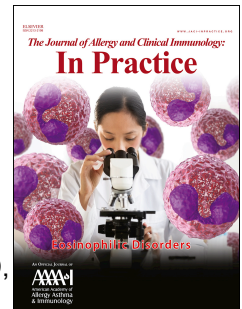


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Safety of Timothy Grass Sublingual Immunotherapy Tablet in Children: Pooled Analyses of Clinical Trials

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Disclosures:

S. Halken was on the Steering committee for the GAP trial, has served on an advisory board for ALK, and is a member of the EAACI AIT guidelines Task Force. G. Roberts was on the Steering committee for the GAP trial and is a member of the EAACI AIT guidelines Task Force. E. Valovirta was the International Coordinating Investigator for the GAP trial, was on the Steering committee for the GAP trial, and has served on advisory boards for ALK-Finland. H. Nolte and V. Hulstrøm are employees of ALK-Abelló, Hørsholm, Denmark. M. Blaiss has served as a consultant for ALK and Stallergenes/Greer.

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The study sponsors designed the study, participated in the analysis and interpretation of the data, and participated in the writing of the report. The authors critically revised the manuscript and made the final decision to submit the article for publication.

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Highlights

1. What is already known about this topic?

The tolerability of timothy grass SLIT-tablet has been demonstrated in multiple pediatric trials.

2. What does this article add to our knowledge?

Pooling of AEs and compilation of safety data from multiple pediatric trials augments data from the individual trials and provides robust evidence for the tolerability and safety of long-term timothy grass SLIT-tablet use in children.

3. How does this study impact current management guidelines?

Allergic rhinoconjunctivitis has a major impact on the child, physically, mentally, and socially. These safety data confirm that timothy grass SLIT-tablet is well tolerated in the pediatric population across geographic regions. Timothy grass SLIT-tablet rarely causes life-threatening allergic reactions such as anaphylaxis; the first dose should be administered in a healthcare setting.

Abstract

Background: Timothy grass sublingual immunotherapy (SLIT)-tablets are indicated for children with allergic rhinitis with or without conjunctivitis (AR/C).

Objectives: To use pooled analyses to assess the short- and long-term tolerability and safety of timothy grass SLIT-tablet in children.

Methods: Data from 9 double-blinded, randomized European or North American trials that included children with AR/C treated up to 3 years with once-daily timothy grass SLIT-tablet or placebo were pooled.

Results: In all, 1818 (SLIT-tablet=923; placebo=895) subjects were included in the analysis. The frequency of treatment-emergent adverse events (AEs) was 86% in the SLIT-tablet and 83% in the placebo groups and of treatment-related AEs (TRAEs) was 59% and 23%, respectively. Most (98%) TRAEs were mild-to-moderate in severity. The two most common TRAEs with SLIT-tablet were oral pruritus (33%) and throat irritation (19%), which had a median onset of 1 day and recurrence of 14.5 and 5 days, respectively. In all, 8% of subjects in the SLIT-tablet and 2% in the placebo groups discontinued due to AEs. There were 7 serious AEs assessed as related to SLIT-tablet, 1 systemic allergic reaction (severe with a drop in blood pressure), 3 epinephrine administrations, no eosinophilic esophagitis events, and no serious airway obstructions. The safety profile was similar in subjects across geographic regions and with and without asthma.

Conclusions: Pooled data indicate that short- and long-term timothy grass SLIT-tablet is well tolerated in children, regardless of geographic region. AEs were generally local, mild, and transient allergic reactions.

Keywords: allergic rhinitis; children; grass; immunotherapy; safety; sublingual

Abbreviations: AE, adverse event; AIT, allergy immunotherapy; AR/C, allergic rhinitis with or without conjunctivitis; EoE, eosinophilic esophagitis; FDA, Food and Drug Administration;

82 GAP, GRAZAX Asthma Prevention trial; MedDRA, Medical Dictionary for Regulatory
83 Activities; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; TEAE,
84 treatment-emergent adverse event; TRAE, treatment-related adverse event.

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Introduction

Allergy immunotherapy (AIT) is an alternative or add-on to pharmacotherapy and avoidance therapy to treat allergic rhinitis with or without conjunctivitis (AR/C) in patients with a documented clinically relevant allergy to the allergen.¹⁻⁴ In contrast to pharmacotherapy, AIT modifies the pathologic mechanisms of AR/C, rather than simply treating symptoms.⁵ Altering the disease can have a sustained and long-term impact on AR/C symptoms and the necessity for pharmacotherapy use several years after AIT is completed.⁶⁻⁸ Of particular importance for children, AIT can prevent the onset of asthma symptoms and asthma medication use.^{6, 9-14}

Two AIT administration methods are in use, subcutaneous (SCIT) and sublingual (SLIT). The benefits and safety of SQ^a timothy grass SLIT-tablet (GRAZAX/GRAS^{TEK}[®], ALK-Abelló, Hørsholm, Denmark) have been demonstrated in over 900 actively-treated children (n=923, timothy grass SLIT-tablet; n=895, placebo) in 9 completed clinical trials.^{12, 15-18} The treatment period was up to 3 years in the phase 3 GRAZAX Asthma Prevention (GAP)¹² and GT-23 (EudraCT no 2009-014923-22) trials, the longest trial duration ever conducted with SLIT-tablets in children. Timothy grass SLIT-tablet is the most documented AIT product for the long-term treatment of AR/C in children and is approved for the treatment of AR/C in adults and children (5 years or older) throughout Europe and in North America.

The timothy grass SLIT-tablets are oral fast-dissolving tablets also known as “fast melts”, developed using Zydis[®] technology^{b, 19}. In vitro experiments indicate that the tablets dissolve and

^a SQ is a method of standardization of biological potency, major allergen content, and complexity of the allergen extract.

^b Zydis[®] fast dissolve tablet technology developed by Catalent[®] Pharma Solutions, Inc. Available at: Catalent.com.

release allergens almost instantly; no chewing or water is needed for tablet administration.¹⁹⁻²²

The fast disintegration and mucoadhesive properties of the tablet mean that it carries a low risk of aspiration and swallowing, making administration particularly suitable for children. Equally

important, the safety profile permits home administration following the first tablet intake in a

clinical setting.^{23, 24} Up to a third of children may experience local oral pruritus, but this usually

disappears after a couple of weeks.¹² Fear of needles and the need for repeated, long-term

injections may make SCIT unappealing for children and their caregivers. SCIT also requires

administration in a clinical setting typically every 1 to 6 weeks with a 30 minute wait period after

the injection,² which can be a burden for patients and caregivers.²⁵ Therefore, there is a need for

increased evidence and awareness of SLIT-tablets as an alternative to SCIT. Physicians and other

healthcare professionals may not be familiar with the tolerability and safety profile of the tablets.

To this end, the objective of this pooled analysis is to provide physicians and other healthcare

professionals with a robust analysis of the short- and long-term tolerability and safety of timothy

grass SLIT-tablet in North American and European children and to better characterize

uncommon events (i.e., systemic allergic reactions and epinephrine use).

Methods

Trial designs

Data from children and adolescents younger than 18 years of age in 9 randomized, double-blind, placebo-controlled clinical trials conducted in Europe and the US are included in this pooled analysis. Details and primary results from 6 of the trials are previously described.^{12, 15-18} Trial identifiers are NCT00310453, NCT00298701, NCT00408616, NCT00550550, NCT01385371, and NCT01061203. Three of the trials that included children or adolescents are not published (EudraCT no 2009-014923-22; NCT00293046, and NCT01740284). Key characteristics of the 9 trials are listed in the **Supplemental Table E1**. All subjects had grass-related AR/C as indicated by a medical history, a positive skin prick test, and specific IgE against *Phleum pratense*. Subjects in all trials except the GAP trial¹² were allowed to have non-severe asthma treated with short-acting beta2-agonist alone or low-dose inhaled corticosteroid, whereas subjects with a medical history of asthma and/or wheezing were excluded from the GAP trial (trial 8). Subjects in all 9 trials received timothy grass SLIT-tablet (75,000 SQ-T/2800 bioequivalent allergen units; approximately 15 µg Phl p 5) or placebo daily. Treatment in the phase 1 trials (trials 1 and 3) and trial 7 only evaluated safety and lasted for 28 days.¹⁵ Treatment in trials 4-6 began at least 8 weeks before the grass pollen season and continued throughout the entire season.¹⁶⁻¹⁸ Treatment in trials 8-9 lasted for 3 years.¹² Epinephrine auto-injectors only were provided in trials 5 and 6, trials conducted in North America per US Food and Drug Administration (FDA) regulatory requirements.

All trials in the analysis were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice and were approved by ethics committees. Written informed consent was obtained from subjects and/or caregivers prior to any trial activities.

Safety and tolerability assessments

All adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), using the current MedDRA version at the time of reporting. All AEs were recoded using MedDRA version 18 for this pooled analysis. In this analysis systemic allergic reactions were defined as investigator-reported “anaphylactic reaction”, “anaphylactic shock”. Events coded as “hypersensitivity” underwent medical review to identify any other potential systemic allergic reactions.

Seriousness, severity, and the possible relationship to the treatment for all AEs were assessed by investigators. AEs that were possibly related to treatment were classified as treatment-emergent (TEAEs) or treatment-related (TRAEs). AEs (including serious AEs) were defined according to the ICH Harmonised Tripartite Guideline E2A.²⁶ TEAEs are any AE that occurs at or after the time of treatment regardless of a causal relationship to treatment. TRAEs are AEs assessed by the investigator as related to treatment. AEs were assessed as mild (awareness of sign/symptom, but easily tolerated), moderate (discomfort that interfered with normal activity), severe (incapacitating with inability to do normal activities or significant effect on clinical status, and warranted intervention), or life-threatening (immediate risk of death). Serious AEs were defined as events that caused death or were life-threatening; resulted in persistent or significant disability/incapacity; resulted in (or prolonged an existing) inpatient hospitalization; that were a congenital anomaly/birth defect (in an offspring of a subject

receiving study drug); or resulted in any other medically important event that may have jeopardized the subject or required intervention.

Data on AEs were unsolicited (ie, not collected via structured questionnaires as has been done in recent SLIT-tablet clinical trials conducted in the United States²⁷) and were obtained during questioning of subjects during study visits. AE collection methods differed between phase 1 and phase 3 trials. In phase 1 trials, an event occurring for a short period of time but on consecutive days in the same subject was reported as a separate event for every single consecutive day this event occurred. In phase 3 trials, such an event counted as one event only, with resolution time equal to the number of consecutive days on which the event occurred. Information on the day of onset, recurrence, and duration of the most common AEs was not collected in all 9 trials and therefore was not part of the pooled analysis. Previously described onset and recurrence data collected in the GAP (trial 8) trial and duration of the most common AEs collected in the phase 1 trials (trials 1 and 3) are reported.

Statistical analyses

All subjects younger than 18 years of age at screening who were enrolled and received at least one dose of the treatment were included in the safety analysis. Analyses were descriptive only, with percentages calculated for categorical variables and mean and standard deviation calculated for continuous variables.

Results

Subjects

In all, 1818 children were treated in the trials and included in the pooled safety analyses (n=923, grass SLIT-tablet; n=895, placebo). The overall mean (SD) age was 10.4 (3.1) years (66% aged 4–11 y; 34% aged 12–17 y) and the majority of subjects were boys (**Table 1**). Most (93%) of the subjects were white. The proportion of subjects with asthma was 18% in the timothy grass SLIT-tablet group versus 16% in the placebo group and the proportion who were polysensitized was 79% in the timothy grass SLIT-tablet group versus 78% in the placebo group (**Table 1**). Overall, 34% of subjects were from North America and 66% were from Europe. Of the 1818 children treated, 1483 (82%) completed the trials. Of the 923 subjects treated with timothy grass SLIT-tablet, 368 (40%) received treatment for more than 1 year (mean exposure=514 days).

Overall safety

A summary of the overall safety with up to 3 years of treatment is shown in **Table 2**. The percentages of children reporting TEAEs in the pooled analysis were similar between the timothy grass SLIT-tablet (86%) and placebo (83%) groups. A greater percentage of children in the timothy grass SLIT-tablet group (59%) experienced TRAEs compared with children in the placebo group (23%). Most (98%) of the TRAEs were assessed as mild-to-moderate in severity. The most common TRAEs with timothy grass SLIT-tablet were oral pruritus (33%) and throat irritation (19%) (**Figure 1**). The primary reason for trial discontinuation was AEs, with a frequency of 8% (n=70) in timothy grass SLIT-tablet treated children and 2% (n=21) in placebo-treated children (**Table 2**). Oral pruritus was the most common AE leading to discontinuation of timothy grass SLIT-tablet (18/70) followed by lip swelling (6/70). Of the 70 subjects who

discontinued timothy grass SLIT-tablet due to AEs, 10 (1%) discontinued due to a severe AE (**Table 2**). The most frequently reported TEAEs (those occurring in $\geq 1\%$ of subjects) led to temporary interruption of timothy grass SLIT-tablet in 5% of subjects and to discontinuation of timothy grass SLIT-tablet in 5% of subjects. When evaluated by geographic region (North American or European), the overall safety profile was similar between the regions (**Table 3**). The safety profile based on the first 28 days of treatment was similar to the overall long-term safety profile of up to 3 years of treatment (**Supplemental Table E2**). The most common AEs were oral pruritus and throat irritation.

There were 7 (<1%) serious AEs assessed as related to timothy grass SLIT-tablet. Only one of the subjects did not recover (severe immune thrombocytopenic purpura). Details of the 7 serious AEs are shown in **Table 4**. None of the treatment-related serious AEs included airway obstruction (defined as laryngeal edema, oropharyngeal swelling, pharyngeal edema, or throat tightness). One subject reported severe lip swelling, one subject reported severe tongue swelling, and 2 subjects reported severe mouth swelling. There were no events of eosinophilic esophagitis (EoE) and no deaths reported in the trials.

Onset, recurrence and duration of AEs

Data collected from the GAP trial (trial 8) indicated that the overall median (min, max) onset for the 2 most common TRAEs (oral pruritus and throat irritation) was day 1 (1.0-875.0) of treatment for oral pruritus and day 1 (1.0-668.0) for throat irritation. The median (min, max) number of days the AEs were recurring was 14.5 (1.0-1122) days for oral pruritus and 5 (1.0-1079) days for throat irritation.¹² The duration of AEs was evaluated in the phase 1 trials (trials 1 and 3) and the mean was found to be 15 to 20 minutes for oral pruritus and throat irritation.¹⁵

Systemic allergic reactions

No events of anaphylactic reaction or anaphylactic shock were reported by investigators. Of the events reported by investigators as hypersensitivity, after medical review 1 event was identified as a systemic allergic reaction. The systemic allergic reaction occurred on day 1 within 5 minutes of first tablet intake and was assessed as severe and classified as a serious AE. The event manifested as dysphagia, respiratory distress, and a drop in blood pressure from a baseline of 110/65 mmHg to 90/55 mmHg (**Table 4**). The subject (aged 10 y) was hospitalized for monitoring, recovered after standard treatment (including epinephrine), and discontinued the timothy grass SLIT-tablet. Other events reported as hypersensitivity were comprised of only local allergic reactions.

There were 2 additional events of epinephrine use in children treated with timothy grass SLIT-tablet. One event assessed as moderate occurred within minutes of tablet administration on day 1 of treatment in a 13 year-old subject and was characterized by lip angioedema, slight dysphagia, and intermittent cough. No wheezing, respiratory distress, urticaria, vomiting/diarrhea, or hypotension were reported and symptoms resolved within minutes after epinephrine was administered at the study site. The subject discontinued the trial. One event assessed as severe occurred on day 3 of treatment in an 18 year-old subject and was characterized by throat irritation and throat swelling. No difficulty breathing or swallowing was reported and the symptoms resolved after self-administered epinephrine. The subject discontinued one month after the event (subject did not tell his parents he self-administered epinephrine and he did not seek medical attention).

Asthma safety

There were no marked differences in the safety profile (including respiratory symptoms) between subjects with asthma and subjects without asthma in any of the trials. One serious AE of asthma worsening assessed as possibly related to timothy grass SLIT-tablet treatment was reported (**Table 4**). This event occurred after 10 months of timothy grass SLIT-tablet treatment when a subject experienced hoarseness and cough after spending time near a freshly mowed lawn. The following evening, the subject's symptoms recurred and he was hospitalized. The subject recovered after treatment with β_2 -agonists and continued timothy grass SLIT-tablet treatment. The timing of SLIT-tablet administration in this subject was not recorded so a temporal relationship cannot be established.

Discussion

SLIT-tablets may be a convenient and appealing alternative to SCIT for children with AR/C and their caregivers. The results of this pooled analysis of 9 clinical trials involving over 900 children treated with timothy grass SLIT-tablet for a mean of 514 days indicates that the tablet is well tolerated short- and long-term in the pediatric population and across geographic regions.

The overall short- and long-term safety profile of timothy grass SLIT-tablet appears to be similar to that of adults. In a previously published pooled analysis of timothy grass SLIT-tablet trials, Bernstein et al²⁸ found that in adults, as in the current analysis, the most common treatment-related AEs were oral pruritus and throat irritation, and that AEs were generally mild-to-moderate. Bernstein et al²⁸ also reported data from a pediatric pool of children treated with timothy grass SLIT-tablets. The current analysis builds upon that previous pooled analysis by the addition of subjects from two phase 1 trials and two phase 3 trials and confirms that timothy grass SLIT-tablet is generally well tolerated in children. Both the previous and current analyses found that most of the reported AEs in the clinical trials were local allergic reactions that were mild and transient, the most frequent of which were oral pruritus and throat irritation. The frequencies of TRAEs, oral pruritus, and throat irritation were similar to those reported in pooled analyses of timothy grass SLIT-tablet in adults and 5-grass SLIT-tablet.^{28, 29} Overall, 8% of children treated with timothy grass SLIT-tablet discontinued due to AEs. Physicians and other healthcare professionals need to be sure to educate patients initiating the timothy grass SLIT-tablets that local allergic reactions may occur but that they typically do not recur for more than 1 to 2 weeks.

The potential for airway obstruction in reaction to timothy grass SLIT-tablet is of particular concern in children due to their narrow airways. In this analysis, no tablet aspirations or serious airway obstructions were reported and severe swellings were limited to 1-2 subjects each experiencing lip, tongue, or mouth swelling. These data indicate there is no safety signal with timothy grass SLIT-tablet in relation to airway obstruction. There were also no events of EoE, although it has been associated with SLIT drops and tablets in case reports and post-marketing data.^{24, 29-31} Isolated cases of EoE have also been reported with SLIT in food-desensitization trials;³² therefore, EoE is monitored as a potential risk. A history of EoE is a contraindication for the timothy grass SLIT-tablet in the United States.²³

The use of epinephrine was infrequent and typically occurred after the first timothy grass SLIT-tablet treatment while the subject was in the clinic for a first-dose-observation, as required in the prescribing information.^{23, 24} In the 2 epinephrine administrations in response to the first dose, epinephrine was evaluated as necessary by experienced healthcare professionals. It is unknown if the subjects would have progressed to life-threatening anaphylaxis if epinephrine had not been administered. These events reiterate the importance of first-dose administration in a healthcare setting experienced with AIT, followed by at least a 30 minute observation period to treat any potential severe or life-threatening reactions.²³ The lack of any severe systemic allergic reactions after the observed first-dose indicate the safety of at-home administration thereafter, although one subject self-administered epinephrine on day 3. The infrequent epinephrine use in the current analysis is in line with the results of a systematic review of 13 trials in which 2597 subjects received timothy grass and 5-grass SLIT-tablets, and epinephrine was administered in response to only 7 AEs related to SLIT-tablet treatment and there were no episodes of anaphylaxis.³³ Furthermore, in a review of 29 timothy grass, ragweed, and house dust mite SLIT-

tablet clinical trials (5 of the grass trials included in the review are in the current pooled analysis), the number of epinephrine administrations for SLIT-tablet related events was 1.80 per 100,000 tablets.³⁴

The use of AIT in patients with asthma is of concern to physicians and other healthcare professionals due to an increased risk of systemic reactions during SCIT.³⁵ No difference in the safety profile between children with or without asthma was observed in the current analysis. One serious event of asthma worsening was reported which potentially had an alternate etiology related to the subject's recent exposure to cut grass. It should be noted that severe asthma was an exclusion criterion in all the trials and the safety of timothy grass SLIT-tablet has not been evaluated in patients with severe and uncontrolled asthma. The generalization of the current analysis to the typical AR/C population is limited in that the majority of the subjects were from the GAP trial which did not include subjects with comorbid asthma and who may have had milder AR/C than the typical patient receiving AIT.

Overall the results of this pooled analysis indicate that short- and long-term SQ timothy grass SLIT-tablet use is well tolerated in children across geographic regions. Most of the reported AEs in the clinical trials were local, mild, and transient allergic reactions as expected with the sublingual administration of grass allergens in sensitized subjects. However, severe systemic allergic reactions can occur and the first dose should be observed in a healthcare setting under the observation of AIT-experienced healthcare providers.

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439 **Table 1.** Demographic characteristics of the pooled population (all treated subjects).

	Timothy Grass SLIT-Tablet	Placebo
Characteristic	n=923	n=895
Age, mean y (SD)	10.2 (3.1)	10.5 (3.1)
4–11 y, n (%)	629 (68)	576 (64)
12–17 y, n (%)	294 (32)	319 (36)
Male, n (%)	603 (65)	568 (63)
White, n (%)	839 (91)	843 (94)
Subjects with asthma, n (%)	164 (18)	146 (16)
Subjects polysensitized, n (%)	724 (79)	700 (78)
Country, n (%)		
Austria	13 (1)	12 (1)
Canada	34 (4)	33 (4)
Denmark	54 (6)	63 (7)
Finland	23 (2)	21 (2)
France	54 (6)	58 (6)
Germany	206 (22)	188 (21)
Italy	33 (4)	33 (4)
Netherlands	1 (<1)	0
Norway	19 (2)	17 (2)

Poland	48 (5)	55 (6)
Spain	76 (8)	60 (7)
Sweden	58 (6)	61 (7)
Switzerland	8 (<1)	8 (<1)
United Kingdom	11 (1)	13 (1)
United States	285 (31)	273 (31)

SD, standard deviation; SLIT, sublingual immunotherapy.

Table 2. AE summary for the pooled population (all treated subjects)

n (%) of Subjects Reporting	Timothy Grass	
	SLIT-Tablet n=923	Placebo n=895
Any TEAE	798 (86)	747 (83)
Any TRAE	548 (59)	206 (23)
Any serious TEAE*	48 (5)	34 (4)
Any serious TRAE*	7 (<1)	1 (<1)
Any severe TEAE [†]	94 (10)	66 (7)
Any severe TRAE [†]	25 (3)	6 (<1)
Any TEAE leading to study discontinuation	70 (8)	21 (2)
Any severe TEAE leading to study discontinuation	10 (1)	5 (<1)
Any TRAE leading to study discontinuation	65 (7)	9 (1)
Any severe TRAE leading to study discontinuation	8 (<1)	2 (<1)

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

*Serious AEs were defined as events that caused death or were life-threatening; resulted in persistent or significant disability/incapacity; resulted in (or prolonged an existing) inpatient hospitalization; or that were a congenital anomaly/birth defect (in an offspring of a subject receiving study drug).

[†]Severe AEs were those assessed as incapacitating, resulting in inability to do normal activities or having a significant effect on clinical status, and that warranted intervention.

Table 3. AE summary by geographic region for the pooled population (all treated subjects)

	North America		Europe	
	Timothy Grass		Timothy Grass SLIT-	
	SLIT-Tablet	Placebo	Tablet	Placebo
n (%) of Subjects Reporting	n=319	n=306	n=604	n=589
Any TEAE	255 (80)	235 (77)	543 (90)	512 (87)
Any TRAE	191 (60)	67 (22)	357 (59)	139 (24)
Any serious TEAE*	1 (0)	2 (1)	47 (8)	32 (5)
Any serious TRAE*	0	0	7 (1)	1 (<1)
Any severe TEAE [†]	18 (6)	11 (4)	76 (13)	55 (9)
Any severe TRAE [†]	7 (2)	0	18 (3)	6 (1)
Any TEAE leading to study discontinuation	25 (8)	6 (2)	45 (7)	15 (3)
Any TRAE leading to study discontinuation	25 (8)	3 (1)	40 (7)	6 (1)
TRAE with associated epinephrine administration	2	0	1	0

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

*Serious AEs were defined as events that caused death or were life-threatening; resulted in persistent or significant disability/incapacity; resulted in (or prolonged an existing) inpatient hospitalization; or that were a congenital anomaly/birth defect (in an offspring of a subject receiving study drug).

[†]Severe AEs were those assessed as incapacitating, resulting in inability to do normal activities or having a significant effect on clinical status, and that warranted intervention.

Table 4. Details of the serious treatment-related AEs in 923 subjects receiving timothy grass SLIT-tablet

Trial Name	Age, y	Serious AE by Preferred MedDRA Term	Severity	Day of Onset	Duration, d	Action Taken	Event Details: Outcome
GAP	8	Dyspnea	Moderate	689	2	None	Subject experienced itching under the tongue subsequent to SLIT-tablet intake. Subject swallowed the SLIT-tablet, developed itching in the throat, started coughing, and developed sense of difficulty breathing: Recovered
GAP	9	Generalized tonic-clonic seizure	Moderate	244	1	SLIT-tablet discontinued	Event occurred while playing football, no signs of a systemic allergic reaction accompanied the event. EEG indicated possible epileptic activity: Recovered
GAP	9	Immune thrombocytopenic purpura	Severe	14	-*	SLIT-tablet discontinued	Presented with multiple hematomas and petechiae after sports incident: Not recovered
GAP	10	Abdominal pain	Moderate	17	3	SLIT-tablet temporarily interrupted	Abdominal pain accompanied by fever: Recovered
GAP	6	Asthma	Moderate	310	2	β 2-agonist; SLIT-tablet continued	Hoarseness and cough after spending time in garden after lawn was mowed;

							relapsed next evening and was hospitalized: Recovered
GAP	11	Anemia	Severe	756	96	SLIT-tablet discontinued	Experienced tiredness after several months; tested for anemia because sister had history of anemia: Recovered
GT-23	10	Hypersensitivity	Severe	1	2	Epinephrine, albuterol, betamethasone, methylprednisolone, cetirizine; SLIT-tablet discontinued	Systemic allergic reaction within 5 minutes of first tablet intake. Dysphagia and respiratory distress with drop in blood pressure to 90/55 mmHg [†] . Episode duration of 30 minutes. Discharged from clinic after 24-hour observation: Recovered

AE, adverse event; SLIT, sublingual immunotherapy.

*Stop date is unavailable.

[†]Baseline blood pressure was 110/65 mmHg. 90/55 mmHg is above the limit for hypotension for this age group (limit is $<70 \text{ mm Hg} + [2 \times \text{age}]$). The event was not reported as anaphylactic shock.

Figure Legend

Figure 1. Treatment-related AEs occurring in $\geq 2\%$ or more of subjects in any treatment group in the pooled population (all treated subjects). AE, adverse event; SLIT, sublingual immunotherapy.