Original Article

Epinephrine Use in Clinical Trials of Sublingual Immunotherapy Tablets

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What is already known about this topic? Allergy immunotherapy can result in systemic allergic reactions and even life-threatening anaphylaxis requiring epinephrine administration.

What does this article add to our knowledge? Epinephrine administrations in response to timothy grass, ragweed, and house dust mite sublingual immunotherapy (SLIT)-tablet-related events are uncommon, typically occur within the first week of treatment, and are rarely self-administered. SLIT-tablet events treated with epinephrine were nonserious.

How does this study impact current management guidelines? Systemic allergic reactions and severe swellings may occur at first SLIT-tablet administration and are manageable with conventional treatment, including epinephrine. Rarely, systemic allergic reactions occur after the first dose.

BACKGROUND: Allergy immunotherapy can result in systemic allergic reactions and even life-threatening anaphylaxis requiring epinephrine administration.
OBJECTIVE: The objective of this study was to describe epinephrine use in the clinical trial development programs of 3 rapidly dissolving sublingual immunotherapy tablets (SLIT-tablets; Merck & Co., Inc., Kenilworth, NJ/ALK, Hørsholm, Denmark/Torii Pharmaceutical Co., Ltd., Tokyo, Japan).
METHODS: Data on epinephrine use were collected from 13 timothy grass SLIT-tablet trials (MK-7243; ≤2800 bioequivalent allergen units/75,000 SQ-T dose, n = 2497; placebo, n = 2139), 5 short ragweed SLIT-tablet trials (MK-3641; ≤12 Amb a 1-U, n = 1725; placebo, n = 770), and 11 house dust mite (HDM) SLIT-tablet trials (MK-8237; ≤12 SQ-HDM; n = 3930; placebo, n = 2246).
RESULTS: In grass SLIT-tablet trials, epinephrine was used 13 times (grass SLIT-tablet, n = 10; placebo, n = 3). Eight administrations were for grass SLIT-tablet-related adverse events (AEs): 4 for systemic allergic reactions and 4 for local mouth and/or throat swelling. In ragweed SLIT-tablet trials, epinephrine was used 9 times in 8 subjects (ragweed SLIT-tablet, n = 7; placebo, n = 1 [2 administrations for protracted anaphylaxis]). Four administrations were for ragweed SLIT-tablet-related AEs: 1 for systemic allergic reaction and 3 for local mouth and/or pharynx/throat swelling. In HDM SLIT-tablet trials, epinephrine was administered 13 times (HDM SLIT-tablet, n = 8; placebo, n = 5). Four administrations were for HDM SLIT-tablet-related AEs: 1 for systemic allergic reaction and 3 for local events. Of the 16 epinephrine administrations for events related to SLIT-tablet treatment, 11 occurred within the first week of treatment (7 administrations on day 1) and 5 were subject self-administered.
CONCLUSIONS: Epinephrine administrations in response to SLIT-tablet-related reactions in clinical trials are uncommon, typically occur within the first week of treatment, and are rarely self-administered. All SLIT-tablet-related events treated with epinephrine were nonserious. © **2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:84-9)**

Key words: *Adrenaline; Allergen immunotherapy; Anaphylaxis; Epinephrine; Safety; Sublingual immunotherapy; Systemic allergic reaction*

Allergy immunotherapy can result in systemic allergic reactions and even life-threatening anaphylaxis.[1-3] Specifically for sublingual immunotherapy (SLIT), swelling of the oral or

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Abbreviations used
AE- Adverse event
AR/C- Allergic rhinitis with or without conjunctivitis
BAU- Bioequivalent allergen units
HDM- House dust mite
ICS- Inhaled corticosteroid
SCIT- Subcutaneous immunotherapy
SLIT- Sublingual immunotherapy

laryngeal pharynx is an additional safety concern. To date, all fatal anaphylactic events associated with allergy immunotherapy have been with subcutaneous immunotherapy (SCIT). No fatal cases of anaphylaxis have been associated with SLIT, and only a few nonfatal systemic allergic reactions defined as anaphylactic events have been reported.[4] The rate of anaphylaxis, as defined by the World Allergy Organization,[5,6] with SLIT has been estimated at 1 case/100,000,000 administrations.[4]

First-line treatment for anaphylaxis is intramuscular administration of epinephrine.[6] In the United States, prescription of autoinjectable epinephrine along with a prescription for approved SLIT products is mandatory.[7-9] However, an epinephrine prescription with SLIT is not required in non-US trials by regulatory agencies or institutional review boards and is not generally provided with SLIT products outside of the United States.[10]

The overall safety and tolerability of 3 rapidly dissolving SLIT-tablets for the treatment of timothy grass (and related grasses), short ragweed, and house dust mite (HDM) allergic rhinitis with or without conjunctivitis (AR/C) has been established in multiple double-blinded, placebo-controlled trials,[11-33] but the treatment of adverse events (AEs) with epinephrine has not been systematically evaluated. The objective of this analysis was to describe epinephrine use in the clinical trial development programs of these SLIT-tablets.

METHODS

Injectable epinephrine use in all of the phase 1, phase 2, and phase 3 double-blinded, placebo-controlled trials conducted for timothy grass SLIT-tablet (MK-7243; GRASTEK/GRAZAX; Merck & Co., Inc., Kenilworth, NJ/ALK, Hørsholm, Denmark), short ragweed SLIT-tablet (MK-3641; RAGWITEK; Merck/ALK), and SQ HDM SLIT-tablet (MK-8237; ACARIZAX/MITICURE; Merck/ALK/Torii Pharmaceutical Co., Ltd., Tokyo, Japan) was evaluated.[11-36] Characteristics for these trials are reported in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org), and specific details for most of these trials have been previously described.[11-33] Some of the phase 1 trials were dose-ranging trials; however, for this report only epinephrine use in subjects receiving any dose evaluated up to the approved dose for timothy grass (2800 bioequivalent allergen units [BAU]/75,000 SQ-T in North America and Europe), short ragweed (12 Amb a 1-U in North America), and SQ HDM SLIT-tablets (up to and including 12 SQ-HDM in Europe) was evaluated. In Japan, 6 SQ-HDM is the approved dose although any epinephrine use up to and including 12 SQ-HDM was evaluated.

The tablets were administered once daily. In the Japanese phase 2/3 SQ HDM SLIT-tablet trials, an up-titration sequence was performed beginning with the 2 SQ-HDM dose for 1 week, followed by the 6 SQ-HDM dose for 1 week (or through the end of the trial for the 6 SQ-HDM group), followed by escalation to the 12 SQ-HDM dose for subjects in the 12 SQ-HDM group.[35,36] Up-titration was not performed in any of the other trials. In all the trials, administration of the first dose (and the second dose in a few of the phase 1 trials) was under medical supervision in an office setting, followed by self-administration at home. Epinephrine autoinjectors were provided to subjects in most of the trials conducted in North America (see Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Site personnel, investigators, and subjects were educated regarding the possible signs and symptoms of systemic allergic reactions in the trials that provided epinephrine. It was clearly instructed in the protocols that self-injectable epinephrine is intended for immediate self-administration for a severe systemic allergic reaction. The investigator or designee was requested to properly educate the subject/parent/guardian on administration of the epinephrine and provide informational materials including an Anaphylaxis Emergency Action plan. Subjects were given a written Anaphylaxis Emergency Action Plan adapted from an American Academy of Allergy, Asthma & Immunology position statement and Simons et al.[37,38] No epinephrine autoinjectors were provided in the European and Japanese trials.

Eligible subjects had a primary diagnosis of AR/C or asthma to the respective allergens, and demonstrated sensitivity to the allergens by the skin prick test and serum-specific IgE. Most of the trials included subjects with a primary diagnosis of AR/C (with or without asthma), whereas 7 trials only included subjects with a primary diagnosis of asthma (with or without AR/C). No epinephrine autoinjectors were provided as emergency rescue medication to subjects in the asthma trials as they were conducted outside of the United States.

The rate of SLIT-tablet treatment-related events with epinephrine administration by number of tablets was calculated by dividing the number of total SLIT-tablet treatment-related events with epinephrine administrations by the total number of exposure days. Daily exposure was considered equivalent to a tablet intake as subjects were required to take a tablet every day. Total exposure was calculated for the phase 2, phase 2/3, and phase 3 trials only, as the phase 1 trials were small, of short duration, and did not have any reported occurrences of treatment-related events with epinephrine administrations.

For this analysis, systemic allergic reactions were defined as investigator-reported "anaphylactic reaction," "hypersensitivity," "systemic allergic reaction," "anaphylaxis," and "allergic reaction." A serious AE was defined as an AE that resulted in death, a life-threatening event, persistent or significant disability/incapacity, congenital anomaly or birth defect, required hospitalization or prolonged existing hospitalization, or was a medically important event as determined by the investigator. According to the protocols, other important medical events may be considered a serious adverse experience when, based on appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the "serious" outcomes of death, life-threatening event, persistent or significant disability/incapacity, and so on. Grading of the intensity of an AE was conducted by the investigator. Mild intensity was defined as awareness of sign, symptom, or event, but was easily tolerated. Moderate intensity was defined as discomfort enough to cause interference with usual activity and may have warranted intervention. Severe intensity was defined as incapacitating with inability to do usual activities or significantly affected clinical status and warranting intervention.

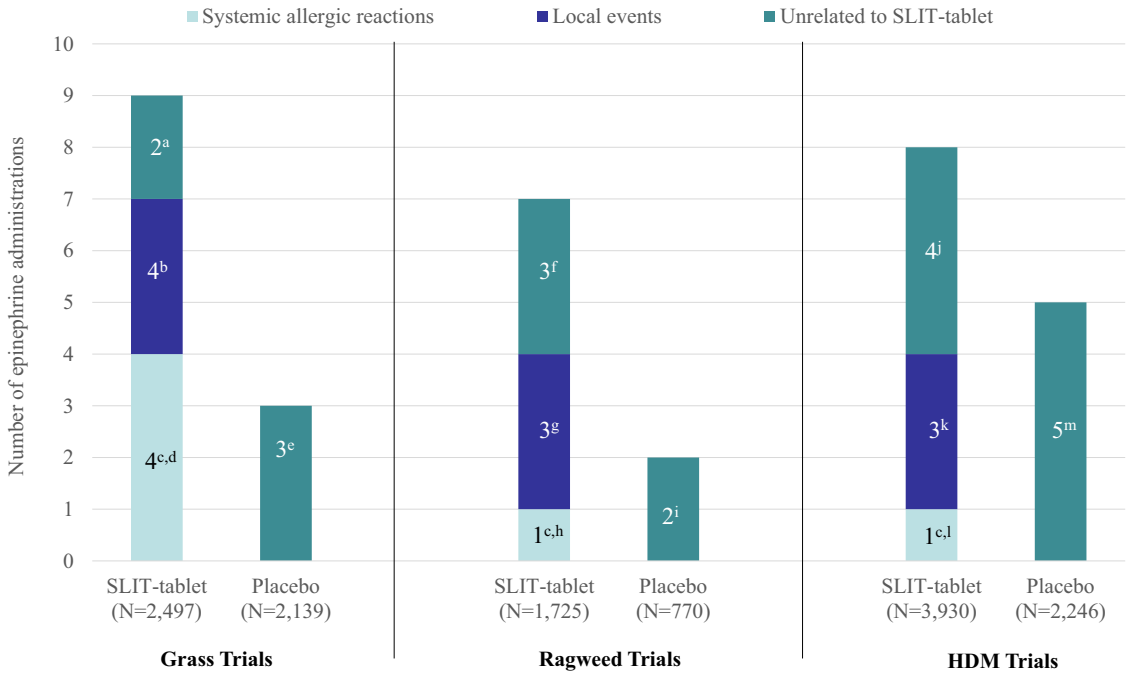

FIGURE 1. Epinephrine administrations in SLIT-tablet trials. [a]In response to bed bug reaction, viral infection. [b]In response to swelling in the mouth and/or throat (n = 2, moderate; n = 2, severe). [c]Defined as investigator-reported "anaphylactic reaction," "hypersensitivity," "systemic allergic reaction," "anaphylaxis," and "allergic reaction." [d](n = 2, mild; n = 2 moderate). [e]In response to anxiety, wheezing, vasculitis. [f]In response to food allergy (n = 2), vomiting/diarrhea (acute gastroenteritis, n = 1). [g]In response to swelling in the mouth and/or pharynx/throat (n = 1, moderate; n = 2, severe). [h](n = 1, severe). [i]In response to serious life-threatening anaphylaxis with protracted symptoms, 2 administrations in the same subject; possible etiology of allergic reaction to latex. [j]In response to dust exposure (n = 1), cancer (n = 2), and melanocytic nevus (n = 1). [k]In response to severe swelling in throat (n = 1), mild mouth/throat pruritus and dysphonia (n = 1), and moderate discomfort of throat and chest (n = 1). [l](n = 1, moderate). [m]In response to a complex constellation of symptoms consistent with systemic allergic reaction of unknown cause (n = 1), dermal cyst (n = 1), cervical dysplasia (n = 1), and food allergies (n = 2). *HDM*, House dust mite; *SLIT*, sublingual immunotherapy.

RESULTS

Subject characteristics

In all, 8152 subjects received up to and including the approved doses of timothy grass (2800 BAU), ragweed (12 Amb a 1-U), and HDM SLIT-tablets (12 SQ-HDM), 6799 subjects received approved doses, and 5155 subjects received placebo. In the grass SLIT-tablet trials, approximately 84% of subjects were polysensitized and approximately 28% of subjects had a history of asthma requiring, at most, low-dose inhaled corticosteroid (ICS). In the ragweed SLIT-tablet trials, approximately 81% of subjects were polysensitized and approximately 18% of subjects had a history of asthma requiring, at most, medium-dose ICS. In the HDM SLIT-tablet trials, approximately 75% of subjects were polysensitized and approximately 56% of subjects had a history of asthma requiring, at most, medium-dose ICS.

Overall epinephrine summary

In total, there were 35 epinephrine administrations in the 29 SLIT-tablet trials (see Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Of these 35 administrations, 25 were in subjects receiving SLIT-tablets and 16 of these 25 administrations were for SLIT-tablet treatment-related events resulting in an event rate of 0.2% (16/8152 subjects) administrations/subject; 15 of the 16 administrations for SLIT-tablet treatment-related events were in subjects receiving approved SLIT-tablet doses for an event rate of 0.2% (15/6799) and 1 administration was in a subject receiving a lower than approved dose (6 Amb a 1-U for ragweed SLIT-tablet). Nine administrations were in subjects receiving SLIT-tablet treatment, but were for events unrelated to treatment. Ten administrations were in placebo subjects resulting in an event rate of 0.2% (10/5155 subjects). The total number of SLIT-tablets received was 891,057 (grass = 370,309; ragweed = 132,125; and HDM = 388,623), resulting in an epinephrine administration rate for SLIT-tablet treatment-related events of 0.002% (16/891,057) or 1.80 administrations per 100,000 tablets. Only 2 of the epinephrine administrations occurred in Europe; both administrations were in response to SLIT-tablet-related local events; these administrations occurred on day 1 and day 74 under medical supervision. There were no epinephrine administrations for events related to SLIT-tablet treatment in the 7 asthma trials.

All of the SLIT-tablet-related events requiring epinephrine were treated successfully with no further complications. All of the AEs assessed as severe and treated with epinephrine were mouth or throat swelling, and none of these compromised the airway or fulfilled the definition of "serious." Approximately 1% of subjects experienced a local swelling assessed as severe.

We attempted to do a risk factor analysis for epinephrine use. However, it was found that because of the low event rate in the

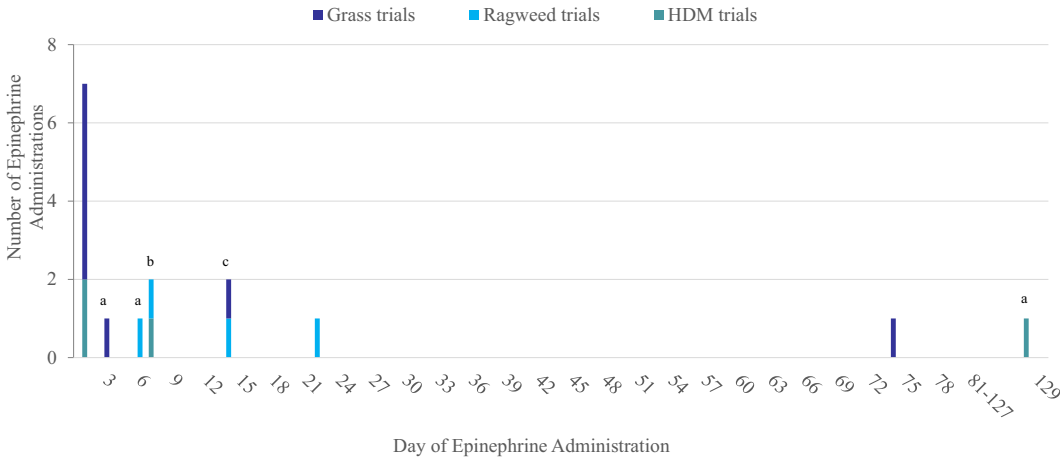

FIGURE 2. Timing of epinephrine administrations in response to events related to SLIT-tablets. [a]Epinephrine self-administered. [b]Epinephrine self-administered for event related to SQ HDM SLIT-tablet. [c]Epinephrine self-administered for event related to ragweed SLIT-tablet. *HDM*, House dust mite; *SLIT*, sublingual immunotherapy.

clinical trials and limited postmarketing data, a risk factor analysis was not possible.

Epinephrine administration in grass trials

In all, 4636 subjects received up to and including the approved dose or placebo in the grass SLIT-tablet trials. Ten administrations occurred in subjects receiving SLIT-tablet and three occurred in subjects receiving placebo (Figure 1). Of the administrations in subjects receiving grass SLIT-tablet, 4 were for treatment-related systemic allergic reactions (all day 1 of treatment) and 4 were for treatment-related local events. Additional details of the systemic allergic reactions are described in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org). None of the events were reported as serious, and no compromise of airways was observed. Additional details of event severity and epinephrine administrations unrelated to SLIT-tablets are given in Figure 1.

Epinephrine administration in ragweed trials

In all, 2495 subjects received up to and including the approved dose or placebo in the ragweed SLIT-tablet trials. Seven administrations occurred in subjects receiving SLIT-tablet, and two occurred in one subject receiving placebo in response to protracted symptoms (urticaria and approximately 1 hour after the tablet intake subject developed cough, dyspnea, pharyngeal pruritus, and thoracic pain; possible etiology of allergic reaction to latex; Figure 1). Of the administrations in subjects receiving ragweed SLIT-tablet, 1 was for a treatment-related systemic allergic reaction (day 6 of treatment) and 3 were for treatment-related local events. Additional details of the systemic allergic reaction are described in Table E3 (available in this article's Online Repository at www.jaci-inpractice.org). None of the SLIT-tablet-related events were reported as serious, and no compromise of airways was observed. Additional details of event severity and epinephrine administrations unrelated to SLIT-tablets are given in Figure 1.

Epinephrine administration in HDM trials

In all, 6176 subjects received SQ HDM SLIT-tablets or placebo. Eight administrations occurred in subjects receiving SQ HDM SLIT-tablet, and five occurred in subjects receiving placebo (Figure 1). Of the administrations in subjects receiving SQ HDM SLIT-tablet, 1 was for a treatment-related systemic allergic reaction (day 1 of treatment) and 3 were for treatment-related local events. Additional details of the systemic allergic reaction are described in Table E4 (available in this article's Online Repository at www.jaci-inpractice.org). None of the events were reported as serious, and no compromise of airways was observed. Additional details of event severity and epinephrine administrations unrelated to SLIT-tablets are given in Figure 1.

Timing of epinephrine administrations

Of the 16 epinephrine administrations for events related to SLIT-tablet treatment, 7 occurred on day 1 of treatment during the medical supervision period. A total of 11 administrations occurred within the first week of treatment (Figure 2). The latest recorded administration was day 128 in a 1-year HDM SLIT-tablet trial. Six of the epinephrine administrations that occurred after day 1 of treatment were for events assessed as severe (preferred terms: swelling and throat irritation on day 3; anaphylactic reaction on day 6; throat tightness on day 7; throat tightness on day 14; pharyngeal edema on day 22; and swollen tongue on day 74).

Self-administered epinephrine

Self-injectable epinephrine has been provided as rescue medication to most subjects in the recent North American trials; a total of 6427 subjects received kits with self-injectable epinephrine. Trial subjects were instructed and trained in its appropriate use, and were asked to seek immediate medical care on its use. Of the 9 epinephrine administrations in the grass trials that provided self-injectable epinephrine, 3 were self-administered; one of these 3 administrations was for an event related to grass SLIT-tablet (Figure 2). The 3 self-administrations were in response to a local event (n = 1), bed bug reaction (n = 1), and anxiety (n = 1). Of the 9 administrations in the ragweed trials that provided self-injectable epinephrine, 5 were self-administered; 2 of the 5 administrations were for events related to ragweed SLIT-tablet (Figure 2). The 5

self-administrations were in response to a severe systemic allergic reaction (n = 1), local event (n = 1), food allergy (n = 2), and acute gastroenteritis (n = 1). Of the 7 administrations in the HDM trials that provided self-injectable epinephrine, 5 were self-administered; 2 of these 5 administrations were for an event related to SQ HDM SLIT-tablet (Figure 2). The 5 self-administrations were in response to local events (n = 2), food allergy (n = 2), and reaction to environmental dust (n = 1).

DISCUSSION

Using data from 29 clinical trials comprising 8152 SLIT-tablet-treated subjects, the safety profile of the timothy grass, ragweed, and SQ HDM SLIT-tablets suggests that systemic and severe local AEs treated with epinephrine administration were uncommon. The epinephrine administration rate per subject was 0.2% for SLIT-tablet treatment-related events and 0.2% with placebo treatment. The number of epinephrine administrations for SLIT-tablet treatment-related events was 1.80 per 100,000 tablets, indicating that the risk of an event requiring epinephrine administration during a 3-year treatment period is very low. No similar compilation of epinephrine use with SCIT has been reported, although in a real-life SCIT AE study (n = 1038) the epinephrine administration rate for AEs was 2% of subjects.[39] In the current analysis, of the 35 total epinephrine administrations, 6 were for events assessed as severe and related to SLIT-tablet by the treating physician. However, none of the events were considered serious and no compromise of airways was observed. Together these data support the favorable safety profile of SLIT.[4]

A limitation of this analysis is that the relationship of the use of epinephrine to SLIT-tablet treatment was not adjudicated by an independent committee. The relationship to each event was assessed by the treating physician. Of the 25 epinephrine administrations in subjects receiving SLIT-tablets, 9 (36%) were for events assessed by the investigator as unrelated to SLIT-tablets. Several of the epinephrine administrations unrelated to SLIT-tablets or in the placebo group were for food-related allergic reactions, whereas some of the reasons for epinephrine administration were questionable. Notably, only 2 of the epinephrine administrations occurred in the European trials. The relatively low administration of epinephrine in Europe does not imply a lack of reactions to SLIT-tablets, nor do we feel the training regarding epinephrine use in the North American trials was lacking or inconsistent with recommended practice. Rather, the increased use of epinephrine in the North American trials may be reflective of a different treatment practice response to AEs by US prescribers with subsequent epinephrine use for milder symptoms. It may also in part be due to the distribution of self-injectable epinephrine in the North American studies as required by the US Food and Drug Administration, because 37% (13/35) of the epinephrine events were self-administered. Only 5 of the 13 self-administrations were for events related to SLIT-tablet treatment; 4 of these 5 events were local events and 1 was for a severe systemic allergic reaction. Self-injectable epinephrine is rarely prescribed with SLIT in Europe,[10] and given the results of the current analysis, the need to prescribe epinephrine autoinjectors to all patients prescribed SLIT-tablets in the United States should be revisited.

A preferred term as assigned by the investigator of "anaphylactic reaction" was assigned to 3 of the systemic allergic reactions treated with epinephrine. When these reactions were evaluated using the criteria developed by the World Allergy Organization[5] or the criteria developed by the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network,[40] they were not considered anaphylaxis as acute cardiovascular or respiratory compromise was not observed.

The majority of epinephrine administrations in response to SLIT-tablet-related events occurred within the first week of treatment. Seven of the administrations were for events that occurred within minutes of the first dose on day 1 when the subjects were under medical supervision. This finding supports the recommended practice of initiating treatment in a health care setting under the supervision of a physician experienced with allergic rhinoconjunctivitis, and where adequate treatment for a severe local or systemic allergic reaction is available.

The analysis of this large clinical trial dataset indicates that epinephrine administrations in response to SLIT-tablet reactions are uncommon and for nonserious events. The systemic and local AEs are easily managed and typically occur within the first week of treatment. Furthermore, epinephrine is rarely self-administered in response to a SLIT-tablet-related event.

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TABLE E1. Characteristics of trials included in the analysis

Protocol number, author, registration number	Phase, population, sex	Randomized total number	Approximate daily treatment duration	Inclusion age (mean age), y	Epinephrine provided to study subjects	Number of epinephrine administrations*
Grass SLIT-tablet						
GT-01, Malling et al[29], NR	Phase 1, AR/C, 57% male	47	Up to 15 wk	≥18 (32.5)	No	0
GT-03, Kleine-Tebbe et al,[28] NR	Phase 1, AR/C, 76% male	84	28 d	≥18 (33.2)	No	0
GT-04, Calderon and Essendrop,[24] NR	Phase 1, AR/C, 63% male	43	28 d	≥18 (24.6)	No	0
GT-09, Ibanez et al,[27] NCT00310453	Phase 1, AR/C, 73% male	30	28 d	5-12 (9.7)	No	0
GT-11, Ibanez et al,[27] NCT00298701	Phase 1, AR/C, 60% male	30	28 d	5-12 (8.0)	No	0
GT-02, Durham et al,[26] NR	Phase 2, AR/C, 62% male	855	24 wk	≥18 (35.0)	No	1 (related to SLIT-tablet, n = 1)
GT-07, Dahl et al,[15] NR	Phase 2, mild to moderate asthma, 68% male	114	24 wk	≥18 (35.7)	No	0
GT-08 (y 1), Dahl et al,[14] NCT00227279	Phase 3, AR/C, 59% male	634	1 y	≥18 (34.2)	No	0
GT-12, Bufe et al,[12] NCT00408616	Phase 3, AR/C, 66% male	253	24 wk	5-16 (10.1)	No	0
GT-14, Murphy et al,[18] NCT00421655	Phase 3, AR/C, 47% male	329	24 wk	≥18 (35.9)	No	3 (related to SLIT-tablet, n = 3)
P05238, Nelson et al,[19] NCT00562159	Phase 3, AR/C, 50% male	439	24 wk	≥18 (35.9)	Yes	2 (related to SLIT-tablet, n = 1; unrelated, n = 1)
P05239, Blaiss et al,[11] NCT00550550	Phase 3, AR/C, 65% male	345	24 wk	5-17 (12.3)	Yes	3 (related to SLIT-tablet, n = 1; unrelated, n = 2)
P08067, Maloney et al,[17] NCT01385371	Phase 3, AR/C, 53% male	1501	24 wk	5-65 (33.5)	Yes	4 (related to SLIT-tablet, n = 2; unrelated, n = 2)
Total		4636†				13
Ragweed SLIT-tablet						
RT-01, Nayak et al,[31] NCT01134705	Phase 1, AR/C, 49% male	53	28 d	18-50 (30.1)	No	0
P06081, Nolte et al,[20] NCT00978029	Phase 2, AR/C, 38% male	203	28 d	≥50 (56.0)	Yes	1 (unrelated, n = 1)
P05233, Nolte et al,[21] NCT00783198	Phase 3, AR/C, 49% male	565	1 y	18-50 (35.4)	Yes	2 (related to SLIT-tablet, n = 1; unrelated, n = 1)
P05234, Creticos et al,[13] NCT00770315	Phase 3, AR/C, 49% male	783	1 y	18-50 (36.5)	Yes	1 (unrelated, n = 1)
P05751, Nolte et al,[20] NCT01469182	Phase 3, AR/C, 42% male	913	28 d	≥18 (41.5)	Yes	5 (related to SLIT-tablet, n = 3; unrelated, n = 2)
Total		2495‡				9
HDM SLIT-tablet						
MT-01, Corzo et al,[25] EudraCT:2005-002151-41	Phase 1, mild to moderate asthma, 38% male	71	28 d	≥18 (28.7)	No	0
MT-03, Corzo et al,[25] EudraCT:2007-000402-67	Phase 1, mild to moderate asthma, 69% male	72	28 d	5-14 (9.1)	No	0
P008, Maloney et al,[23] NCT01678807	Phase 1, AR/C, 63% male	195	28 d	12-17 (14.4)	Yes	0
203-1-1,[34] JapicCTI-111624	Phase 1, mild to moderate asthma, 100% male	48	14	20-49 (30.8)	No	0

MT-02, Mosbech et al,[30] NCT00389363	Phase 2/3, mild to moderate asthma requiring ICS (100-800mcg/dbudesonide), 53% male	604	1 y	≥14 (31.6)	No	0
P003, Nolte et al,[22] NCT01644617	Phase 2, AR/C, 47% male	124	24 wk	≥18 (27.3)	No	0
P001, Nolte et al,[32] NCT01700192	Phase 3, AR/C, 41% male	1482	Up to 1 y	≥12 (35.1)	Yes	7 (related to SLIT-tablet, n = 3; unrelated, n = 4)
MERIT, Demoly et al,[16] NCT01454544	Phase 3, AR/C, 50% male	992	1 y	≥18 (32.3)	No	1 (related to SLIT-tablet, n = 1)
MITRA, Virchow et al,[33] NCT01433523	Phase 3, asthma not well-controlled by ICS (400-1200 mcg budesonide), 52% male	834	18 mo	≥18 (33.4)	No	0
203-3-1,[35] JapicCTI-12847	Phase 2/3, asthma not well-controlled by ICS (200-400 mcg fluticasone), 51% male	826	Up to 19 mo	18-64 (38.2)	No	4 (unrelated, n = 4)
203-3-2,[36] JapicCTI-121848	Phase 2/3, AR/C, 46% male	946	1 y	12-64 (26.9)	No	1 (unrelated, n = 1)
Total		6176§				13

AR/C, Allergic rhinitis with or without conjunctivitis; *BAU*, bioequivalent allergen units; *HDM*, house dust mite; *ICS*, inhaled corticosteroid; *NR*, not registered; *SLIT*, sublingual immunotherapy tablet.
*Only includes administrations in subjects receiving up to and including the approved doses of SLIT-tablets and placebo.
†Total only includes subjects receiving up to and including the 2800 BAU dose (approved dose) and placebo.
‡Total only includes subjects receiving up to and including the 12 Amb a 1-U dose (approved dose) and placebo.
§Total only includes subjects receiving up to and including the 12 SQ-HDM dose (highest approved dose) and placebo.

TABLE E2. Grass SLIT-tablet-related systemic allergic reactions treated with epinephrine in grass trials

Preferred term	Symptoms/signs of the reaction	Intensity	Day of onset	Treatment	Epinephrine self-administered	Discontinued trial
Anaphylactic reaction	Swelling of lips, oral itch, and dysphagia	Moderate	1	Epinephrine, cetirizine	No	Yes
Drug hypersensitivity	Chest discomfort, dysphagia, dysphonia, oral pharyngeal itch, swelling and irritation, rash	Mild	1	Epinephrine, loratadine, prednisone	No	Yes
Anaphylactic reaction	Oral itch, sneezing, rhinorrhea, and throat irritation	Mild	1	Epinephrine, loratadine	No	No
Hypersensitivity	Lip swelling, dysphagia, and intermittent cough	Moderate	1	Epinephrine	No	Yes

SLIT, Sublingual immunotherapy.

TABLE E3. Ragweed SLIT-tablet-related systemic allergic reactions treated with epinephrine in ragweed trials

Preferred term	Symptoms/signs of the reaction	Intensity	Day of onset	Treatment	Epinephrine self-administered	Discontinued trial
Anaphylactic reaction	Oral symptoms, throat swelling, dyspnea, nausea, light-headedness	Severe	6	Epinephrine, diphenhydramine, prednisone, ranitidine	Yes	Yes

SLIT, Sublingual immunotherapy.

TABLE E4. SQ-HDM SLIT-tablet-related systemic allergic reactions treated with epinephrine in HDM trials

Preferred term	Symptoms/signs of the reaction	Intensity	Day of onset	Treatment	Epinephrine self-administered	Discontinued trial
Hypersensitivity	Itchy palms, facial flushing, dyspnea, presyncope, throat swelling	Moderate	1	Epinephrine, desloratadine, pseudoephedrine	No	Yes

HDM, House dust mite; *SLIT;* sublingual immunotherapy; *SQ*, standardized quality.