

EXPERT
REVIEWS

Oral/sublingual *Phleum pretense* grass tablet (Grazax/Grastek) to treat allergic rhinitis in the USA

Expert Rev. Clin. Immunol. 10(11), 1437–1451 (2014)

Harold S Nelson

National Jewish Health, 1400 Jackson St, Denver, CO 80206, USA
Tel.: +1 303 398 1562
Fax: +1 303 398 1476
nelson@njhealth.org

With the approval of two grass tablets and one ragweed tablet for sublingual immunotherapy (SLIT) by the US FDA in April 2014, the practice of allergy immunotherapy (AIT) in the USA has dramatically changed. Until this time, there were no approved allergen extracts for sublingual administration and physicians who prescribed SLIT for their patients did so without full knowledge of proper dosing or assurance of its safety. Now sublingual allergen tablets are available that have proven safe and effective doses. This article describes, in detail, the studies that have been conducted with a timothy grass SLIT tablet and draws some comparisons to the alternative 5-grass SLIT tablet. It also attempts to predict what will be the impact of the introduction of these tablets on the practice of AIT in the USA over the next few years.

KEYWORDS: AIT • allergy immunotherapy • grass immunotherapy • SCIT • SLIT • subcutaneous immunotherapy • sublingual immunotherapy

The burden of allergic rhinitis

In 1819, John Bostock, a London-based physician presented a paper describing recurrent symptoms that he had since childhood [1]. In June of each year, he would experience itching and smarting of the eyes, a fullness in the head with violent fits of sneezing, a sensation of tightness in the chest with difficulty breathing and a degree of general indisposition. These symptoms spontaneous subsided in late July, but left him with a degree of weakness and languor that persisted for 4–6 weeks longer. Because these symptoms occurred in him and others at the time of first haying, the condition became known as ‘hay fever’. At the time of Bostock’s description, the condition was quite rare, but over the 19th century it became more common in England. Later in that century, another English physician, Charles Blackley, established that the cause of this condition was not hay, but rather the pollen of grasses [1]. During the 20th century, there was a marked increase in allergic sensitization and allergic diseases in the ‘Westernized Countries’ of the world and allergic rhinitis became a common disorder [2,3].

Several questionnaire-based surveys have been conducted in the USA to assess the prevalence of allergic rhinitis and its physical and psychological impact on those who reported having this condition (TABLE 1) [2,4–6]. The prevalence in these surveys of physician-diagnosed nasal allergies with symptoms or medication use within the last year was reported to be 6.4–22%, a lower figure than that often quoted for the prevalence of allergic rhinitis and probably an underestimate of the true prevalence since many sufferers, especially those with mild symptoms, do not consult physicians for their condition [3]. Allergic rhinitis may be seasonal, perennial or both. In a 2500 adult subset of the respondents to the Allergies in America survey, 79% said that their symptoms were more frequent or occurred only during certain periods of the year; the most frequent time being in the Spring [4]. When they were asked how bothersome their symptoms were at that time, 20–40% stated that they were extremely bothered by watery eyes, repeated sneezing, itchy red eyes, rhinorrhea or nasal blockage and that their symptoms impacted their daily life

Table 1. Questionnaire surveys of allergic rhinitis in the USA.

Survey (date)	Method	Responses	Primary outcome	Results	Ref.
Burden of Rhinitis in America (2004)	Mail questionnaire to 15,000 households	66.7% response n = 19,678 individuals	Self-reported, physician-diagnosed nasal allergies Self-reported symptoms attributed to nasal allergy	With symptoms: ≥7 days/year 22% ≥30 days/year 11.9% With symptoms: ≥7 days/year 30.2% ≥30 days/year 15.7%	[2]
Allergies in America (2006)	Telephone questionnaire to 30,927 households	61,655 ≥18 years	Self-reported, physician diagnosed nasal allergies with symptoms or medication use in last year	14%	[4]
Pediatric Allergies in America (2007)	Telephone questionnaire to 35,757 households	8119 households with children 4–17 years of age	Physician diagnosed nasal allergies symptomatic within the last year	13%	[5]
National Health and Nutrition Examination Survey (2005–2006)	12,862 representative of the US population invited to participate	9950 (77%) age ≥1 year	Physician-diagnosed 'hay fever' with symptoms in last 12 months Rhinitis in past 12 months without cold or flu	6.4% 33.4%	[6]

moderately (25%) or 'a lot' (15%) [4]. When their symptoms were at their worst, they reported frequently feeling tired (44%), miserable (29%) or irritable (26%) and their symptoms interfered with their work moderately (35%) or 'a lot' (20%) [4]. Among 500 children 4–17 years of age with physician-diagnosed nasal allergy, 62% reported only seasonal symptoms and 76% indicated symptoms were worse in the Spring [5]. One-third of these children's parents reported the allergies interfered with outdoor activities. Interference with sleep [5,7] and reduced quality of life [7] were also frequent complaints.

Treatment of allergic rhinitis

The ideal but often impractical treatment of allergic rhinitis is allergen avoidance. Most patients depend on symptomatic pharmacologic management including oral and topical antihistamines, decongestants, leukotriene antagonists and topical corticosteroids. In a minority of sufferers allergen immunotherapy is employed. When respondents in Allergies in America were queried about their use of medication for their allergic rhinitis, 41% were very satisfied with the results with over-the-counter medication, 52% were very satisfied with non-steroidal prescription medication, but only 34% were very satisfied with intranasal corticosteroids (INCS) [4]. The lower level of satisfaction with INCSs probably reflects that they were used in the more severe cases. Two meta-analyses of randomized controlled trials have assessed the effectiveness of medication for allergic rhinitis [8,9]. The effectiveness over placebo was 5% for the leukotriene antagonists, 7–9% for antihistamines and 17–26% for INCS. Compared with these results, the degree of relief of symptoms with allergy immunotherapy (AIT) is quite respectable, generally exceeding 20% for both symptoms and rescue medication use.

Allergy immunotherapy

Subcutaneous immunotherapy

AIT was introduced over 100 years ago, initially as a prophylactic treatment for 'hay fever' caused by grass pollen [10]. Subsequently, AIT was extended to treating asthma and sensitivity to hymenoptera venom and a variety of pollen, mold, dander and insect extracts were employed [1]. For most of the century since AIT was introduced, the extracts have been injected subcutaneously (SCIT), but in the last three decades, with increasing frequency, it has been administered sublingually (SLIT). SCIT has been shown to be very effective when administered in appropriate doses and for a sufficient duration [11]. Effective and less- or ineffective doses have been defined in multiple double-blind, placebo-controlled clinical trials [11]. AIT appears to modify the underlying immunologic response to the allergen administered as shown by reducing the development of new sensitivities, the incidence of asthma in patients with only allergic rhinitis and by persisting improvement for years after a successful course of AIT [11]. The downside of SCIT is that extracts are being injected to which the patient is allergic and to which they may react not only locally, but also systemically with reactions that may be severe and even fatal [12]. For this reason, SCIT with native allergens must be administered with a prolonged build-up and even when maintenance doses are reached safety concerns dictate that the injections, which may go on for several years, be administered in a medical facility [12]. For this reason, many patients who would benefit from AIT do not receive it and current efforts are directed toward altering either the extracts or the route of administration to improve the safety and convenience of AIT.

Sublingual immunotherapy

An alternative to SCIT, which offers both enhanced safety and the convenience of home administration, is to give the allergen extract sublingual [13]. A systematic search of English-language, randomized, placebo-controlled trials of SLIT, published through 22 December 2012, revealed 36 studies with 2985 participants that addressed effectiveness in allergic rhinitis or rhinoconjunctivitis [14]. Ten of these studies employed grass pollen extracts. The evidence was graded to be of moderate strength in support of SLIT treatment for improving rhinitis and conjunctivitis symptoms, decreasing medication use and improving quality of life. Transient local reactions consisting of itching in the mouth and throat and swelling of the tongue or lips are common with the commencement of SLIT, but for the most part cease to occur after a week or two. Systemic reactions rarely occur and no fatal or near-fatal reactions have been reported [13]. Because of the advantages of safety and home administration, SLIT has achieved widespread popularity among European physicians but has been used by only a few American allergists [15]. Practice patterns favoring the adoption of SLIT in Europe include the common use of only one allergen in treatment and that the final product is often provided by the extract manufacturer as a named-patient product [15]. In the USA, on the other hand, most patients receive a mixture of several non-cross-reactive allergens and this mixture is prepared in the physician's office. The greatest impediment to use of SLIT by US allergists, however, has been the lack of any allergenic products with USA FDA approval for administration other than by injection [16]. In April 2014, this situation was changed by the FDA approval of three sublingual tablets, two for grass pollen extract, a 5-grass SLIT tablet (Oralair manufactured by Stallergenes S.A. Antony, France and marketed by Greer Laboratories, Lenoir, NC, USA) and a timothy SLIT tablet (Grastek developed by ALK-Abelló, Horsholm, Denmark and marketed by Merck, Whitehouse Station, NJ, USA) and one for short ragweed (Ragwitek, developed by ALK-Abelló, Horsholm, Denmark and marketed by Merck, Whitehouse Station, NJ, USA).

Stallergenes 5-grass SLIT tablet

The Stallergenes 5-grass sublingual tablet has been extensively studied in Europe [17–19] and in one pivotal trial in the USA [20]. The tablet contains a mixture of equal proportions of five members of the Pooideae subfamily of grasses: (orchard [*Dactylis glomerata*], Kentucky blue [*Poa pratensis*], perennial rye [*Lolium perenne*], sweet vernal [*Anthoxanthum odoratum*] and timothy [*Phleum pratense*]) [17]. The 300IR tablet contains approximately 25 µg of the group 5 major allergens of these grasses [17]. A Phase II study compared 100IR, 300IR and 500IR daily dosing of the tablets initiated 4 months prior to the grass pollen season. The clinical response to 100 IR was not better than that to placebo, both 300IR and 500IR were significantly superior to placebo but the 500 IR was not superior to the 300IR. Therefore, the 300IR dose was carried forward in development [17]. In a 5-year study, the 300IR tablet was administered pre- and co-seasonally beginning either 2 or

4 months prior to the grass pollen season for a total of 3 years [18]. There was no significant difference between the 2- and 4-month pre-seasonal treatment groups. Reduction in daily combined symptoms score of the two groups combined was 18.6% the first year, 38.2% the second year and 39.6% the third year, with no significant difference between 2 and 4 months of pre-seasonal treatment [19]. The persisting effect on symptoms and medication use in the two seasons after discontinuation of SLIT was documented. The first year the daily combined score was reduced 28.2% again with no advantage for the 4-month over the 2-month pretreatment [19]. In those subjects who continued under observation for a second year of post-treatment follow-up, the reduction in daily combined score was again 28.2% and again with no difference between 2 and 4 months of pretreatment [19]. A single study was conducted in the USA to obtain registration for the product; it demonstrated a 28.2% reduction in the daily combined symptom/medication score [20].

Comparison of ALK-Abelló & Stallergenes grass SLIT tablets

There are important differences between the two SLIT grass tablets approved by the FDA. One is the number of grass pollen extracts contained in the tablet, another is the design of the studies used to establish the long-term safety and efficacy of the products and a third is the use or non-use of an initial build-up in dosing.

Cross-reactivity of grasses

The important grasses of the USA fall into three subfamilies of the grass family Poaceae: Pooideae containing the highly cross-reactive Northern Pasture grasses such as brome, meadow fescue, ryegrass, Kentucky blue, timothy, orchard, sweet vernal, velvet and the cereal grains; Chloridoideae represented mainly by Bermuda grass and Panicoideae represented largely by Johnson and Bahia grasses (TABLE 2) [21]. The prevalence of positive skin tests to 10 common allergens was assessed in a representative sample of the US population, 6–59 years of age, in the third National Health and Nutrition Examination Survey. Forty percent of the population was found to be skin prick test positive to at least one of the six outdoor allergens. This included 18.1% who reacted to Bermuda grass extract and 26.9% who reacted to the representative Northern Pasture grass, perennial rye [22].

Since the five grasses included in the Stallergenes tablet are all in the subfamily Pooideae both it and the timothy SLIT tablet will not completely cover the allergenicity of the Bermuda, Johnson and Bahia grasses. The relevant question is whether the cross-reactivity of timothy with the other members of the subfamily provides protection equal to that achieved using five different grasses. There is a long tradition of using timothy pollen as a representative for the other members of this subfamily. Noon [10] in the initial study of AIT studied several members of the subfamily, found all to elicit reactions in sensitive patients, but found timothy to yield the most active extract and used it exclusively for his immunotherapy trials.

Table 2. Botanical classification of some members of the grass family – Poaceae.

Subfamily	Tribe	Genus species	Common name
Pooideae	Poeae	<i>Poa pratensis</i>	June/Kentucky blue
		<i>Festuca pratensis</i>	Meadow fescue
		<i>Lolium perenne</i>	Perennial rye
		<i>Dactylis glomerata</i>	Orchard
		<i>Anthoxanthum odoratum</i>	Sweet vernal
	Phalarideae	<i>Anthoxanthum odoratum</i>	Sweet vernal
	Agrostideae	<i>Agrostis alba</i>	Red top
Panicoideae	Paniceae	<i>Phleum pratense</i>	Timothy
		<i>Paspalum notatum</i>	Bahia
		<i>Sorghum halepense</i>	Johnson
Chloridoideae	Chlorideae	<i>Cynodon dactylon</i>	Bermuda

Modified from [21].

The members of the Pooideae subfamily have two predominant allergens, group 1 and group 5. Across the Pooideae, there is 90% sequence homology for group 1 allergens and 55–80% for group 5 allergens [23]. Sensitivity to group 1 allergens is demonstrable in 95% of Pooideae-sensitized patients, while sensitivity to group 5 allergens is demonstrable in 65–85% in various studies [24]. Together the IgE directed toward these two allergens comprises 60–80% of all the Pooideae-specific IgE in groups of sensitized patients [24]. However, sequence analysis is not sufficient to predict the degree of immunologic cross-reactivity [24], which has been addressed at the B-cell level by IgE-inhibition studies and at the T-cell level by stimulation studies.

A radioallergosorbent inhibition study was conducted in the USA examining cross-allergenicity among grasses from the three subfamilies of the family Poaceae [25]. In this study, timothy extract inhibited reactions to June, meadow fescue, red top and rye as much as to timothy, but slightly less for sweet vernal. Bermuda appeared to be allergenically distinct from the Northern Pasture grasses, while Johnson and Bahia grasses showed both shared and unique allergenicity. A 5000-fold excess of timothy pollen extract completely inhibited binding of IgE to four different grass pollen mixes, each containing 5–10 different Pooideae grass pollen extracts [26]. The ability to inhibit radioallergosorbent reactions to group 1 and 5 allergens of the five grasses in the Stallergenes tablet by either the individual grass extract or the mixture of the five extracts was tested in the sera of a number of European and the US patients [23]. Two patterns emerged: 62 and 15% of sera had IgEs directed toward group 1 and group 5 allergens of the five species, respectively that could be completely blocked by the individual extracts as well as by the 5-grass mixture. The remaining sera had IgEs against group 1 or 5 allergens that were not totally blocked by at least one of the individual extracts. Failure of complete blocking by timothy extract against the group 1 allergens of the four other Pooideae species occurred in serum from some patients.

Since the response to immunotherapy is thought to be largely a T-cell response, cross-reactivity in T-cell stimulation studies may be most relevant in assessing the effectiveness of timothy monotherapy versus a grass-mixture for AIT. Peripheral blood mononuclear cells from eight grass-allergic subjects were cultured with the group 1 and group 5 allergens of the five grasses used in the Stallergenes tablet [23]. All of the patients' peripheral blood mononuclear cells responded to between 3 and 9 of the 10 allergens. In three of the eight patients, there was no response to Phl p 1 and in two of the eight no response to Phl p 5. T-cell epitopes were derived from timothy, Kentucky, orchard, rye, velvet, barley and canary grasses and cross-reactivity of CD4⁺ T cells was determined for these epitopes [27]. The investigators

found some T-cell epitopes from the other Pooideae species that were minimally cross-reactive with group 1 and group 5 timothy allergens. Further, they demonstrated that the frequency in the blood of allergic patients of T cells recognizing these minimally cross-reactive epitopes was similar to the frequency recognizing the timothy-derived epitopes and, furthermore, the minimally cross-reactive epitopes were of Th2-phenotype and were activated during the pollen season.

Another way to assess cross-reactivity within the Northern Pasture grasses is to examine the response to immunotherapy. The potential effectiveness of timothy monotherapy for treating grass pollen-induced allergic rhinitis was demonstrated by the study of Varney *et al.* [28]. Forty English subjects with severe grass pollen-induced allergic rhinitis, uncontrolled by symptomatic medication, underwent a single pre- and co-seasonal course of AIT with timothy pollen extract. Compared with those treated with placebo, the active treatment group experienced a 61% reduction in median symptoms and a 79% reduction in median rescue medication use during the grass pollen season. Sixty Norwegian adults with allergic rhinitis caused by grass pollen were treated for 3 years with a partially purified timothy extract, a crude timothy extract or a mixture of orchard, meadow fescue, ryegrass and June grass [29]. Attempts were made to administer biologically equivalent amounts of each treatment. At the end of 3 years, the reduction in symptoms with the purified timothy was significantly superior to that with the 4-grass mix and the reduction in medication use with the purified timothy was significantly superior to results with both the crude timothy and the 4-grass extracts.

A reflection of the generation of Treg in response to AIT is the specific IgG4 response. Sera of 29 subjects who received 28 days of timothy SLIT tablet based AIT and 20 subjects who had received SCIT for 1–3 years with timothy pollen extract were tested for IgG4 antibody levels against extracts of timothy and 9 other members of the subfamily Pooideae [26].

The Spearman rank correlation coefficients between levels of IgG4 measured for timothy and for the other individual grasses varied from 0.92 to 0.98 and for four mixes of 5–10 members of the Pooideae subfamily the rank coefficient was 0.99. In another study, SCIT for a few months with timothy pollen extract increased timothy-specific IgG4 by 3.6-fold and to a mixture of five Pooideae grasses by 5.8-fold [30]. In the same study, the late cutaneous reaction to timothy was reduced by 56%, while that to the 5-grass mix was reduced by 54%.

In summary, studies examining the sequence homology, specific IgE inhibition and T-cell stimulation indicate incomplete cross-allergenicity of timothy with other members of the Pooideae subfamily. On the other hand, in AIT studies timothy monotherapy appears to provide similar effectiveness to AIT with grass-mixes.

Long-term studies

Most of the trials with the timothy SLIT tablet and the 5-grass SLIT tablet were single grass pollen season studies in which treatment was initiated 8–16 weeks prior to the onset of the pollen season. When Stallergenes conducted a 3-year treatment, 2-year follow-up study they continued the same pattern, initiating treatment either 2 or 4 months before the season, continuing treatment through the season, then stopping until the next year [18]. ALK-Abello', on the other hand, in their 3-year treatment study with the timothy SLIT tablet continued treatment without interruption for the 3 years [31]. Using the two different regimens both tablets produced significant clinical improvement that persisted for the 2 years of post-treatment follow-up.

Initiation of treatment

An initial build-up to the maintenance dose is required with SCIT due to the potential for severe systemic reactions. With the introduction of SLIT, this practice continued, although often the period of build-up was markedly truncated. In the development of the timothy SLIT tablet, it was decided that it was safe to forego the build-up in dose and initiate treatment with the maintenance dose tablet. In the development of the 5-grass SLIT tablet, on the other hand, a short build-up of dosing was employed and this continues with the approved product, which has a day 1 dose of 100 IR, a day 2 dose of 200 IR and on day 3 and onward a dose of 300 IR [19].

Introduction to the drug

The timothy SLIT tablet (Grastek) rapidly dissolves after placement under the tongue. It contains the same timothy pollen extract that has been provided for many years by ALK-Abello' for subcutaneous injection. This timothy extract is of standardized quality (SQ) and contains approximately 20 µg of the major allergen of timothy, Phl p 5, per 100,000 SQ units. The approved tablet contains 75,000 SQ or 2800 FDA bioequivalent allergen units (BAU) with approximately 15 µg of the major allergen Phl p 5 [32]. Non-active components of the tablets include fish gelatin, mannitol and sodium hydroxide. The timothy SLIT tablet was approved in April 2014 by the FDA

for treatment of allergic rhinitis with or without conjunctivitis in patients 5–65 years of age [32]. Treatment is to be initiated at least 12 weeks prior to the onset of each grass pollen season. To obtain sustained effectiveness for one grass pollen season after cessation of treatment timothy, SLIT tablets may be taken daily for 3 years [32].

Pharmacokinetics & pharmacodynamics of the sublingual route

Studies of the fate of sublingually placed allergens were performed with radiolabeled major allergens of *Parietaria* and *Dermatophagoides pteronyssinus* [33]. The protein solutions were held under the tongue for several minutes, and then swallowed. There was no evidence of radioactivity in the blood until after the solution was swallowed. There was evidence of persistence of the allergen sublingually for several hours. Studies have revealed that the allergens cross the oral mucosa within 15–30 min and are taken up by antigen-presenting cells, predominantly Langerhans cells and myeloid dendritic cells [34]. These antigen-presenting cells migrate to draining cervical lymph nodes where they present allergen-derived peptides to naïve T cells resulting in the induction of IFN-γ and IL-10-producing Treg. A prospective 1-year study of the immunologic response in patients receiving SLIT revealed an early Treg response that waned and was replaced by an allergen-specific shift from Th2- to Th1-predominant cytokine expression [35].

Pre-clinical studies

Pre-clinical studies performed in animals included: single-dose sublingual and intravenous studies in mice, multiple-dose sublingual toxicology studies in mice up to 6 months and in dogs up to 12 months in duration, genetic toxicology studies and sublingual reproductive toxicology studies in mice [36].

Clinical efficacy

Three Phase I studies were conducted in adults [37–39] and two in children (TABLE 3) [40]. The adult studies were dose-escalation in design, with the next higher dose not initiated until there was preliminary safety data on the lower dose. In general, a broad range of doses were tolerated without severe systemic reactions, but there was a clear pattern of increasing frequency and duration of treatment-related adverse reactions (TRAEs) with increasing dosing, resulting in a decision to go forward with 75,000 SQ as the maximum dose [36].

Phase II studies

One large Phase II dose-finding study was conducted in Europe and Canada [41]. A total of 855 adult subjects with grass season rhinoconjunctivitis, confirmed by positive prick skin test and *in vitro* test for timothy, and without confounding allergies or significant asthma outside the grass pollen season received either placebo, or 2500, 25,000 or 75,000 SQ timothy SLIT tablets. The two lowest doses of timothy SLIT tablet did not provide significant improvement versus placebo. For all subjects, the 75,000 SQ dose reduced mean symptom

Table 3. Phase I studies with the timothy sublingual immunotherapy tablet.

Study (year), study number	Subjects	Doses	Results	Ref.
Malling <i>et al.</i> (2006) GT-01	n = 52 18–65 years Moderate-to-severe grass ARC	Single dose escalation: 2500; 25,000; 75,000; 125,000; 375,000 SQ Pre-seasonal 8 weeks: 2500; 25,000; 75,000 SQ Pre- and co-seasonal: 2500; 25,000; 75,000 SQ	Two episodes, one moderate one severe of throat constriction with 375,000 SQ single dose so study continued with 75,000 SQ as top dose	[37]
Kleine-Tebbe <i>et al.</i> (2006) GT-03	n = 94 18–65 years Grass ARC	Dose escalation, 28 days treatment: 25,000; 75,000; 150,000; 300,000; 500,000; 750,000; 1,000,000 SQ	TRAEs increased with doses. One or more TRAEs recurred for entire 28 days with 150,000 to 500,000 SQ. Conjunctivitis and eye itching with 750,000 and 1,000,000 SQ	[38]
Calderon <i>et al.</i> (2006) GT-04	n = 43 18–65 years Grass ARC and asthma	Dose escalation, 28 days treatment: 75,000; 150,000; 300,000; 500,000 SQ	TRAEs progressively more frequent and persistent with increasing dose. Mean recurrence of oral pruritus 6.3 days with 75,000 and 18.6 days with 500,000 SQ	[39]
Ibanez <i>et al.</i> (2007) GT-09, GT-11	n = 60 5–12 years grass ARC	75,000 SQ daily for 28 days outside the grass pollen season	Two active treatment subjects withdrew due to multiple TRAEs in one and severe asthma attack 16 h after dosing on day 17	[40]

ARC: Allergic rhinoconjunctivitis; SQ: Standardized quality; TRAE: Treatment-related adverse reactions.

scores by 16% and medication scores by 28%. When only patients who initiated treatment per protocol, that is, at least 8 weeks prior to the grass pollen season were considered the improvement in symptoms was 21% ($p = 0.002$) and medication use 29% ($p = 0.012$). Efficacy of the 75,000 SQ dose was supported by significant improvement in the Rhinoconjunctivitis Quality of Life Questionnaire scores, number of well days and specific IgG and blocking antibody activity. All three doses were well tolerated with adverse events mainly located within the mouth or throat, of mild or moderate intensity and on average recurring for about 1 week in the 75,000 SQ group.

Phase III studies

The 75,000 SQ strength was the only effective dose in the GT-02 dose ranging study that compared 2500, 25,000 and 75,000 SQ doses. The 75,000 SQ dose was then assessed for safety and efficacy in children in GT-09 and GT-11 and proved to have no safety concerns [36]. Safety data from GT-01, GT-02, GT-03 and GT-04 indicated that the 75,000 SQ dose was the highest that was well tolerated; subjects receiving 75,000 SQ had only mild TRAEs, whereas more than 20% of those receiving 150,000–750,000 SQ doses experienced moderate TRAEs [36]. Based on efficacy and safety, the 75,000 SQ (2800 BAU) strength of the timothy SLIT tablet was selected for Phase III studies.

Six Phase III randomized, double-blind, placebo-controlled studies were conducted with the 75,000 SQ tablet in a total of 3094 evaluable subjects (TABLE 4, FIGURE 1) [42–47]. Three studies were in adults [42–44], two in children and adolescents [45,46] and one included both age groups [47]. Two studies were conducted in Europe [42,46], one in the USA [43] and three in the USA and

Canada [44,45,47]. The inclusion criteria for these studies were similar. Subjects were required to have a history of allergic rhinoconjunctivitis during the grass pollen season with no confounding allergies. Confirmation of sensitivity to timothy was required by both prick skin testing and a class II *in vitro* test (≥ 0.7 kU/l). Asthma was allowed, but could not be severe and at enrollment an FEV1 $\geq 70\%$ predicted was required. The primary outcomes in the European studies were the daily rhinoconjunctivitis symptom score (DSS) and the daily rhinoconjunctivitis medication score (DMS), while in the North American studies the primary outcome was the total combined score over the entire grass pollen season, calculated as the addition of the DMS and DSS. The DSS was based on grading 0–3 (no symptoms to severe symptoms) of 6 symptoms: runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes and watery eyes. DMS was based on a score of 6 points for desloratadine 5 mg or loratadine 10 mg once daily, 1 point for each spray of budesonide nasal spray and 1.6 points for each 5 mg prednisone tablet. Except in GT-08, eye drops (levocabastine in GT-12 and olopatadine in North American studies) were also allowed at 1.5 points per drop. Asthma medication was allowed, when needed, but not included in the DMS.

The first study in Europe confirmed the safety and efficacy of the 75,000 SQ tablets that had been reported in the Phase II study. The first North American study, on the other hand, failed to meet its primary outcome [43]. The reasons for this are not clear; however, the subjects in this study had high levels of symptoms at the beginning of the grass pollen season suggesting that symptom scores were in part driven by factors other than grass pollen exposure. The pooled data from the six studies, including GT-14 that did not meet its primary

Table 4. Phase III studies with timothy sublingual immunotherapy tablet.

Study	Location	Evaluable subjects	Duration	Outcomes	Ref.
GT-08 (1st year)	Europe	n = 568, ARC 18–65 years	≥16 weeks pre- and co-seasonal	ARC symptom score ↓ 30% ($p < 0.0001$) RC medication score ↓ 38% ($p < 0.0001$) Entire grass pollen season	[42]
GT-14	USA	n = 289 ARC 18–65 years	8–16 weeks pre- and co-seasonal	TCS ↓ 14% N.S. DSS ↓ 6% N.S. DMS ↓ 27%, N.S. Entire grass pollen season	[43]
PO5238	North America	n = 391 ARC 18–65 years	16 weeks pre- and co-seasonal	TCS ↓ 20% ($p = 0.005$) DSS ↓ 18% DMS ↓ 26% Entire grass pollen season	[44]
PO5239	North America	n = 307 ARC 5–17 years	16 weeks pre- and co-seasonal	TCS ↓ 26% ($p = 0.001$) DSS ↓ 26%, DMS ↓ 81% Entire grass pollen season	[45]
GT-12	Germany	n = 238 ARC 5–16 years	8–23 weeks pre- and co-seasonal	DSS ↓ 24% DMS ↓ 34% Asthma SS ↓ 64% Entire grass pollen season	[46]
PO8067	North America	n = 1301 ARC 5–65 years	16 weeks pre- and co-seasonal	TCS ↓ 23% ($p < 0.001$) DSS ↓ 20% DMS ↓ 35% Entire grass pollen season	[47]

ARC: Allergic rhinoconjunctivitis; DMS: Daily rhinoconjunctivitis medication score; DSS: Daily rhinoconjunctivitis symptom score; TCS: Total combined score.

outcome are provided in TABLE 5. It is evident that the timothy SLIT tablets were equally effective when assessed for the entire grass pollen season or only the peak weeks.

Other outcomes that were assessed during some or all of the Phase III trials included asthma symptom/medication scores, the Rhinitis Quality of Life Questionnaire, Phl p 5-specific immunoglobulin G, subclass 4 and functionally measured IgE blocking factor [36]. Although only a minority of subjects in each study had asthma and asthma symptom scores were low, there were significantly lower asthma symptom scores during the grass pollen season in PO5238 (21%) and GT-12 (64%) in the groups receiving active treatment. Rhinitis Quality of Life Questionnaire was assessed in all Phase III trials except GT-12, the German pediatric study. Except for the failed North American trial (GT-14), there was a consistent and statistically significant improvement of 12–26% in the active treatment group compared with placebo.

Long-term extension of GT-08

After the initiation of GT-08, it was decided to extend the study to include 3 years of continuous treatment and 2 years of follow-up after completion of treatment. Only 351 participants enrolled in the extension and 241 completed the 5-year study. The efficacy results for the 5 years are presented in TABLE 6. Although the FDA only accepted the first year of

follow-up as meeting their criteria of efficacy, the results for the second year were clinically and statistically significant [36].

Additional analyses of the Phase III studies

In the analysis of the extended GT-08 study, it was noted that grass pollen seasons varied considerably in their pollen counts over the 5 years. This led to an analysis of the relationship between grass pollen counts over the first 20 days of the grass

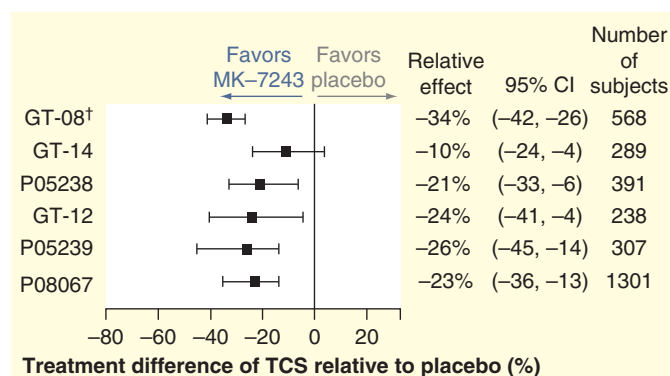


Figure 1. Analysis of total combined scores or the entire grass pollen season across all Phase III trials.

†Year one data.

Reprinted with permission from [36].

Table 5. Pooled analysis results for the entire and peak grass pollen season total combined score, daily rhinoconjunctivitis symptom score and daily rhinoconjunctivitis medication score in six Phase III trials of timothy sublingual immunotherapy tablet.

Endpoint	Timothy SLIT tablet value (number of subjects)	Placebo value (number of subjects)	Difference active versus placebo (%)	95% CI	p-value
Entire grass	Pollen season				
TCS	5.19 (1500)	6.47 (1594)	-19.8	(-24.1, -15.5)	<0.001
DSS	3.74	4.50	-16.8	(-21.0, -12.5)	<0.001
DMS	1.45	1.97	-26.7	(-34.4, -18.6)	<0.001
Peak grass	Pollen season				
TCS	6.04 (1482)	7.71 (1562)	-21.6	(-26.0, -17.1)	<0.001
DSS	4.25	5.20	-18.2	(-22.3, -14.0)	<0.001
DMS	1.79	2.51	-28.6	(-36.3, -20.4)	<0.001

DMS: Daily rhinoconjunctivitis medication score; DSS: Daily rhinoconjunctivitis symptom score; SLIT: Sublingual immunotherapy; TCS: Total combined score.
Adapted with permission from [36].

pollen season and total combined scores in six trials with timothy SLIT tablet [48]. It was found that the treatment effect was highly dependent on pollen exposure with the magnitude of improvement being greater with higher pollen exposure.

In three studies with 480 subjects receiving the 75,000 SQ timothy SLIT tablet treatment was initiated 4–35 weeks prior to the grass pollen season. A significant reduction in average daily rhinoconjunctivitis symptom and medication scores during the grass pollen season was observed with pre-seasonal treatment of at least 8 weeks and the effect increased with increasing length of pre-seasonal treatment ($p < 0.00001$) [49].

Pooled data from six randomized, double-blind, placebo controlled trials was used to compare the efficacy and safety of treatment with timothy SLIT tablets in mono- and polysensitized subjects [50]. Eighty percent of subjects in the studies were

polysensitized. There was no difference in the response to treatment between the two groups.

Potential unblinding from local application site reactions

Due to the high frequency of adverse events in the mouth and pharynx during the first weeks of therapy with timothy SLIT tablets, it is possible that many patients receiving active drug will be unblinded. This could result in a greater therapeutic effect being reported by actively treated patients with, as opposed to those without, local side effects. In actuality, adult subjects receiving timothy SLIT tablets and experiencing application site reactions ($n = 619$) had somewhat higher mean combined scores for the entire grass pollen season than those who did not ($n = 492$) [36].

Table 6. Rhinoconjunctivitis symptom scores, medication scores and quality of life during five grass pollen seasons.

	GT-08 first year	Season 2	Season 3	Follow-up season 1	Follow-up season 2
N (timothy SLIT)	282	172	160	142	137
N (placebo)	286	144	127	115	104
RC symptom score					
Difference in means	31%	36%	29%	26%	25%
p-value	<0.0001	<0.0001	<0.001	<0.001	0.004
RC medication score					
Difference in means	38%	45%	40%	29%	20%
p-value	<0.0001	<0.0001	<0.001	0.022	0.114
Mean rhinitis quality of life questionnaire season peak					
Difference in means	25%	29%	32%	28%	26%
p-value	<0.0001	0.0003	<0.0001	0.0011	0.0047

Adapted with permission from [31].

Table 7. Incidence of treatment-related adverse reactions in Phase II and Phase III studies.

Subjects with at least one AE	Adult		Pediatric	
	<i>Timothy SLIT tablet</i> <i>n</i> = 1669	<i>Placebo</i> <i>n</i> = 1645	<i>Timothy SLIT tablet</i> <i>n</i> = 447	<i>Placebo</i> <i>n</i> = 434
Treatment-related AE	1111 (67%)	389 (24%)	260 (58%)	104 (24%)
Treatment-related serious AE	0	1 (0.1%)	0	0
Discontinued due to treatment-related AE	81 (5%)	15 (1%)	28 (6%)	3 (1%)

AE: Adverse event; SLIT: Sublingual immunotherapy.
Adapted with permission from [36].

Safety

Sublingual immunotherapy is associated with a high incidence of recurring oropharyngeal symptoms with initiation of treatment. Each episode lasts a few minutes to a few hours and they usually cease to occur after an average duration of about 1 week [36]. Systemic reactions are uncommon, a few episodes of anaphylaxis have been reported but fatal or near-fatal reactions have not been reported to date [34]. SLIT is considered sufficiently safe for it to be administered by the patient at home [32]. As a safeguard, the first dose is administered under medical supervision. In addition in the USA, by FDA mandate, the patients are provided with and instructed in the use of an epinephrine auto-injector to be used in the event of a systemic reaction to the home-administered tablet [32].

In the Phase II and III development of the 75,000 SQ timothy tablet, 1669 adults and 447 children and adolescents received active treatment [36]. The occurrence of treatment-related adverse reactions is given in TABLE 7 and the AEs that were reported by $\geq 2\%$ in one or more treatment groups are given in TABLE 8.

In the Phase II and III studies, a total of eight subjects reported nine systemic allergic reactions; none was considered serious and there were no cases of anaphylactic shock [36]. Six occurred with the first administration of the tablet, two occurred on the second day, one of these in a patient who had had a reaction with the first dose and one occurred on day 42. Five were not treated while epinephrine was administered in four cases TABLE 9 [36].

A study was conducted, primarily to assess safety, in 114 subjects with mild-to-moderate grass pollen-induced asthma as

Table 8. Treatment-related adverse reactions reported by $>2\%$ in one or more treatment groups.

Treatment-related AE	Adult		Pediatric	
	<i>Timothy SLIT tablet</i> <i>n</i> = 1669	<i>Placebo</i> <i>n</i> = 1645	<i>Timothy SLIT tablet</i> <i>n</i> = 447	<i>Placebo</i> <i>n</i> = 434
	<i>Percent reporting</i>	<i>Percent reporting</i>	<i>Percent reporting</i>	<i>Percent reporting</i>
Ear pruritus	12.5	1.1	7.2	0.5
Eye pruritus	3.0	1.8	3.4	2.1
Lip swelling	4.0	0.2	7.2	0.5
Lip pruritus	2.3	0.4	2.9	0.2
Oral pruritus	26.7	3.5	24.4	2.1
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
Tongue swelling	2.8	0.1	2.5	0
Dyspepsia	2.3	0.1	2.0	0
Throat irritation	22.6	2.8	21.3	2.5
Pharyngeal edema	3.4	0.1	2.9	0
Oropharyngeal pain	1.6	1.0	4.0	1.4
Dry throat	1.7	0.4	2.7	0.5

AE: Adverse event; SLIT: Sublingual immunotherapy.
Adapted with permission from [36].

Table 9. Symptoms experienced in four patients receiving epinephrine for systemic symptoms.

Symptoms/signs of reaction	Intensity	Day of occurrence	Treatment
Swelling of lips, oral itching, dysphagia	Moderate	1	Cetirizine, epinephrine
Chest discomfort, dysphagia, dysphonia, oral/pharyngeal itching, swelling and irritation, rash	Mild	1	Loratadine, epinephrine, prednisone
Oral itching, sneezing, rhinorrhea and throat irritation	Mild	1	Loratadine, epinephrine
Lip swelling, dysphagia and intermittent cough	Moderate	1	Epinephrine

Adapted with permission from [36].

well as rhinoconjunctivitis [51]. There were no significant differences between the treatment groups for asthma symptom or medication scores and no evidence of asthma deterioration with the active treatment.

Two studies have examined the safety of introducing treatment with timothy SLIT tablet during the grass pollen season [52,53]. In the first study, 219 subjects received timothy SLIT tablets and 57 placebo beginning during the grass pollen season and continuing for 8–10 weeks [52]. Treatment-related AEs were reported by 58% of the active and 40% of the placebo, but none was serious. Three percent of the active and 2% of the placebo groups were withdrawn due to AEs. In an open-label, observational study 620 patients who began treatment during the grass pollen season were compared with 42 who began treatment after the season [53]. Adverse reactions occurred with the first dose in 34.7% of those beginning seasonally and 50.0% beginning post-seasonally. Reactions led to discontinuation of treatment in 7.4 and 11.9%, respectively. However, there were two serious TRAEs in the in-season group: an episode of nausea, diarrhea, vomiting, stomach pain, hypotension and fainting 5 h after the first dose, symptoms clearing without treatment in 2 h; and asthma, swollen lips and tongue, and loss of voice on the fifth day, clearing in 2 h following treatment with antihistamines, corticosteroids and a β -adrenergic agonist.

In the 3-year extension of GT-08, in which timothy SLIT tablets were administered daily throughout the year, most TRAEs occurred early in the course of treatment [31]. In a 3-year open-label, observational trial conducted in France, treatment was initiated at least 4 months before the grass pollen season each year and continued through the pollen season, but was then discontinued after on average 5.5 months of treatment each year [54]. Adverse reactions with administration of the first tablet were recorded each year. Reactions that were 'easily tolerated' occurred in 54.6, 38.4 and 33.6% in the three consecutive years. Reactions lasting >30 min, requiring symptomatic medication or leading to study discontinuation occurred in 2.2% the first year, 0.3% the second year and were not experienced with initiation the third year.

Safety of timothy SLIT tablet versus SCIT

A large placebo-controlled trial of timothy SCIT was conducted in the UK [55]. The timothy grass extract was from the same source as that used in manufacturing timothy SLIT tablets and the higher of two maintenance doses was similar (100,000 SQ units). Among the participants receiving the higher dose, early

grade 2 systemic reactions occurred in 17.2% and grade 3 in 4.4%. This compared with 7.8% grade 2 and no grade 3 reactions in the placebo group. Furthermore, the occurrence of fatal systemic reactions with SCIT is well documented [56]. To date, none has been reported with SLIT [57]. Thus, the greater safety of SLIT over SCIT is well documented.

While the timothy SLIT tablet is clearly safer than the same extract delivered by injection, caution is indicated in administering timothy SLIT tablets to patients who have had systemic reactions to grass SCIT. Two patients in the Netherlands who had systemic reactions to grass SCIT experienced anaphylactic reactions immediately following the first administration of the timothy SLIT tablet [58].

Regulatory history

The timothy SLIT tablet marketed in Europe by ALK-Abello' under the proprietary name Grazax received its first approval in 2006 [36]. As of December 2013, it was marketed in 20 countries. The same timothy SLIT tablet marketed by Merck under the proprietary name Grastek received FDA approval for the US marketing in April 2014 [32].

Post-marketing surveillance studies

Post-marketing safety data are derived from 24 observational/non-interventional surveillance studies and pharmacovigilance data from use of the timothy SLIT tablet in the European market [36]. The observational/non-interventional studies provide data on roughly 8500 subjects. The type and frequency of TRAEs were consistent with those observed in the randomized trials. Serious local reactions occurred in nine patients. There were six systemic allergic reactions considered by the physician to be serious, but no episodes of anaphylactic shock. There were 20 serious asthma events, none associated with respiratory compromise. These three types of reactions occurred in a total of 27 subjects (0.32%).

Pharmacovigilance depends on spontaneous reporting and hence is not useful to estimate incidence. However, as of 30 April 2013, 37 serious systemic reactions but no deaths had been reported [36]. In 70% of patients, the systemic allergic reaction occurred on the first day of exposure to the timothy SLIT tablet and all but two occurred within the first month of treatment. One episode of anaphylactic shock was reported. It occurred within 2 min of first exposure and responded promptly to administration of epinephrine and corticosteroids. An additional seven patients received epinephrine due to

hypotension not classified as 'shock' and six were hospitalized for observation. Asthma episodes were reported in most of the other 72 reported serious adverse events. None required assisted ventilation or intubation.

Cost-effectiveness

Three studies of cost-effectiveness of the timothy SLIT tablets have been reported [59–61]. The first two of these studies employed data from the first year of GT-08, the second study concentrating on those subjects who also had asthma. The approach was a societal perspective, including both the direct healthcare costs and the indirect costs (productivity) [59]. The analysis was limited for reasons of homogeneity to 493 subjects from the UK, Germany, the Netherlands, Sweden and Denmark. Data were derived from the study except for physician visits in the placebo group, which were derived from the literature. The results were projected for 9 years on the assumption that 3 years of SLIT would be followed by 6 years of remission of symptoms. Subjects receiving active treatment were projected to gain 0.222 additional quality-adjusted life years (QALYs) over the 9 years. The active treatment group also had less physician visits, medication use and productivity loss. The calculated cost, in Euros, per QALY varied from 12,930 to 18,263 in the seven Northern European countries, which is well within the UK guidelines that a cost <29,000 Euros per QALY is considered cost-effective. The second study examined 151 subjects in the same study who also had asthma [60]. Methods were similar to the first study, except reduced productivity was estimated from the literature. In this analysis, the gain in QALY over the 9 years was estimated to be 0.197 at a cost per QALY of 4319 Euros. The third study used data from the GT-12 study conducted in children in Germany [61]. A model to evaluate the timothy SLIT tablet compared with placebo examined management of symptoms, impact on resource use and development of asthma, again using a 9-year perspective. The data from the study was supplemented by the number of physician visits, which was based on a European survey, the likelihood of developing asthma derived from the PAT study [62] and impact of asthma on health-related quality of life derived from the literature. In this analysis, the cost per QALY was 12,168 Euros, again, well below the UK threshold of 29,000 Euros.

Adherence

Adherence to SLIT has been reported to decline to low levels over the course of 1 or several years. A study of adherence to AIT was conducted in the Netherlands using a community pharmacy database [63]. Only 7% of patients prescribed SLIT completed a 3-year course of treatment and the median duration of adherence to treatment for SLIT was only 0.6 years. Adherence to SCIT was examined in the same study, the 3-year completion rate was 23% and the median adherence to treatment was 1.7 years. Thus, SCIT adherence was about three-times that of SLIT by either measure. There is little information on adherence that specifically relates to the timothy SLIT tablet. One study did examine adherence by 261 European subjects to the tablet over the course of a year, comparing

adherence with and without an electronic compliance device container with a programmable acoustic alarm [64]. Subjects returned to the clinic to record adherence after 2, 24 and 48 weeks. Excellent compliance, defined as $\geq 90\%$ was recorded by 79% using the device and 78% not using the device.

Future directions

A multinational, parallel-group, double-blind, placebo-controlled, randomized trial examining the prevention by the timothy SLIT tablet of the development of asthma in children with grass-induced rhinoconjunctivitis is underway [65]. Children 5–12 years will be treated for 3 years with timothy SLIT tablets or placebo and they will be followed for an additional 2 years after completing treatment. Thus far, 812 children have been reported to have been randomized into this study, termed Grazax asthma prevention.

Conclusion

The timothy SLIT tablet is the result of years of clinical investigations. First, monotherapy with timothy was chosen, based on studies indicating that there was a high degree of cross-reactivity with other members of the Pooideae subfamily and that immunotherapy with timothy effectively reduced symptoms in northern-grass allergic subjects. Dose ranging studies were performed and a sublingual dose of 75,000 SQ units or 2800 FDA BAU was selected that contains 15 μg of the major timothy allergen Phl p 5. The same dose was found to be safe and effective in children and adolescents. Six pre- and co-seasonal Phase III studies with over 3000 evaluable subjects were conducted, three in adults, two in children and adolescents and one in both. One US adult study did not meet its primary end point, but the other five demonstrated reductions in the total combined score over the entire grass pollen season ranged from 20 to 30%. Additionally, one adult Phase III study was extended to include 3 years of continuous treatment followed by two post-treatment observational years. This study demonstrated that the 3 years of active treatment were followed by persisting and significant benefit for the next 2 years. In all the developmental studies, safety has been carefully monitored. While brief and transient local application site reactions occur in about half the subjects, these have usually ceased to occur within a few weeks. Rare systemic reactions have been reported, often with the first dose that is administered under observation in a physician's office. No near-fatal or fatal reactions have been reported, even in post-marketing data from Europe where the tablets have been approved and have been in use for over 8 years.

Expert commentary

AIT remains the only treatment for allergic rhinitis or allergic asthma that is disease modifying, that is, that has a persisting benefit after completion of a prescribed course of treatment. Despite this, and despite the fact that the degree of symptom reduction with AIT exceeds that regularly accomplished with antihistamines or topical corticosteroids, subcutaneous AIT is greatly underutilized. The reasons are the concerns for safety and the resulting requirement that all injections must be

administered in a physician's office. Many patients dislike 'shots' and dislike to or do not have time to make weekly and monthly visits to the physician's office and then wait the requisite 30 min after each injection. Sublingual immunotherapy is much less likely to result in a systemic reaction, and those that have occurred have not been near-fatal or fatal. Therefore, after a first safety dose in the physician's office, it is taken by the patient at home. This should appeal to many patients, some of whom would be willing to tolerate the inconvenience of SCIT for the relief it offers, plus many for whom SCIT is not a viable option but a home-administered treatment would be. We do not know how much each of these types of patients has contributed, but we do know that in many European countries new prescriptions for SLIT far exceed those for SCIT. The major limitation of SLIT is that only one allergen extract is in each tablet. It is good that both grass and ragweed SLIT tablets have been approved, as that will allow treatment of the two major warm weather allergens in the USA. There are not much data available as to how many patients will find treatment of grass and ragweed sensitivity sufficient. Although most SCIT patients now receive multiple allergens in their injections, it is not clear how many of these allergens are the cause of significant clinical symptoms and how many represent inconsequential sensitization. Certainly, the introduction, at a later time, of tablets for treating house dust and cat allergy will expand the number of patients for whom SLIT can provide relief for their major allergies. Will there be SLIT tablets for other allergens, such as trees, western weeds, molds and dogs? With the possible exception of the introduction of a birch pollen tablet, it is unlikely that tablets will be developed for the many unstandardized allergens. Will there be a multiallergen tablet? Very likely not, this would require an extremely expensive development program to meet FDA requirements for approval.

Five-year view

Since treatment with the timothy SLIT tablet should be initiated 12 or more weeks prior to the onset of the pollen season, its approval in April 2014 has come too late for effective use in

this year. For subsequent years, the success of commercialization of the timothy SLIT tablet will depend on several factors: the appropriate patients must be identified in the middle of the winter and placed on treatment; since these are patients who have not elected for immunotherapy in the past, they may not be consulting a specialist in allergic disease; this suggests that identifying the appropriate patients and getting them to the physician's office in the middle of the winter will depend to a large extent on aggressive direct-to-patient advertising. Therefore, the success in promoting the use of the timothy SLIT tablets may depend greatly on the strategies and investments of the manufacturer/marketer. Given the availability of both a Northern Pasture grass and a short ragweed tablet, there probably exist a large number of patients who would be interested in reducing their allergic rhinitis symptoms during the warm months of the year (June through September) when it is pleasant to be out doors. The success of these tablets will depend on identifying those patients. One limiting factor will be the regions in the USA where these two pollens predominate. Certainly in the southern states there are grasses that differ significantly from the Northern Pasture grasses for which the timothy SLIT tablet will provide little or no benefit. Also with short ragweed, there are non-cross-reactive weeds predominating in the western states for which the ragweed tablet will provide no benefit.

Information source

The reader is referred to the US Food and Drug Administration/Allergenic Products Advisory Committee/2013 meeting materials 11–12 December 2013. This site contains FDA briefing documents for both the timothy and the 5-grass SLIT tablets.

Financial & competing interests disclosure

HS Nelson has been a consultant for Merck and a consultant and investigator for Circassia. The author has 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.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Grastek is a rapidly dissolving tablet for sublingual administration containing 2800 bioequivalent allergen units, or 75,000 standardized quality units of timothy pollen extract.
- Timothy pollen is cross-reactive with other members of the Pooideae subfamily or Northern Pasture grasses, but has limited or no cross-reactivity with southern grasses such as Bermuda, Bahia and Johnson grasses.
- Treatment with the tablets should be initiated at least 12 weeks before the onset and continued through the pollen season.
- When administered continuously for 3 years, cessation was followed by persisting clinical benefit for the 2 years that were monitored.
- The first dose should be administered in a health care setting under observation by a physician, but subsequent doses are taken at home on a once-daily schedule.
- Local administration site adverse reactions, mostly itching and occasional swelling are experienced by about half the patients. They are brief and usually recur only for the first 1–2 weeks.
- Systemic reactions are rare, usually mild to moderate, have never been fatal or near fatal.
- The US FDA has mandated that patients be prescribed and taught how to use an epinephrine auto-injector for use in the event of a systemic reaction.

References

Papers of special note have been highlighted as:
• of interest

1. Nelson HS. Some highlights of the first century of immunotherapy. *Ann Allergy Asthma Immunol* 2011;107:417-21
2. Nathan RA, Meltzer EO, Derebery J, et al. The prevalence of nasal symptoms attributed to allergies in the United States: findings from the burden of rhinitis in an America survey. *Allergy Asthma Proc* 2008;29:600-8
3. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004;24:758-64
4. Meltzer EO, Blaiss MS, Naderio RM, et al. Burden of allergic rhinitis: allergies in America, Latin America, and Asia-Pacific adult surveys. *Allergy asthma Proc* 2012;33: S113-41
5. 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:S43-70
6. Hoppin JA, Jaramillo R, Salo P, et al. Questionnaire predictors of atopy in a US population sample: findings from the National Health and Nutrition Examination Survey, 2005-2006. *Am J Epidemiol* 2011;173:544-52
7. Meltzer EO, Nathan R, Derebery J, et al. Sleep, quality of life, and productivity impact of nasal symptoms in the United States: Findings from the Burden of Rhinitis in America survey. *Allergy Asthma Proc* 2009;30:244-54
8. Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med* 2004;116:338-44
9. 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
10. Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911;1572-3
11. Nelson HS. Subcutaneous injection immunotherapy for optimal effectiveness. *Immunol Allergy Clin North Am* 2011;31: 211-26
12. Cox L, Nelson H, Lockey R. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127: S1-S55
- **An evidence-based summary of the practice of allergy immunotherapy in the USA.**
13. Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J* 2014;7:6-doi 10.1186/1939-4551-7-6
- **An evidence-based summary of the status of sublingual immunotherapy (SLIT) as of 2013.**
14. Lin SY, Eekosima N, Kim MJ, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA* 2013;309:1278-88
15. Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. *Ann Allergy Asthma Immunol* 2009;103:451-9
16. Sikora JM, Tankersley MS. Perception and practice of sublingual immunotherapy among practicing allergists in the United States: a follow-up study. *Ann Allergy Asthma Immunol* 2013;110:194-7
17. 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: 1338-45
18. Didier A, Malling HJ, Worm M, et al. Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis. *Clin Exp Allergy* 2013;43:568-77
- **Reports the Stallergenes 5-year study result through the 4th year, demonstrating disease-modifying effect with only pre- and co-seasonal treatment.**
19. Oralair: Food and Drug Administration Allergenic Products Advisory Committee Briefing Document. Available from: www.fda.gov/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/allergenicproductsadvisorycommittee/ucm367268.htm 11-12 December 2013
- **Summarizes all the studies on the Stallergenes 5-grass tablet up to the time of US FDA approval.**
20. Cox L, Casale TB, Nayak AS, et al. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a U.S. study: the importance of allergen-specific serum IgE. *J Allergy Clin Immunol* 2012;130:1327-34
21. Weber RW. Aerobiology of outdoor allergens. In: Adkinson NF Jr, Bochner BS, Burks AW, Busse WW, Holgate ST, Lemanske RF Jr, O'Hehir RE, editors. Middleton's allergy: principles and practice. Elsevier/Saunders; Philadelphia, USA: 2014
22. Arbes SJ, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the Third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 2005;116:377-83
23. Chabre H, Bouyon B, Huet A, et al. Molecular variability of group 1 and 5 grass pollen allergens between Pooideae species: implications for immunotherapy. *Clin Exp Allergy* 2009;40:505-19
24. Gangl K, Niederberger V, Valenta R. Multiple grass mixes as opposed to single grasses for allergen immunotherapy in allergic rhinitis. *Clin Exp Allergy* 2013;43: 1202-16
25. Martin BG, Mansfield LE, Nelson HS. Cross-allergenecity among the grasses. *Ann Allergy* 1985;54:99-104
26. Heji C, Wurtzen PA, Kleine-Tebbe J, et al. Phleum pretense alone is sufficient for allergen-specific immunotherapy against allergy to Pooideae grass pollens. *Clin Exp Allergy* 2009;39:752-9
27. Archila LD, DeLong JH, Wambre E, et al. Grass-specific CD4+ T-cells exhibit varying degrees of cross-reactivity. *Clin Exp Allergy* 2014;44(7):986-98
28. Varney VA, Gaga M, Frew AJ, et al. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. *BMJ* 1991;302:265-9
29. Frostad AB, Grimmer O, Sandvik L, et al. Clinical effects of hyposensitization using a purified allergen preparation from Timothy pollen as compared to crude aqueous extracts from timothy pollen and a four-grass pollen mixture respectively. *Clin allergy* 1983;13:337-57
30. Martinez-Cocera C, Sastre J, Cimarra M, et al. Immunotherapy with a Phleum pretense allergen extract induces an immune response to a grass-mix allergen extract. *J Invest Allergol Clin Immunol* 2010;20: 13-19
31. Durham SR, Emminger WE, 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
- **Presents the data from the ALK-Abello' 5-year study with the timothy SLIT tablet, demonstrating disease-modifying effect with 3 years of continuous treatment.**

32. Grastek®. prescribing information Merck Sharp & Dohme Corp. a subsidiary of Merck & Co, Inc, Whitehouse Station, NJ 08889, USA. 2014
33. Bagnasco M, Altrinetti V, Pesce G, et al. Pharmacokinetics of Der p 2 allergen and derived monomeric allergoid in allergic volunteers. *Int Arch Allergy Immunol* 2005;138:197-202
34. Calderon MA, Simons FER, Malling H-J, et al. Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. *Allergy* 2012;67:302-11
35. Bohle B, Kinaciyan T, Gerstmayr M, et al. Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific T-cell tolerance, and immune deviation. *J Allergy Clin Immunol* 2007;120:707-13
36. MK-7743 timothy Grass Pollen Extract Tablets Advisory Committee Meeting Briefing Document. Available from: www.fda.gov/AllergenicProductsAdvisoryCommittee/2013MeetingMaterial/. 11–12 December 2013
- **Summarizes the results of all studies conducted with the timothy SLIT tablet up to the time of FDA approval.**
37. Malling HJ, Lung L, Ipsen H, Poulsen L. Safety and immunological changes during sublingual immunotherapy with standardized quality grass allergen tablets. *J Invest Allergol Clin Immunol* 2006;16:162-8
38. Kleine-Tebbe J, Ribel M, Herold DA. Safety of a SQ-standardised grass allergen tablet for sublingual immunotherapy: a randomized, placebo-controlled trial. *Allergy* 2006;61:181-4
39. Calderon M, Essendrop M. Specific immunotherapy with high dose SQ standardized grass allergen tablets was safe and well tolerated. *J Invest Allergol Clin Immunol* 2006;16:338-44
40. Ibanez MD, Kaiser F, Knecht R, et al. Safety of specific sublingual immunotherapy with sQ standardized grass allergen tablets in children. *Ped Allergy Immunol*. 2007;18:516-22
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;117:802-9
42. 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;118:434-40
43. Murphy K, Gawchik S, Bernstein D, et al. A phase 3 trial assessing the efficacy and safety of grass allergy immunotherapy tablet in subjects with grass pollen-induced allergic rhinitis with or without conjunctivitis, with or without asthma. *J Negat Results Biomed* 2013;12:10-19
44. Nelson HS, Nolte H, Creticos P, et al. Efficacy and safety of timothy grass allergic immunotherapy tablet in North American adults. *J Allergy Clin Immunol* 2011;127:72-80
45. 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
46. 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
47. 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
- **Presents the results of the largest allergy immunotherapy trial ever conducted, with over 1500 participants.**
48. Durham SR, Nelson HS, Nolte H, et al. Magnitude of efficacy measurements in grass allergy immunotherapy trials is highly dependent on pollen exposure. *Allergy* 2014;69:617-23
49. Calderon MA, Birk AO, Andersen JS, Durham SR. Prolonged preseasonal treatment phase with Grazax sublingual immunotherapy increases clinical efficacy. *Allergy* 2007;62:958-61
50. 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;68:252-5
51. Dahl R, Stendert A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006;61:185-90
52. Reich K, Gessner C, Kroker A, et al. Immunologic effects and tolerability profile of in-season initiation of a standardized-quality grass allergy immunotherapy tablet: A Phase III, multicenter, randomized, double-blind, placebo-controlled trial in adults with grass pollen-induced rhinoconjunctivitis. *Clin Therapeut* 2011;33:828-40
53. Schwab J-A, Wolf H, Schnitker J, Wustenberg E. Safety and tolerability of an intra-seasonal initiation of the SQ-standardised grass allergy immunotherapy tablet: a non-interventional observational study investigating the feasibility during routine administration. *Clin Drug Investig* 2013;33:719-26
54. Wessel F, Chartier A, Meunier J-P, Magnan A. Safety and tolerability of an SQ-standardized grass allergy immunotherapy tablet (GRAZAX) in a real-life setting for three consecutive seasons – the GRAAL Trial. *Clin drug Investig* 2012;32:451-63
55. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:319-25
56. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI and ACAAI surveillance study of subcutaneous immunotherapy, Year 3: what practices modify the risk of systemic reactions? *Ann Allergy Asthma Immunol* 2013;110:274-8
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;131:1361-7
58. De Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. *Allergy* 2009;64:963-4
59. Bachert C, Vestenbaek U, Christensen J, et al. Cost-effectiveness of grass allergen tablet (GRAZAX) for the prevention of seasonal grass pollen induced rhinoconjunctivitis – a Northern European perspective. *Clin Exp Allergy* 2007;37:772-9
- **This study addresses the important question of the cost-effectiveness of treatment with the timothy SLIT tablet.**
60. Nasser S, Vestenbaek U, Bariot-Mathiot A, Poulsen PB. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. *Allergy* 2008;63:1624-9
61. Ronaldson S, Taylor M, Bech PG, et al. Economic evaluation of SQ-standardized grass allergy immunotherapy tablet. *Clinicoecon Outcomes Res* 2014;6:187-96
62. 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;62:943-8
63. Kiel MA, Roder E, van Wijk RG, et al. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. *J Allergy Clin Immunol* 2013;132:353-60
- **This study highlights the important problem of patient adherence to a 3-year SLIT treatment program.**
64. Alesina R, Milani M, Pecora S. A multicenter, randomized, parallel-group trial assessing compliance, tolerability, safety, and efficacy to treatment with grass allergy tablets in 261 patients with grass pollen rhinoconjunctivitis. *J Allergy* 2012;2012:673502
65. Valovirta E, Berstad AKH, de Blic J, et al. Design and recruitment for the GAP trial, investigating the preventive effect on asthma development of an SQ-standardized grass allergy immunotherapy tablet in children with grass pollen-induced allergic rhinoconjunctivitis. *Clin Therapeut* 2011;33:1537-46