a double blind (double dummy) study. *Clin Exp Allergy.* **1996**;26:1253–1261.
 54. Ventura MT, Carretta A, Tummolo RA, et al. Clinical data and inflammation parameters in patients with cypress allergy treated with sublingual swallow therapy and subcutaneous immunotherapy. *Int J Immunopathol Pharmacol.* **2009**;22:403–413.
 55. Yukselen A, Kendirli SG, Yilmaz M, et al. Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. *Int Arch Allergy Immunol.* **2012**;157:288–298.
 56. Di Bona D, Plaia A, Leto-Barone MS, et al. Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a meta-analysis-based comparison. *J Allergy Clin Immunol.* **2012**;130:1097–107 e2.
 57. Dretzke J, Meadows A, Novielli N, et al. Subcutaneous and sublingual immunotherapy for seasonal allergic rhinitis: a systematic review and indirect comparison. *J Allergy Clin Immunol.* **2013**;131:1361–1366.
 58. Nelson H, Cartier S, Allen-Ramey F, et al. Network meta-analysis shows commercialized subcutaneous and sublingual grass products have comparable efficacy. *J Allergy Clin Immunol Pract.* **2015**;3:256–66 e3.
 59. Dahl R, Roberts G, de Blic J, et al. SQ grass sublingual allergy immunotherapy tablet for disease-modifying treatment of grass pollen allergic rhinoconjunctivitis. *Allergy Asthma Proc.* **2016**;37:92–104.
 60. Bernstein DI, Epstein T, Murphy-Berendts K, et al. Surveillance of systemic reactions to subcutaneous immunotherapy injections: year 1 outcomes of the ACAAI and AAAAI collaborative study. *Ann Allergy Asthma Immunol.* **2010**;104:530–535.
 61. Epstein TG, Liss GM, Murphy-Berendts K, et al. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008–2012: an update on fatal and nonfatal systemic allergic reactions. *J Allergy Clin Immunol Pract.* **2014**;2:161–167.
 62. Epstein TG, Liss GM, Murphy-Berendts K, et al. Risk factors for fatal and nonfatal reactions to subcutaneous immunotherapy: national surveillance study on allergen immunotherapy (2008–2013). *Ann Allergy Asthma Immunol.* **2016**;116:354–9 e2.
 63. Calderon MA, Simons FE, Malling HJ, et al. Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. *Allergy.* **2012**;67:302–311.
 64. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol.* **2011**;127:S1–55.
 65. Horak F, Ziegelmayer P, Ziegelmayer 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;124:471–7, 7 e1.
66. Nolte H, Maloney J, Nelson HS, et al. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. *J Allergy Clin Immunol*. 2015;135:1494–501 e6.
 67. Wang DH, Chen L, Cheng L, et al. Fast onset of action of sublingual immunotherapy in house dust mite-induced allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial. *Laryngoscope*. 2013;123:1334–1340.
 68. Vaswani R, Garg A, Parikh L, et al. Non-adherence to subcutaneous allergen immunotherapy: inadequate health insurance coverage is the leading cause. *Ann Allergy Asthma Immunol*. 2015;115:241–243.
 69. Nolte H, Casale TB, Lockett RF, et al. Epinephrine use in clinical trials of sublingual immunotherapy tablets. *J Allergy Clin Immunol: In Practice*. 2017;5:84–89.
 70. Hankin CS, Cox L. Allergy immunotherapy: what is the evidence for cost saving? *Curr Opin Allergy Clin Immunol*. 2014;14:363–370.
 71. Leatherman B, Skoner DP, Hadley JA, et al. The Allergies, Immunotherapy, and Rhinoconjunctivitis (AIRS) survey: provider practices and beliefs about allergen immunotherapy. *Int Forum Allergy Rhinol*. 2014;4:779–788.
 72. Benninger M, Farrar JR, Blaiss M, et al. Evaluating approved medications to treat allergic rhinitis in the United States: an evidence-based review of efficacy for nasal symptoms by class. *Ann Allergy Asthma Immunol*. 2010;104:13–29.
 73. Didier A, Malling HJ, Worm M, et al. 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.
 74. Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol*. 2012;129:717–25 e5.
 75. de Blay F, Kuna P, Prieto L, et al. SQ HDM SLIT-tablet (ALK) in treatment of asthma—post hoc results from a randomised trial. *Respir Med*. 2014;108:1430–1437.
 76. Nolte H, Bernstein DI, Nelson HS, et al. Efficacy of house dust mite SLIT-tablet in North American adolescents and adults in a randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2016;138:1631–1638.
 77. Eifan AO, Shamji MH, Durham SR. Long-term clinical and immunological effects of allergen immunotherapy. *Curr Opin Allergy Clin Immunol*. 2011;11:586–593.
 78. Carson S, Lee N, Thakurta S. Drug class reviews. IN: Drug class review: newer antihistamines: final report update 2. Portland (OR): Oregon Health & Science University Portland; 2010. Oregon 97239. All rights reserved.
 79. Scadding G. Optimal management of nasal congestion caused by allergic rhinitis in children: safety and efficacy of medical treatments. *Paediatr Drugs*. 2008;10:151–162.
 80. Nayak A, Langdon RB. Montelukast in the treatment of allergic rhinitis: an evidence-based review. *Drugs*. 2007;67:887–901.
 81. Sastre J, Mosges R. Local and systemic safety of intranasal corticosteroids. *J Investig Allergol Clin Immunol*. 2012;22:1–12.
 82. Jonas DE, Wines RCM, DeMonte M, et al. drug class reviews. IN: Drug class review: controller medications for asthma: final update 1 report. Portland (OR): Oregon Health & Science University; 2011. Copyright (c) 2011 by Oregon Health & Science University.
 83. Walters EH, Gibson PG, Lasserson TJ, et al. Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. *Cochrane Database Syst Rev*. 2007;(1):CD001385.
 84. Nelson HS, Weiss ST, Bleecker ER, et al. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006;129:15–26.
 85. Loke YK, Blanco P, Thavarajah M, et al. Impact of inhaled corticosteroids on growth in children with asthma: systematic review and meta-analysis. *Plos One*. 2015;10:e0133428.
 86. Nelson HS. Oral/sublingual Phleum pretense grass tablet (Grazax/Grastek) to treat allergic rhinitis in the USA. *Expert Rev Clin Immunol*. 2014;10:1437–1451.
 87. Nelson HS, Maloney J, Calderon M, et al. Occurrence and duration of local adverse reactions is similar for the ragweed (MK-3641), grass (MK-7243), and house dust mite (MK-8237) sublingual immunotherapy tablets and consistent with an immediate IgE-mediated reaction. *Ann Allergy Asthma Immunol*. 2014;113:A7.
 88. Nolte H, Amar N, Bernstein DI, et al. Safety and tolerability of a short ragweed sublingual immunotherapy tablet. *Ann Allergy Asthma Immunol*. 2014;113:93–100 e3.
 89. Oralair: Company briefing. Available from: <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/AllergenicProductsAdvisoryCommittee/UCM377851.pdf>.
 90. Ragwitek (short ragweed pollen allergen extract tablet for sublingual use). Full Prescribing Information, Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA, 2014.
 91. Grastek: Company briefing. Available from: <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/allergenicproductsadvisorycommittee/ucm378093.pdf>, 2014.
 92. Ragwitek: Company briefing. Available from: <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/allergenicproductsadvisorycommittee/ucm382840.pdf>, 2014.
 93. ODACTRA (House dust mite allergen extract tablet for sublingual use). Full Prescribing Information, Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA, 2017.
 94. Creticos PS, Bernstein DI, Casale TB, et al. Coseasonal initiation of allergen immunotherapy: a systematic review. *J Allergy Clin Immunol Pract*. 2016;4:1194–1204.e4.
 95. Nolte H, Bernstein DI, Kleine-Tebbe J, et al. Safety of year-round initiation with SQ house dust mite sublingual immunotherapy tablet. *J Allergy Clin Immunol*. 2017;139:AB61.
 96. Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*. 2007;62:943–948.
 97. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol*. 2002;109:251–256.
 98. Novembre E, Galli E, Landi F, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2004;114:851–857.
 99. Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. *Ann Allergy Asthma Immunol*. 2009;103:451–459. quiz 9-61, 95.
 100. Nelson H, Blaiss M, Nolte H, et al. Efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet in mono- and polysensitized subjects. *Allergy*. 2013;68:252–255.

	Northeastern US	Southern US	Ontario, Canada	Japan	UK	Australia	Germany
January							
February							
March							
April		 	 				
May	 	 	 		 		 
June			 		 		
July	 		 				
August	 						
September						 	
October						 	
November							
December							



Trees



Grass



Ragweed