

SQ grass sublingual allergy immunotherapy tablet for disease-modifying treatment of grass pollen allergic rhinoconjunctivitis

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ABSTRACT

Background: Allergy immunotherapy is a treatment option for allergic rhinoconjunctivitis (ARC). It is unique compared with pharmacotherapy in that it modifies the immunologic pathways that elicit an allergic response. The SQ Timothy grass sublingual immunotherapy (SLIT) tablet is approved in North America and throughout Europe for the treatment of adults and children (≥ 5 years old) with grass pollen-induced ARC.

Objective: The clinical evidence for the use of SQ grass SLIT-tablet as a disease-modifying treatment for grass pollen ARC is discussed in this review.

Methods: The review included the suitability of SQ grass SLIT-tablet for patients with clinically relevant symptoms to multiple Pooideae grass species, single-season efficacy, safety, adherence, coseasonal initiation, and cost-effectiveness. The data from the long-term SQ grass SLIT-tablet clinical trial that evaluated a clinical effect 2 years after a continuous 3-year treatment period were presented in the context of regulatory criteria that define a clinically meaningful effect.

Results: This trial demonstrated that the clinical effect of the SQ grass SLIT-tablet is maintained, which is also supported by the immunologic findings.

Conclusion: Therefore, the SQ grass SLIT-tablet has an indication as a disease-modifying therapy in Europe, and a sustained effect is recognized in the United States.

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The nasal and ocular symptoms of allergic rhinoconjunctivitis (ARC) can be very bothersome for patients and often require treatment.¹ Allergy immunotherapy (AIT) is a treatment option for ARC that is unique compared with pharmacotherapy in that it modifies the immunologic pathways that elicit an al-

lergic response.² Long-term disease-modifying effects with some AIT products and formulations have been demonstrated in double-blind, placebo-controlled (DBPC) trials.^{3–6}

AIT is generally administered either subcutaneously (SCIT), or sublingually (SLIT) *via* liquid drops or dissolvable tablets. The SQ grass SLIT-tablet Grazax, also known as Grastek in North America (*Phleum pratense*; 75,000 SQ-T/2800 bioequivalent allergy units; ALK, Hørsholm, Denmark/Merck and Co., Inc., Kenilworth, NJ), is approved throughout Europe and in North America for the treatment of adults and children (≥ 5 years old) with grass pollen-induced ARC. The clinical development for the SQ grass SLIT-tablet encompassed a total of 5830 patients enrolled in randomized, controlled phase 1–3b trials, with eight completed or ongoing phase III, DBPC trials (Fig. 1),^{7–14} and 24 postauthorization–postmarketing studies with >8700 patients. The purpose of this review was to discuss the clinical evidence for the

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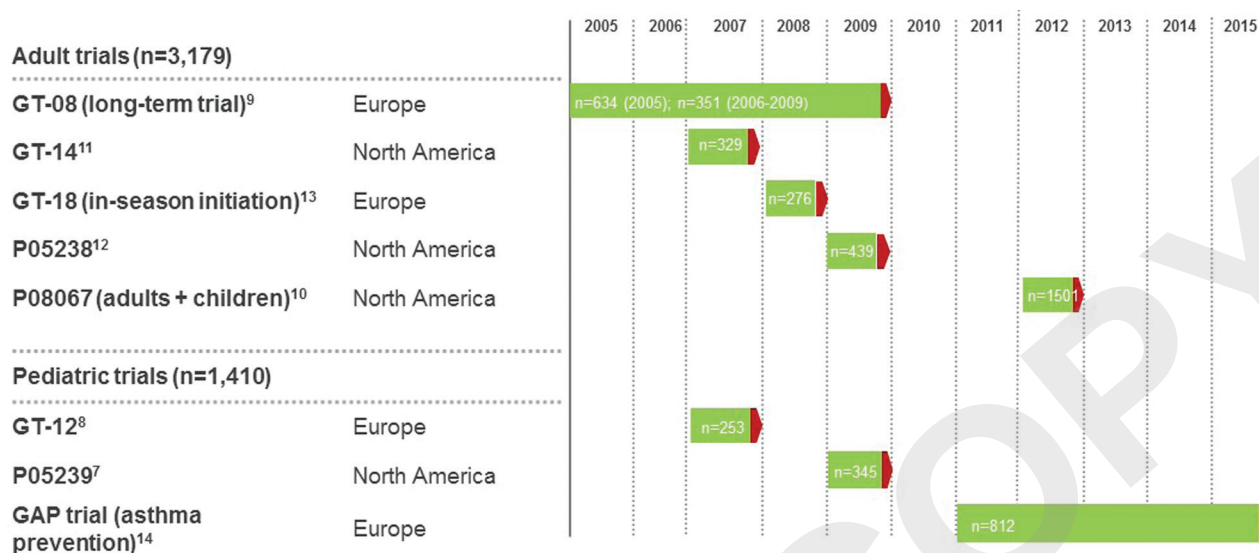


Figure 1. SQ grass SLIT-tablet double-blind, placebo-controlled, phase III, completed and ongoing trials. SLIT = Sublingual immunotherapy.

use of SQ grass SLIT-tablet as a disease-modifying treatment for grass pollen ARC.

Description of SQ grass SLIT-tablet

SQ grass SLIT-tablet is a once-daily grass AIT tablet for sublingual use. By using freeze-drying ZYDIS technology (Catalent Pharma Solutions, Somerset, NJ), the SQ grass SLIT-tablet is produced as a lyophilisate that dissolves within 2–10 seconds after contact with a wet surface such as the oral mucosa.¹⁵ Therefore, the risk of aspiration in children is considered minimal. SQ grass SLIT-tablet contains a Timothy grass extract (*P. pratense*) of biologic origin, and all aspects of the manufacturing process, from pollen collection, to extract preparation, to batch-to-batch potency, are standardized to ensure a high-quality consistent product.¹⁵ In Europe, the potency of SQ grass SLIT-tablet is labeled in SQ units as determined by an in-house reference preparation. SQ-grass is the dose unit for the SQ grass SLIT-tablet. SQ is a method for standardization on biologic potency, major allergen content, and complexity of the allergen extract. In the United States, the potency is 2800 bioequivalent allergy units based on U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research's potency assay.

SQ grass SLIT-tablet contains allergen extract from one species of grass, Timothy grass (*P. pratense*). Timothy grass is part of the Pooideae subfamily, which also includes meadow fescue, perennial rye, Kentucky blue grass, orchard grass, and sweet vernal.¹⁶ There is considerable evidence of cross-reactivity among the Pooideae species, whereas there is less cross-reactivity between *P. pratense* and non-Pooideae grasses.^{17–19} The first line of evidence for Pooideae intraspecies cross-reactivity is the amino acid sequence homology among

the most predominant major allergens in this family, groups 1 and 5. The amino acid sequence homology is ~90% among the group 1 allergens and ranges from 55% to 85% among the group 5 allergens.^{20–22} Further evidence of cross-reactivity was reported by Johansen *et al.*,¹⁷ who examined the specific immunoglobulin E (IgE) in the sera of 49 patients who were sensitized to grass pollen against eight different Pooideae species allergens before and after the addition of *P. pratense* pollen extract. In 98–100% of the serum samples, the presence of *P. pratense* extract completely inhibited the binding of patient grass IgE antibodies for all eight of the species tested, which indicated extensive IgE cross-reactivity (Fig. 2). Additional evidence for cross-reactivity of *P. pratense* versus other Pooideae species is found in the immunologic responses of patients treated with SQ grass SLIT-tablet. Allergen-specific IgG4 against extract mixes that contained 5 to 10 Pooideae species allergens was quantified after SQ grass SLIT-tablet treatment and compared with *P. pratense*-specific IgG4.²³ The correlation coefficients between *P. pratense*-specific IgG4 and the other Pooideae allergen-specific mixes were all 0.99, which indicated a high degree of cross-reactivity among the treatment-induced IgG4 antibodies.

T-cell responses play an important role in AIT tolerance induction.² Therefore, cross-reactivity at the T-cell level, in addition to antibody cross-reactivity, may be important when considering which extracts to use for AIT in patients polysensitized to more than one grass species. Several studies demonstrated that patients sensitized to Pooideae species have a broad T-cell epitope repertoire, and not all the epitopes are cross-reactive.^{24–26} However, it has been demonstrated that AIT by using only immunodominant epitopes can in-

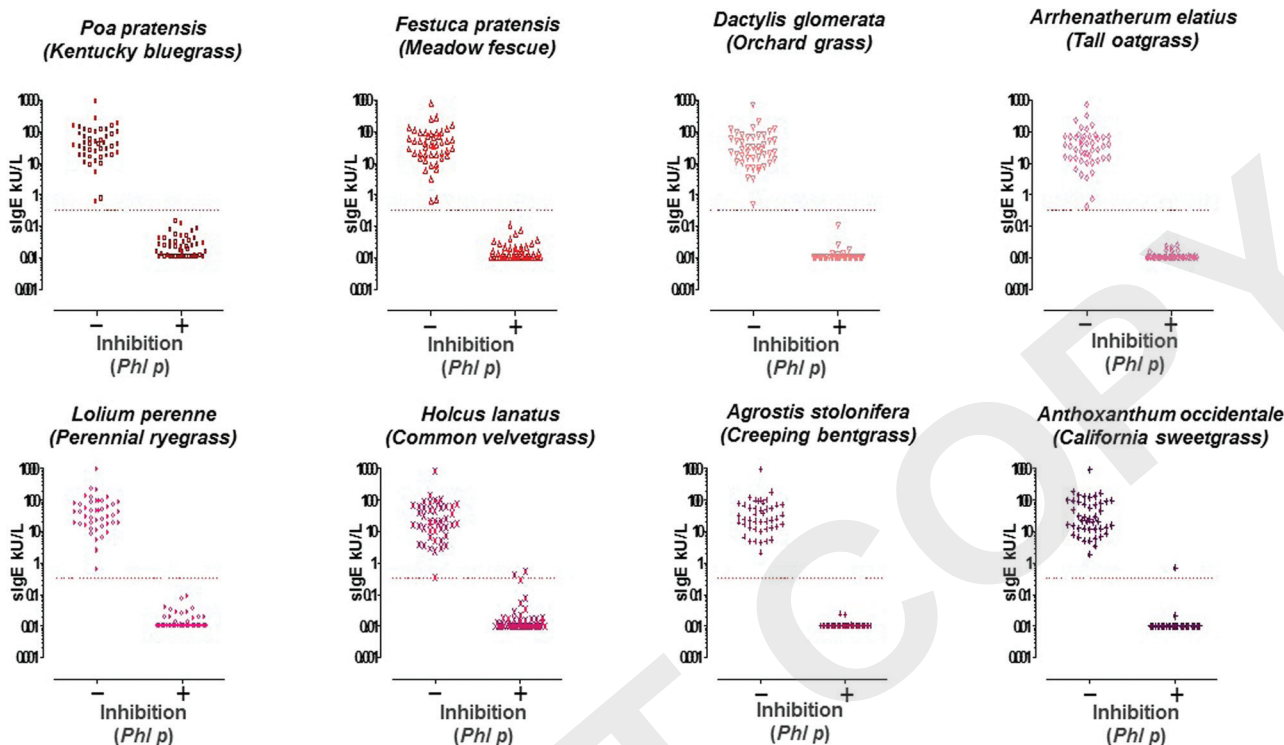


Figure 2. Specific immunoglobulin E (IgE) measured by ADVIA Centaur immunoassay (Siemens Medical Solutions, Diagnostics, Tarrytown, NY) in the sera of 49 subjects allergic to Timothy grass before (–) and after (+) addition of nonlabeled *Phleum pratense* (Phl p) pollen extract. The tests were performed only for sera that displayed a positive IgE response to the species in question. Adapted with permission from Ref. 17.

duce a generalized T-cell-mediated tolerance response, which indicated AIT with a single allergen extract is capable of generating a sufficient immunologic response against related species.^{27,28} Furthermore, Hejl *et al.*²³ demonstrated that strong proliferation of *P. pratense* group 1- and group 5-specific T cells was induced by extracts from four of the five non-*P. pratense* tested Pooideae species. Collectively, these data indicate that SQ grass SLIT-tablet is suitable to induce T-cell tolerance in patients allergic to grass pollen with clinically relevant symptoms to Pooideae grass species.

Mechanism of Action

The exact mechanism of tolerance induced by SLIT-tablet is not known but appears to be a complex process that involves both cellular and humoral immunity (reviewed in Matsuoka *et al.*²⁹). In brief, allergen in the extract is taken up by antigen-presenting cells in the sublingual tissue, which induce T-regulatory cells that inhibit specific T-cell responses to the allergen, and initiate the release of anti-inflammatory cytokines and mediators (*e.g.*, interleukin 10 and transforming growth factor- β). These cytokines attenuate mast cell, basophil, and eosinophil activity. In addition, AIT increases the production of specific IgG4 antibodies that interfere with IgE-allergen complexes on antigen-presenting cells and effector cells, *e.g.*, basophils.

End Points of SLIT-Tablet Clinical Trials

Regulatory and clinical organization guidelines recommend that the primary efficacy outcome for an AIT trial reflects both ARC symptoms and rescue medication use (*e.g.*, a total combined symptom and medication score [TCS]).^{30–32} Although efforts to standardize AIT outcomes are underway, there is currently no consistent method of calculating the TCS.³³ In the SQ grass SLIT-tablet trials that reported a TCS, the TCS was calculated as the sum of the daily symptom score (DSS) and the daily medication score (DMS) (medication scores weighted based on duration and clinical effect) averaged over the entire grass pollen season (Supplemental Table 1).^{7,10,12} Daily rhinoconjunctivitis symptoms, including four nasal symptoms and two ocular symptoms, were measured on a scale of 0 (none) to 3 (severe) in accordance with FDA and European Medicines Agency (EMA) guidance as well as clinical guidance from the World Allergy Organization.^{30,31,34} If a patient scored each symptom as severe, then the total DSS would be 18. Because optional symptom-relieving medications can improve symptoms scores, their use in a study must be appropriately accounted for to properly assess the treatment effect of the AIT under study. Hence, there typically is a hierarchy of treatments, with each step-up reserved for those pa-

tients who did not obtain relief with medication prescribed at the lower step. Predefined values were assigned to each class of medication to represent the symptomatic relief provided by the rescue medication. The maximum achievable DMS, if all available rescue medications were used, would be 36. Hence, the maximum TCS (DSS + DMS) in these trials was 54. However, in reality, due to the very low use of oral corticosteroids, the full scale was close to 20 points and, therefore, balanced against the symptom scale of 18. A different method of calculating TCS has been used for the 5-grass SLIT-tablet (Oralair; Stallergenes, London, United Kingdom). The key U.S. trial that reported a TCS (known as a combined score in 5-grass SLIT-tablet trials) as the primary end point used the formula $(\text{DSS}/[\text{number of symptoms assessed}] + \text{DMS})/2$.³⁵ For the DSS (known as the rhinoconjunctivitis total symptom score in 5-grass SLIT-tablet trials), symptoms were scored on a scale of 0–3, and the DMS (known as the rescue medication score) was calculated by using a weighted score for each medication (Supplemental Table 1). The rescue medication score used a different weighted scoring system than the system used in the SQ grass SLIT-tablet trials. The maximum TCS when using this method is 3.³⁶ When the FDA was considering approval of SQ grass SLIT-tablet and 5-grass SLIT-tablet, the efficacy outcome used to determine the clinical efficacy from each trial was the average of the TCS over the entire season, as calculated by each sponsor (Supplemental Table 1). In the trials in which the TCS was not the primary end point, it was assessed *post hoc*.^{37,38}

Evidence for Single-Season Efficacy

The efficacy of SQ grass SLIT-tablet for a single grass pollen season was demonstrated in clinical trials and was reviewed elsewhere.³⁹ Briefly, three phase III trials were conducted in adults only. The TCS was measured as the primary efficacy end point in one of these studies and improved 20% versus placebo ($p = 0.005$).¹² In the other two trials, TCS assessed *post hoc* was improved 34% ($p < 0.001$) and 10% ($p = \text{not significant}$) versus placebo.^{38,40} The trial that did not achieve statistically significant improvement in TCS versus placebo (assessed *post hoc*) was the first SQ grass SLIT-tablet trial conducted in North America.¹¹ The lack of sensitivity to treatment effect in the study was thought to be due to selection bias by a higher proportion of subjects who reported high baseline symptoms and minimal symptom worsening during the grass pollen season. As a consequence, three additional North American trials^{7,10,12} were conducted, and the subjects were rigorously trained in the use of the symptom and medication scoring system.

Efficacy in children has been demonstrated in two phase III trials. The TCS was assessed as the primary end point in one trial and improved 26% ($p = 0.001$),⁷ and 24% (no p value was calculated) when assessed *post hoc* in the second trial.³⁸ In the largest clinical trial of AIT conducted to date, which included 1501 adults and children, the TCS was assessed as the primary end point and improved 32% versus placebo in the pediatric subgroup ($p = 0.02$).¹⁰

There has been a concern that subjects with multiple sensitizations may have more severe allergy than patients who were monosensitized and, therefore, would be less likely to show an optimal effect against the treatment allergen. In a *post hoc* analysis of data pooled from six randomized, DBPC SQ grass SLIT-tablet trials, the efficacy in subjects who were monosensitized and subjects who were polysensitized was assessed ($N = 1871$).⁴¹ In both the SQ grass SLIT-tablet and placebo groups, ~80% of the subjects were polysensitized. The improvements in TCS versus placebo were similar in polysensitized and monosensitized subjects, at 26% and 28%, respectively (both $p < 0.0001$ versus placebo). These data indicate that SQ grass SLIT-tablet is effective for the treatment of grass allergy, regardless of sensitization status.

When considering different treatment options, a comparison of efficacy is useful information. However, there have been no head-to-head comparisons of SQ grass SLIT-tablet versus pharmacotherapy, SCIT, or SLIT-drops. Due to study design issues, *e.g.*, the regulatory requirement to allow pharmacotherapy in AIT trials, and difficulties in double-blinding SLIT versus SCIT, head-to-head studies would be difficult to conduct. Indirect comparisons can be made, but a number of caveats must be considered, as previously discussed by Calderon *et al.*⁴² Results from meta-analyses determined that the treatment effects of intranasal antihistamines, oral antihistamines, and leukotriene receptor antagonists were 7%, 9%, and 5% greater than placebo, respectively.^{43,44} Nasal corticosteroids appeared to have a greater symptomatic treatment effect than other pharmacotherapies, with a difference from placebo of 26% in one meta-analysis⁴³ and 17% in a separate meta-analysis.⁴⁴ In clinical trials, SQ grass SLIT-tablet has demonstrated a single-season treatment effect as measured by the DSS, which ranged from 6 to 31% versus placebo.^{11,38} The placebo groups in these studies were allowed to use ARC rescue medication. However, in one study, the subjects who received SQ grass SLIT-tablet and did not take any rescue oral antihistamine had a 26% improvement in the Rhinoconjunctivitis Quality of Life Questionnaire score ($p = 0.014$) during the pollen season compared with subjects who took only oral antihistamine,⁴⁵ which indicates that the significant clinical effect with SQ grass SLIT-tablet ob-

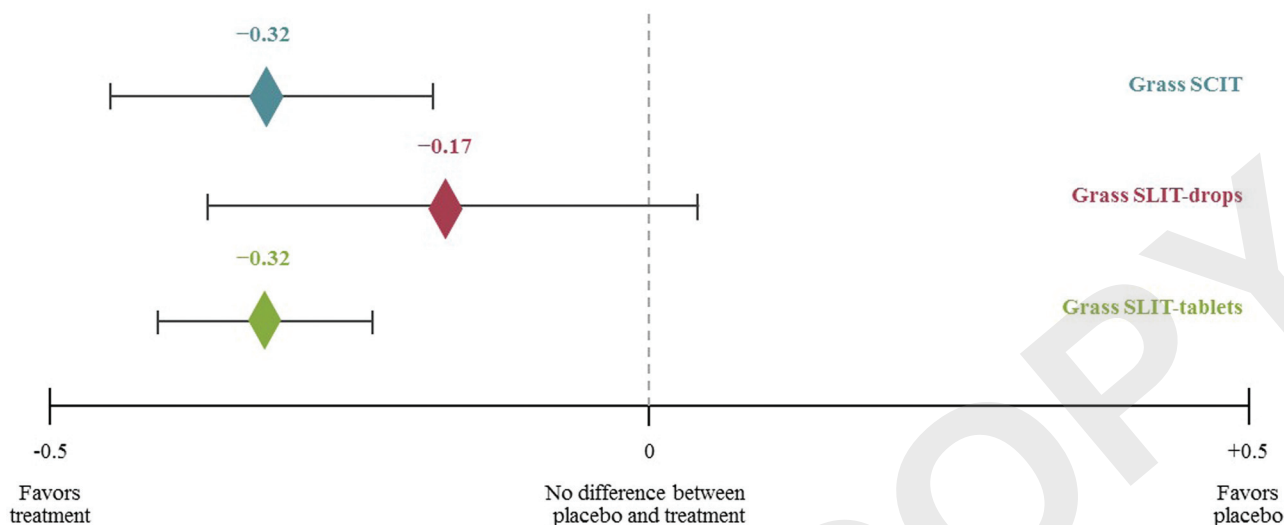


Figure 3. Comparative efficacy of symptom scores among SCIT, SLIT-drops, and SLIT-tablets versus placebo for grass ARC. Data represent the standardized mean differences from placebo with 95% confidence intervals as calculated by using a random effects model that accounts for between-study variability. Adapted with permission from Ref. 46. SCIT = Subcutaneous immunotherapy; SLIT= sublingual immunotherapy; ARC = allergic rhinoconjunctivitis.

served in the clinical trials was not simply due to the rescue medications used by some subjects.

In 2015, Nelson *et al.*⁴⁶ published a meta-analysis of randomized, double-blind, placebo-controlled (or active comparator) grass AIT trials that compared the treatment effect of commercially available SCIT versus SLIT drops versus SLIT-tablets for grass ARC. Of the 14 grass SLIT-tablet trials included, 7 were for SQ grass SLIT-tablet. By using a random effects model, which takes into account between-study variability, the standardized mean difference (SMD [95% confidence interval {CI}]) from placebo for symptom scores was -0.32 (95% CI, -0.45 to -0.18) for grass SCIT, -0.32 (95% CI, -0.41 to -0.23) for grass SLIT-tablets, and -0.17 (95% CI, -0.37 to 0.04) for grass SLIT-drops (Fig. 3). There was no significant difference in symptom or medication scores for grass SLIT-tablets versus either grass SCIT or grass SLIT-drops. Thus, grass SLIT-tablets appear to be equally efficacious to grass SCIT. These data are only applicable to adults because no DBPC trials of grass SCIT in children were available for comparison. The largest heterogeneity, with a wide CI which exceeded the line of “no difference between placebo and treatment,” was seen between trials conducted with grass SLIT-drops, which is reflected in the lower SMD for this product class compared with grass SCIT and grass SLIT-tablets. It is unclear why the SMD was lower for grass SLIT-drops versus tablets, but potential reasons include heterogeneity in the formulations, lower allergen-related potency, or lack of standardization with drops versus tablets.

Recently, another meta-analysis, by Di Bona *et al.*,⁴⁷ was published, which focused on the grass SLIT-tablets. The analysis included almost the same studies as

the meta-analysis published by Nelson *et al.*⁴⁶ and demonstrated similar results. When using a random effects model, the SMD (95% CI) from placebo for symptom scores was -0.28 (95% CI, -0.37 to -0.19). Although meta-analyses generally prove useful to obtain a better understanding of how well the treatment works, the caveat with new and large multicenter SLIT immunotherapy trials versus pharmacotherapy with enriched patient populations, and the older and smaller single-center SCIT studies, is the difficulty in assessing the treatment effect in a highly symptomatic patient population exposed to different levels of pollen across many regions of the countries.⁴⁸ In the absence of head-to-head trials, inference on a possible difference in the magnitude of a clinically important effect between SLIT-tablets and current allergic rhinitis treatment must be interpreted with caution.

Safety

The safety of SQ grass SLIT-tablet was assessed in a pooled analysis of eight phase II and phase III clinical trials, with a total of 4195 adults and children; 2116 of the subjects were treated with SQ grass SLIT-tablet.⁴⁰ There were no treatment-related deaths or serious adverse events (AE) reported. In addition to events specifically reported by the investigators, the trials’ sponsor reviewed all epinephrine administrations in the pooled data base for potential systemic allergic reactions as well as identified subjects with potential anaphylaxis as defined by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network.⁴⁹ In the pooled data set, there were nine systemic allergic reactions in eight different subjects

Table 1 Pharmacovigilance reports of anaphylactic shock* with Timothy grass immunotherapy#

Product	Estimated Exposure	No. Cases of Anaphylactic Shock Reported
SQ grass SLIT-tablet, 75,000 SQ-T	~49 million tablets sold ~134,000 patient treatment years	1
Grass SCIT, 100,000 SQ-U/mL	~0.5 million injections sold ~47,000 patient treatment years	21

SLIT = sublingual immunotherapy; SCIT = subcutaneous immunotherapy.

*Anaphylactic shock as described by the reporting health care provider.

#The reporting period was postcommercialization of SQ grass SLIT-tablet in Europe (2006–2013).

Source: Ref. 40.

treated with SQ grass SLIT-tablet, which gave an incidence rate of 0.42% (9 events per 2116 treated subjects). None of these reactions were assessed as serious or severe, and there were no cases of airway obstruction (acute severe asthma) or anaphylactic shock. Most of the systemic reactions ($n = 6$) occurred on day 1 of treatment, which supports the safety of at-home administration after the first SLIT-tablet is taken while in the office under medical supervision. One of the subjects who experienced a systemic reaction on day 1 experienced another systemic reaction on day 2. The remaining two systemic reactions occurred on day 2 and day 42 but did not require medication or medical attention. Of the nine systemic reactions, four were treated with epinephrine, details of which were previously reviewed.³⁹ Four additional epinephrine administrations in response to local AEs with SQ grass SLIT-tablet treatment were described. In the United States, the FDA requires that epinephrine be prescribed along with the SQ grass SLIT-tablet; however, this is not common practice in Europe or Canada.

As is typical for SLIT products,⁵⁰ the most common treatment-related AEs in the pooled data base were local AEs, such as oral pruritus, throat irritation, and ear pruritus. Details of these local AEs were previously reviewed, and results from a phase I dose-finding study indicate that the incidence of local AEs is dose-dependent.^{39,51} Pruritus and irritation effects may affect tolerance and adherence but are not a safety concern. However, severe or serious local swellings are of potential clinical concern. Local swellings were reported in 20% of subjects. A small percentage (0.8%) of the local swellings was assessed as severe; however, more than half of these subjects remained in their respective trials. The most common local AEs reoccurred for a median range of 1 to 8 days. The duration in minutes was not captured in the studies in the pooled data base but in pooled data from two phase I, randomized, DBPC trials in children ($N = 60$), the five most common local AEs resolved within a median range of 6 to 46 minutes after SQ grass SLIT-tablet administration.⁵²

Because asthma is a risk factor for systemic reactions with SCIT⁵³ and asthma is often a concomitant condition with ARC,⁵⁴ the safety of AIT products in patients with asthma is an important consideration. The safety in subjects with a history of well-controlled, mild asthma from the pooled SQ grass SLIT-tablet data base was evaluated and published by Maloney *et al.*⁵⁵ Of the 1669 adults and 446 children who received SQ grass SLIT-tablet, 415 (25%) and 140 (31%), respectively, had reported asthma. Analysis of the data indicated that there was no increase in the incidence of systemic allergic reactions or severe local swellings in the subjects with asthma versus the subjects without asthma, nor was there any indication of asthma worsening or exacerbation. In analyses of other subpopulations in the pooled data base, the safety profiles were similar when based on race, in adults versus children and in monosensitized versus polysensitized subjects.⁴⁰

The safety profile of SQ grass SLIT-tablet obtained during the clinical development program is supported by >9 years of marketed use in Europe and 24 noninterventional studies of real-life use that included more than 8700 patients. Pharmacovigilance data collected from 2006 to 2013 indicate that SQ grass SLIT-tablet is well tolerated.⁴⁰ During the 7-year pharmacovigilance time period, which represented ~134,000 patient-treatment years for SQ grass SLIT-tablet and 47,000 patient-treatment years with grass SCIT, 1 case of anaphylactic shock was reported for SQ grass SLIT-tablet versus 21 cases with grass SCIT (Table 1) (Alutard, 100,000 SQ-U/mL; ALK).⁴⁰ Cases of patients with serious systemic reactions to SQ grass SLIT-tablet have been reported during the pharmacovigilance time period and generally occurred on the first day of exposure during the 30-minute in-office observation period.⁴⁰ A few cases occurred at doses subsequent to the initial dose but were readily detected and readily managed by standard care. Recently, isolated cases of eosinophilic esophagitis, which has been identified as a concern with SLIT in general, were reported in postmarketing experiences.^{40,56} In the United States, a history of eosinophilic esophagitis is a contraindication.⁵⁷

Adherence

Prescribing information for SQ grass SLIT-tablet recommends treatment initiation at least 8 weeks (in Canada), 12 weeks (in the United States), or 2–4 months (in Europe) before the start of pollen season; subsequent treatment may be taken daily for 3 years. Real-world patient adherence to SQ grass SLIT-tablet was evaluated in one study, which was a retrospective analysis of prescription data from a Swedish drug registry.⁵⁸ A total of 999 patients who initiated treatment with either grass SCIT or SQ grass SLIT-tablet were included in the analysis. Compliance was 90% and 82% for SQ grass SLIT-tablet and grass SCIT, respectively, whereas persistence after 2 years was 55% and 57% for SQ grass SLIT-tablet and grass SCIT. The investigators concluded that the compliance and persistence of SQ grass SLIT-tablet was comparable with grass SCIT. Thus, persistence with SQ grass SLIT-tablet, and with SLIT treatment in general, appears to have the same difficulties as other long-term therapies.⁵⁹

Safety of Coseasonal Initiation

Although the prescribing information for SQ grass SLIT-tablet recommends preseasonal initiation, coseasonal initiation would enable patients to start developing allergen tolerance without the need to wait until the end of the season. The safety of coseasonal initiation with SQ grass SLIT-tablet has been evaluated in one DBPC trial of 276 subjects¹³ and one prospective, open-label, observational trial of 620 subjects who initiated coseasonally and 42 subjects who initiated postseasonally.⁶⁰ In the DBPC trial,¹³ there were no serious treatment-related AEs and one severe treatment-related AE (nausea) with SQ grass SLIT-tablet treatment. Anaphylactic reactions were reported in four patients (2%) treated with SQ grass SLIT-tablets; the reactions were assessed as mild to moderate.

In the open-label observational trial,⁶⁰ reactions assessed as severe were reported in 7.7% of subjects who initiated SQ grass SLIT-tablet coseasonally and 11.9% of subjects who initiated postseasonally. There were two serious treatment-related AEs in subjects who initiated coseasonally. One of the serious treatment-related AEs was reported by a 44-year old man who experienced an asthma attack, dyspnea, swollen lips, swollen tongue, and loss of his voice on day 5 of treatment. The symptoms were treated with antihistamines, corticosteroids, and β -sympathomimetics, and the patient discontinued treatment. The other serious treatment-related AE was reported by a 73-year-old woman who experienced nausea, fainting, hypotension, bradycardia, diarrhea, vomiting, and stomach pain 5 hours after the first tablet was administered. No treatment was administered, and the symptoms disappeared after 2 hours; the patient discontinued treat-

ment. No serious treatment-related AEs were reported in subjects who initiated postseasonally. The investigators of these studies concluded that the tolerability profile with coseasonal initiation was similar to previous clinical trials in which treatment was initiated outside the grass pollen season.

Health Economics

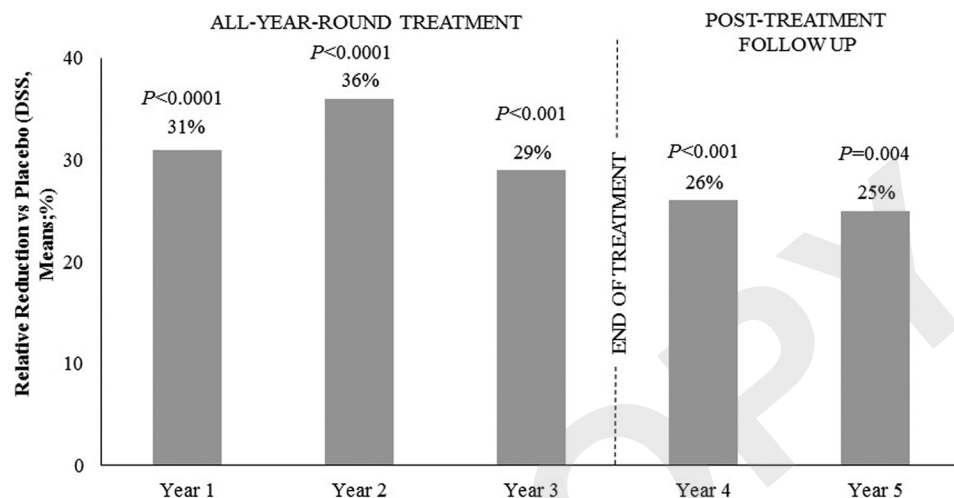
The ability of AIT to modify the immunologic mechanisms of ARC means that there is the potential to reduce ARC symptoms and pharmacotherapy use for an extended period of time, which could result in cost savings.⁶¹ Several studies examined the cost-effectiveness of SQ grass SLIT-tablet versus pharmacotherapy by using patient resource utilization data prospectively collected from single-season DBPC trials. With the assumption that treatment would be sustained for several years, all the studies demonstrated that SQ grass SLIT-tablet was cost effective based on cost per quality adjusted life years gained.^{62–64}

A budget impact analysis that compared SQ grass SLIT-tablets with grass SCIT was conducted from a Danish health care perspective.⁶⁵ The model assumed that patients who received SQ grass SLIT-tablet treatment were treated for 3 years, and patients who received grass SCIT were treated for either 3 or 5 years. The number of treatments, office visits, and office procedures were estimated based on reviews of clinical trials and standard practice for AIT in Denmark. Overall, the cost savings for a full course of treatment decreased 48% with SQ grass SLIT-tablet versus grass SCIT.

Regulatory Approach to AIT

Current SCIT products in North America have not undergone formal clinical review and approval according to a typical drug approval process. The current products were grandfathered in under a manufacturer license for allergenic extracts. Until now, only three AIT products (all SLIT-tablets) have undergone a formal FDA drug approval process in the United States. However, in recent years, the EMA regulatory requirements have been implemented that required documentation of clinical efficacy and safety of AIT products. These requirements are beginning to be translated into national regulatory and clinical treatment guidelines. For example, to achieve marketing authorization for frequently used allergen preparations (*i.e.*, Fagales tree and grass pollen, house-dust mites) in Germany requires completion of a “successful” DBPC trial.⁶⁶ “Success” could be defined as meeting World Allergy Organization or EMA standards. The World Allergy Organization defines a clinically meaningful difference for efficacy of an AIT product as at least a 20% improvement over placebo as measured by a global clin-

Figure 4. Primary efficacy outcome for the SQ grass SLIT-tablet long-term trial (from Ref. 4). Treatment was administered daily all-year-round for 3 years. Follow-up was conducted at years 4 and 5. The primary efficacy end point was the DSS over the entire grass pollen season. The pollen season threshold was 10 grains/m³. SLIT = Sublingual immunotherapy; DSS = daily symptom score.



ical score (e.g., TCS).³¹ In contrast, the EMA guidelines for AIT trials, essential for European market authorization procedures, state that the study sponsor should provide, and justify, the definition of the clinically meaningful difference, which is not necessarily demonstrated by a statistically significant difference from placebo for the primary efficacy end point.³⁰

Claims for efficacy as defined by the EMA depend on the trial duration³⁰: to demonstrate treatment of ARC symptoms, short-term trials that show efficacy in the first pollen season are required; to demonstrate a sustained clinical effect, maintenance of efficacy during 2–3 treatment years is required; and to demonstrate long-term and a disease-modifying effect, sustained efficacy in posttreatment years is required. The FDA's pivotal trial approval criteria for SLIT products is dependent on statistical robustness; a point estimate, either mean or median, of at least –15% improvement relative to placebo with a 95% CI upper limit of at least –10% is considered the clinically meaningful difference for the primary trial outcome and must be demonstrated for the duration of the trial (e.g., each year of the trial).⁶⁷ The practical implication is that the trials require large sample sizes to adjust for the significant variability in environmental factors, such as pollen season and individual fluctuations in allergen exposure that may impact symptom load and medication use, and thus the primary study end point.⁴⁸

Posttreatment Efficacy and Disease-Modifying Effect

The long-term and disease-modifying effects of grass SCIT were demonstrated in DBPC trials. One trial demonstrated that 3–4 years of Timothy grass SCIT decreased ARC symptom scores, rescue medication use, and immunologic reactivity for at least 3 years after completion of treatment.⁵ In a DBPC trial with a 6-grass hypoallergenic SCIT product, significant improvements in the area under the curve for the symp-

tom-medication score and the symptom score were observed in subjects 3 years after completing 3 years of grass SCIT treatment compared with placebo.³ In a small study of 13 subjects, all the subjects received Timothy grass SCIT for 2 years, followed by a 2-year randomized, double-blind period in which seven subjects continued to receive SCIT, and six subjects received placebo for 2 years.⁶⁸ After 2 years of placebo, the TCS remained low and similar to the TCS reported after the 2-year SCIT period. DBPC AIT trials with nongrass allergens also demonstrated the persistence of a clinical benefit for up to several years after completion of SCIT treatment.^{69–71} In addition, data on the long-term benefits of AIT were collected in several non-DBPC studies of varying size.^{72–78}

There have been few DBPC trials that investigated the long-term effects of grass SLIT. In the DBPC Efficacy, safety and tolerability of Coseasonal ultra-Rush sublingual ImmunoTherapy (ECRIT) study, 1 year after completing treatment, significant improvement in the ARC symptom score was observed for subjects who received 3 years of coseasonal 5-grass SLIT-drop versus placebo.⁶ Two DBPC trials on the long-term effects of grass SLIT-tablets were conducted. In GT-08, the subjects received either SQ grass SLIT-tablet or placebo for 3 continuous years and were followed-up at 1 year (year 4) and 2 years (year 5) after completion of treatment.⁴ The coprimary end points were the DSS and DMS. A statistically significant difference in the mean DSS from placebo was observed at years 4 and 5, which corresponded to a 25% and 26% improvement, respectively (Fig. 4). A statistically significant difference in the mean DMS from placebo was observed at year 4, which corresponded to a 29% improvement, whereas the 20% improvement observed at year 5 was not statistically significant. Sustained statistically significant increases from placebo in IgE blocking factor and *P. pratense*-specific IgG4 antibodies were observed

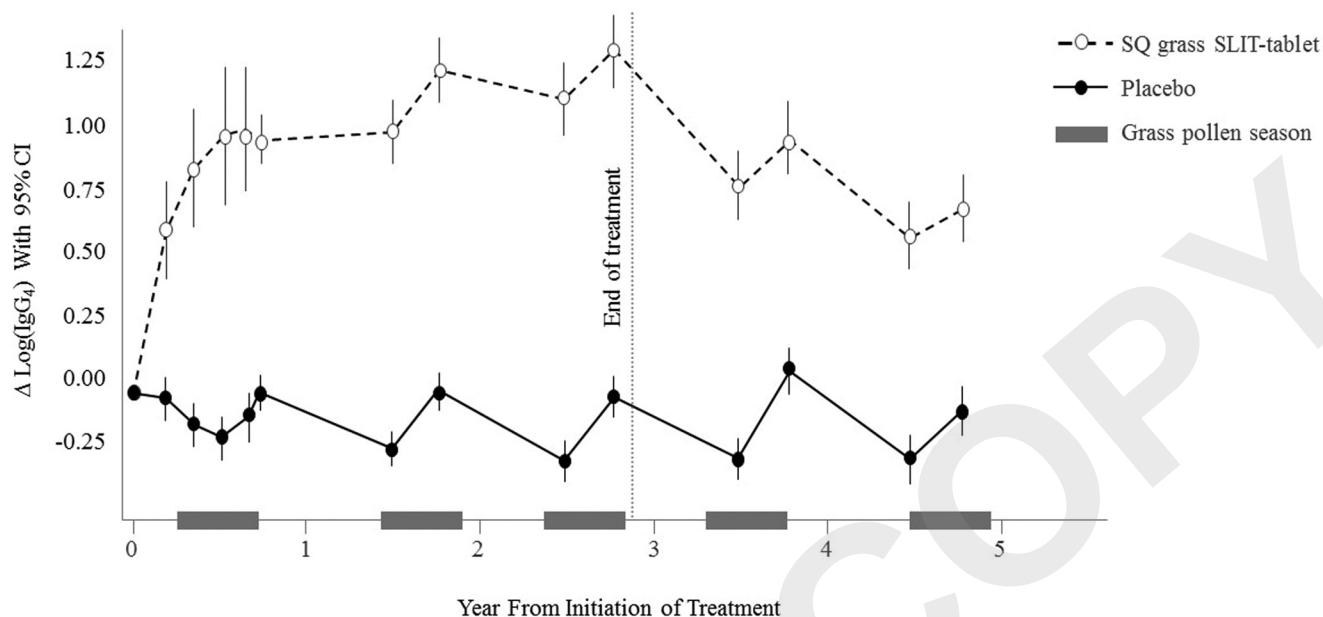


Figure 5. Long-term immunologic changes in IgG4 with SQ grass SLIT-tablet treatment. Adapted with permission from Ref. 4. Treatment was administered daily all year round for 3 years. Follow-up was conducted at years 4 and 5. Differences were significant at all assessments. IgG4 = Immunoglobulin G4; SLIT = sublingual immunotherapy.

at years 4 and 5 in subjects treated with SQ grass SLIT-tablet (Fig. 5).

In study VO53.06, the subjects received either 300 IR 5-grass SLIT-tablet administered beginning 4 months before the pollen season (4M), 300 IR 5-grass SLIT-tablet administered beginning 2 months before the pollen season (2M), or placebo pre-seasonally for 3 years, and were followed-up at 1 year (year 4) and 2 years (year 5) after completion of treatment.^{37,79} The primary end point was the average adjusted symptom score. The average adjusted symptom score is a scoring system that adjusts the daily rhinoconjunctivitis total symptom score for rescue medication use, based on a last-observation-carried-forward method (Supplemental Table 1).³⁶ A statistically significant difference in symptom score was observed at year 4 after treatment for the 300 IR (4M) dose but not year 5 (Fig. 6). A description of the immunologic data was limited to reporting an increase in the *P. pratense*-specific IgG4 end point: baseline ratio at year 4 in the 5-grass SLIT-tablet groups versus placebo.

After treatment discontinuation, there may be a carry-over effect of AIT in which efficacy slowly abates over several months or over years, which would not be a true sustained disease-modifying effect. Thus, to assess diminished long-term effects, it appears reasonable to evaluate the long-term clinical benefit and sustainability of the immunologic changes for at least 2 years after treatment and preferably longer. Based on the GT-08 data, SQ grass SLIT-tablet fulfilled the EMA definition of a long-term and disease-modifying effect by demonstrating statistically significant differences

versus placebo for DSS at years 4 and 5, which led to a label indication in Europe for SQ grass SLIT-tablet as a “disease-modifying treatment.” The 5-grass SLIT-tablet does not have a labeled indication as a disease-modifying treatment.

When considering an indication of sustained effect from the 5-year trials of SQ grass SLIT-tablet and 5-grass SLIT-tablet, the FDA defined the clinically meaningful difference as at least a 15% improvement with a 95% CI upper limit of at least 10% relative to placebo. The FDA used the *post hoc* outcomes of an averaged combined score for 5-grass SLIT-tablet and TCS for SQ grass SLIT-tablet (Supplemental Table 1). The FDA criterion was met at year 4 for SQ grass SLIT-tablet but not at year 5 (Fig. 7 A).³⁸ The FDA criterion was not met for either year 4 or year 5 for the 5-grass SLIT-tablet (4M) dose (Fig. 7 B).³⁷ Subsequently, SQ grass SLIT-tablet, but not 5-grass SLIT-tablet, is recognized by the FDA in the product label as having a sustained effect.^{57,80} It is important to note that these SLIT-tablet trials were not powered *a priori* for the FDA statistical criterion as this criterion was not known before the study starts; therefore, the sample size in the last year of the trials impacted successfully meeting this statistical criterion.

CONCLUSION

SQ grass SLIT-tablet has demonstrated well-documented clinical efficacy, tolerability, and cost-effectiveness. Based on long-term clinical data, the disease-modifying and sustained effects of SQ grass SLIT-

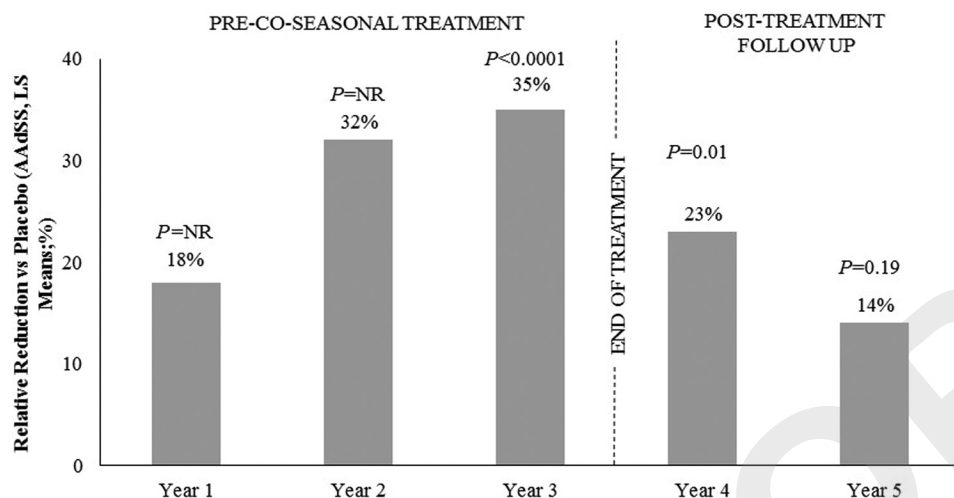


Figure 6. Primary efficacy outcome* for 5-grass SLIT-tablet long-term trial (from Refs. 37, 79, 83, 84) (year 2 data were presented by Didier et al., at the European Academy of Allergy and Clinical Immunology, Istanbul, Turkey, June 11–15, 2011). Treatment was administered daily pre-seasonally for 3 years. Only results for the dose initiated 4 months before the pollen season are shown. Follow-up was conducted at years 4 and 5. *The primary efficacy end point was the AAAdSS over years 3, 4, and 5 for the entire grass pollen season. The AAAdSS for years 1 and 2 was assessed post hoc. The pollen season threshold was 30 grains/m³. SLIT = Sublingual immunotherapy; AAAdSS = average adjusted symptom score.

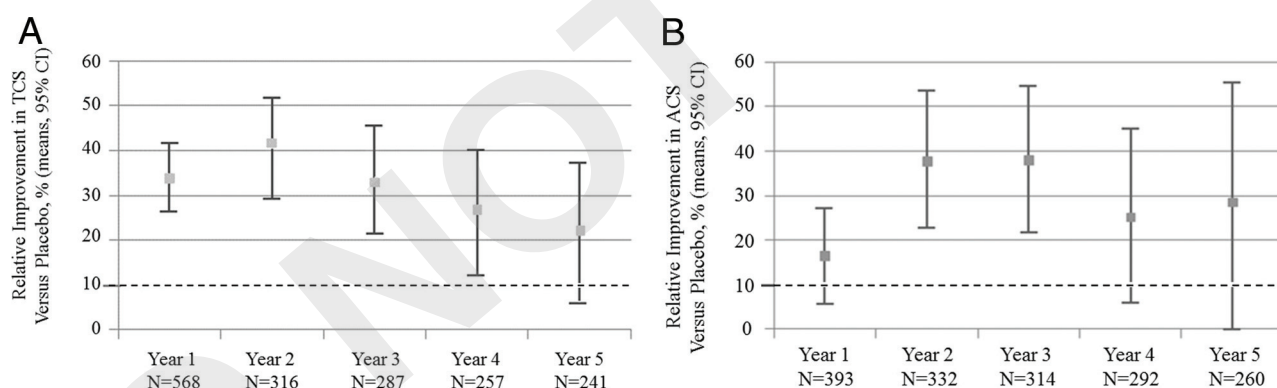


Figure 7. Analysis of efficacy as determined by FDA criterion for (A) SQ grass SLIT-tablet and (B) 5-grass SLIT-tablet by using data from 5-year trials (see Refs. 37, 38). Only results for the 5-grass SLIT-tablet dose initiated 4 months before the pollen season are shown. The FDA defines the clinically meaningful difference as at least a –15% improvement relative to placebo with a 95% CI upper limit of at least –10%. The dashed line indicates the 95% CI upper limit criteria. FDA = U.S. Food and Drug Administration; ACS = average combined score; SLIT = sublingual immunotherapy; CI = confidence interval; TCS = total combined score.

tablet have been recognized by regulatory authorities. The disease-modifying effect of SQ grass SLIT-tablet has not been evaluated in children. However, there is evidence that the clinical response for a single season is similar in adults and children, with comparable improvements versus placebo in symptom and medication scores, and comparable changes in immunologic response.⁸¹ It, therefore, is assumed that the long-term effect observed in adults are class effects and will extend to children. Long-term disease-modifying effects of SQ grass SLIT-tablet in children (ages 5–12 years) for up to 2 years after a 3-year treatment period will be evaluated in the ongoing Grazax Asthma Prevention trial.¹⁴ The Grazax Asthma Prevention trial is the first randomized DBPC trial to determine the preventive

effect of SLIT treatment on asthma development in children. More than 800 children have been randomized, which represents the largest AIT trial in children to date.

SLIT may be a desirable treatment option for patients because of the convenience of home administration and the well-tolerated safety profile. It may also appeal to patients who want to avoid or cannot adhere to repeated injections and frequent office visits. In the United States, physicians occasionally use SCIT extracts for off-label SLIT administration without scientific evidence of effect although dose justification studies have not been performed with these extracts,⁸² which indicates that there is a need for proper allergen studies with liquid drops before this practice is implemented. In

contrast, SQ grass SLIT-tablets are a well-documented treatment alternative to SCIT. The demonstrated efficacy and tolerability, as well as the rapid dissolution of the tablet, indicates that SQ grass SLIT-tablet may be particularly suitable for children.

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