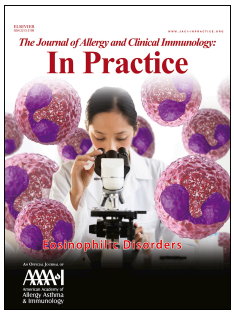
Journal Pre-proof



Anaphylaxis in Clinical Trials of Sublingual Immunotherapy Tablets

Hendrik Nolte, MD, PhD, Moisés A. Calderon, MD, David I. Bernstein, MD, Graham Roberts, DM, Ryuji Azuma, MSc, Ruta Gronskyte Juhl, PhD, Veronica Hulstrøm, MD, PhD

PII: S2213-2198(23)01253-9

DOI: https://doi.org/10.1016/j.jaip.2023.11.011

Reference: JAIP 5151

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 6 April 2023

Revised Date: 3 November 2023

Accepted Date: 7 November 2023

Please cite this article as: Nolte H, Calderon MA, Bernstein DI, Roberts G, Azuma R, Juhl RG, Hulstrøm V, Anaphylaxis in Clinical Trials of Sublingual Immunotherapy Tablets, *The Journal of Allergy and Clinical Immunology: In Practice* (2023), doi: https://doi.org/10.1016/j.jaip.2023.11.011.

Anaphylaxis in Clinical Trials of Sublingual Immunotherapy Tablets

Hendrik Nolte, MD, PhD[1], Moisés A. Calderon, MD[2], David I. Bernstein, MD[3], Graham Roberts, DM[4], Ryuji Azuma, MSc[5], Ruta Gronskyte Juhl, PhD[6], Veronica Hulstrøm, MD, PhD[6*]

[1]ALK, Bedminster, NJ, USA; [2]University of Costa Rica, San Jose, Costa Rica; [3]Bernstein Allergy Group Inc, and Department of Internal Medicine, The University of Cincinnati College of Medicine, Cincinnati, OH, USA; [4]The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport Isle of Wight, UK, NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK, and University of Southampton, Southampton, UK; [5]Torii Pharmaceutical Co., Ltd., Tokyo, Japan; [6]ALK, Hørsholm, Denmark

*Current affiliation is GlaxoSmithKline, Belgium

Email addresses: veronica.x.hulstrom@gsk.com; moisescalderonzapata@gmail.com; bernstdd@ucmail.uc.edu; g.c.roberts@soton.ac.uk; ryuji.azuma@torii.co.jp; RutaGronskyte.Juhl@alk.net; Hendrik.Nolte@alk.net

Corresponding author:

Hendrik Nolte, MD, PhD
ALK
US Highway 135 Route 202/206
Bedminster NJ 07921
Telephone: (+1) 516 767 1800
Email: Hendrik.nolte@alk.net

Funding source: Funding for these studies was provided by ALK, Hørsholm, Denmark, Merck & Co., Inc., Kenilworth, NJ, USA, and Torii Pharmaceutical Co., Ltd., Tokyo, Japan. For this analysis, ALK was involved in the study design, analysis and interpretation of the data, and the writing of the report. Torii was involved in reviewing the report. Merck had no role in this analysis. The decision to submit the manuscript was made by all authors.

Disclosures: H. Nolte and R. Gronskyte Juhl are employees of ALK. D.I. Bernstein has received grant support from Aimmune, ALK, Amgen, AstraZeneca, Avillion, Biocryst, Genentech, GlaxoSmithKline, Leo, Novartis, Novum, Regeneron, Shire, and TEVA and served as an advisor for ALK America, Aquestive, Gerson-Lehman, Guidepoint Global and Regeneron. M.A. Calderon has received lecture and consultant honorarium and served as an advisor for ALK-Abello. G. Roberts has served as an investigator for ALK and is president of the British Society for Allergy and Clinical Immunology. R. Azuma is an employee of Torii Pharmaceutical Co.V. Hulstrøm is a former employee of ALK.

Word counts: abstract=253; main text=3306

Abstract

Background: There is no consensus method to identify anaphylaxis in sublingual immunotherapy (SLIT) trials. Standardized MedDRA Queries (SMQs) are standardized groupings of MedDRA terms used in drug safety monitoring.

Objective: To develop a method to identify potential anaphylaxis in SLIT-tablet trials using SMQ searches and case definitions of anaphylaxis adopted from the National Institute of Allergy and Infectious Disease.

Methods: The SMQ search tool contained 2 criteria including treatment-emergent adverse events (AEs): 1) narrow MedDRA terms related to anaphylaxis, and 2) all AEs with broad MedDRA terms from at least 2 of 3 categories (respiratory/skin/cardiovascular) occurring on the same day. Criteria were applied to a pooled dataset of all subjects from 48 timothy grass, ragweed, house dust mite and tree SLIT-tablet trials (SLIT-tablet, N=8200; placebo, N=7033). Additional search strategies were any treatment-emergent AE with MedDRA preferred term "hypersensitivity" and epinephrine administrations. Identified potential cases underwent blinded independent medical expert review. Non-anaphylaxis cases were designated local AEs or mild-to-moderate systemic reactions.

Results: Using the SMQ search tool and after subsequent medical review, 8 anaphylaxis cases were identified; 3 were considered treatment-related, resulting in a proportion of anaphylaxis cases/subject of 0.02% (2/8200) with SLIT-tablet and 0.01% (1/7033) with placebo. One additional anaphylaxis case related to SLIT-tablet was identified by the preferred term "hypersensitivity". The 3 anaphylaxis cases associated with SLIT-tablet treatment were not life-threatening. The epinephrine administration rate was 17/8200 (0.2%) with SLIT-tablet treatment and 2/7033 (0.03%) with placebo.

Conclusion: SMQ search criteria for identifying potential anaphylaxis related to SLIT were developed. Anaphylaxis was rare for SLIT-tablets.

Trial registrations: (MITI3001; NCT02596321), (MT-01; EudraCT:2005-002151-41), (MT-03; EudraCT:2007-000402-67), (MT-04; NCT01433523), (MT-06; NCT01454544), (MT-09; CTR20170800), (P001; NCT01700192), (P003; NCT01644617), (P008; NCT01678807), (P009; EudraCT: 2012-005621-70), (TO-203-1-1, JapicCTI-111624), (TO-203-3-1, JapicCTI-121847), (TO-203-3-2; JapicCTI-121848), (TO-203-3-3; JapicCTI-152953), (GRAS3001, NCT02245360), (GT-01, not registered), (GT-02, not registered), (GT-03, not registered), (GT-04, not registered), (GT-07, not registered), (GT-08; NCT00227279), (GT-09; NCT00310453), (GT-10; NCT00293046), (GT-11; NCT00298701), (GT-12; NCT00408616), (GT-14; NCT00421655), (GT-16; NCT00413556), (GT-17; NCT01728285), (GT-18, NCT00773240), (GT-19, NCT01740284), (GT-20, NCT02437786), (GT-21; EudraCT: 2009-011235-12), (GT-22; EudraCT: 2009-014522-41), (GT-23; EudraCT: 2009-014923-22), (GT-24; NCT01854736),

(P006; NCT02256553), (P05238; NCT00562159), (P05239; NCT00550550); (P08067; NCT01385371), (P05233; NCT00783198), (P05234; NCT00770315), (P05751; NCT01469182), (P06081; NTC00978029), (P008; NCT02478398), (TT-01; EudraCT identifier: 2007-003234-42), (TT-02; NCT01675791), (TT-03; NCT02481856), (TT-04; EudraCT-2015-004821-15)

Highlights

What is already known about this topic?

- Anaphylaxis is possible with any allergy immunotherapy treatment
- Despite well-known criteria to identify anaphylaxis in general, there is no consensus method to identify anaphylaxis in relation to SLIT clinical trials
- Standardized SMQ searches are a useful tool for drug safety monitoring

What does this article add to our knowledge?

- The SMQ search tool can be used to identify potential anaphylaxis related to SLIT and may be used to harmonize consistent anaphylaxis reporting across allergy immunotherapy formulations
- In a large dataset of SLIT-tablet trials, anaphylaxis was rare for SLIT-tablets when using the proposed SMQ search criteria and after medical expert review

How does this study impact current management guidelines?

- The SMQ search tool may be used to monitor safety of current and future SLIT products using a simple common algorithm
- Anaphylaxis with the SLIT-tablets is rare

Keywords: allergic rhinitis; allergy immunotherapy; anaphylaxis; systemic allergic reaction; epinephrine; house dust mite; ragweed; tree; grass; sublingual immunotherapy; standardized MedDRA queries; Sampson criteria

Abbreviations: AEs, adverse events; AR/C, allergic rhinitis with or without conjunctivitis; BAU, Bioequivalent Allergy Unit; HDM, house dust mite; MedDRA, Medical Dictionary for Regulatory Activities; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SMQ, standardized MedDRA queries; WAO, World Allergy Organization

Introduction

Sublingual immunotherapy (SLIT)-tablets are a treatment option for allergic rhinitis with or without conjunctivitis (AR/C) and allergic asthma. There is general agreement that SLIT is safer than subcutaneous immunotherapy (SCIT),[1, 2] but all allergy immunotherapy may carry a risk of anaphylaxis. Comparison of anaphylaxis rates between SLIT and SCIT or between SLIT products has been hindered by variable clinical presentations of the rare systemic allergic reactions elicited by SLIT or SCIT (i.e., at differing dosages or with differing major allergen content), low event rates requiring very large trial sample sizes to obtain adequate power, as well as the absence of a consensus method to identify anaphylaxis elicited by SLIT.[3] Physicians may interpret and report systemic allergic reactions differently and report events using different terminology. Thus, the reported incidence of anaphylaxis cases varies considerably and can be both over and underestimated in clinical trials depending on the variability in reporting of adverse events (AEs) and the method of analysis. A robust and standardized approach is needed to better understand the nature and frequency of anaphylaxis events for SLIT products.

In 2006, a National Institute of Allergy and Infectious Disease (NIAID) panel introduced a set of clinical criteria (aka “Sampson criteria”) to define anaphylaxis that can essentially be summarized as the co-occurrence of a constellation of specific signs and symptoms in more than 1 organ system.[4] The intent of the panel was to apply these criteria to anaphylaxis elicited by food allergy. A multinational Joint Task Force sponsored by the World Allergy Organization (WAO) recognized challenges applying the NIAID criteria to SCIT anaphylaxis and subsequently developed a novel system for grading the severity of SCIT systemic allergic reactions.[5] This grading system was later adapted for application to SLIT. Under this system, Grade 3 and 4 systemic reactions are considered anaphylaxis.[6]

The NIAID criteria and the WAO systemic reaction grading system work well in any clinical practice setting. With the complexity and subjectivity of the constellation of signs and symptoms, a standardized method of applying these NIAID criteria to large clinical trial datasets has not been developed. In clinical trials, safety data reported by the investigator are coded using standardized terminology using preferred terms listed in the Medical Dictionary for Regulatory Activities (MedDRA) to describe the AE and other medical terms, as necessary. This results in a consistent coding terminology with a hierarchy of terms organized by System Organ Class. Standardized MedDRA Queries (SMQs) are standardized and validated groupings of MedDRA terms that relate to a defined medical condition or area of medical interest and are intended to aid in case identification.[7] SMQ search tools are commonly used in drug safety monitoring. SMQs include narrow and broad terms. Narrow terms indicate high certainty of the medical condition of interest, whereas broad terms are less specific and require further evaluation and interpretation. The SMQs have been developed since the early 2000's and are used by academia, industry, public health, and government sectors for detecting safety signals in AE safety databases. An SMQ to identify anaphylaxis exists but has rarely been used for incidence reporting in the published literature.

Our goal was to implement a novel and objective method using the SMQ search tool and case definitions of anaphylaxis adopted from the NIAID that could be applied systematically to identify anaphylaxis in subjects participating in SLIT-tablet clinical trials. The identification method was then applied to a large, comprehensive dataset collected during the clinical development of SLIT-tablets for timothy grass pollen, ragweed pollen, tree pollen, and HDM. The dataset was also analyzed using searches for the MedDRA term "hypersensitivity" and epinephrine administrations.

Methods

SMQ search tool

The SMQ search tool used 2 separate search criteria to identify potential anaphylaxis. Criteria 1 was a narrow search of the investigator-recorded treatment-emergent adverse event (AE) MedDRA preferred terms (version 19.0) that represent core anaphylactic reaction terms (e.g., category A of the algorithm, **Supplemental Table EI**). Criteria 2 was essentially application of the NIAID criteria for anaphylaxis,[4] and consisted of a broad SMQ search of the investigator-recorded treatment-emergent AE MedDRA preferred terms for signs and symptoms possibly indicative of anaphylactic reactions (e.g., categories B, C, or D, **Supplemental Table EI**) and an algorithmic tool combining preferred terms from 2 or more system disorders (e.g. respiratory [category B], cutaneous [category C], or cardiovascular [D] or additional gastrointestinal preferred terms). Specifically, all treatment-emergent AEs with a preferred term from category B (i.e., cough, dyspnea) AND a term from category C (i.e., angioedema/urticaria/pruritus/flush) that occurred on the same day OR all treatment-emergent AEs with a term from category D (i.e., hypotension) AND a term from category B (i.e., cough, dyspnea) OR a term from category C (i.e., angioedema/urticaria/pruritus/flush) that occurred on the same day were identified as potential cases of anaphylaxis.

Data sources

Data from the safety analysis population of all 48 clinical trials of any phase (1-4) conducted in the evaluation of timothy grass, ragweed, HDM, and tree SLIT-tablet (Grastek®/Grazax®, Ragwitek®/Ragwizax, Acarizax®/Odactra®/Miticure®, and Itulatek®/Itulazax®, respectively;

ALK, Hørsholm, Denmark and Torii Pharmaceuticals Co., Ltd., Tokyo, Japan) for the treatment of AR/C or allergic asthma were included in the analysis. Safety monitoring was generally similar in all of the trials and used the same MedDRA preferred term coding. The relatedness and intensity (mild, moderate, or severe) of AEs were assessed by the investigators. All data were analyzed only for placebo and the approved doses in North America and Europe, which are once daily 2800 BAU (75,000 SQ-T in Europe) for the timothy grass SLIT-tablet, 12 Amb a 1-U (12 SQ-Amb in Europe) for the ragweed SLIT-tablet, 12 SQ-HDM for the HDM SLIT-tablet, and 12 SQ-Bet for the tree SLIT-tablet.

Identification of potential anaphylactic reactions

Data from the clinical trials were retrospectively searched for potential anaphylactic reactions using 3 different search strategies (**Table I**). The first search strategy was the SMQ search tool. The second search strategy was any investigator-recorded treatment-emergent AE with the MedDRA preferred term of "hypersensitivity". The third search strategy was epinephrine administrations used as a surrogate marker of systemic allergic reaction.

Physician panel review of identified potential anaphylactic reactions

Information for each potential anaphylactic reaction identified by the three search strategies was entered into Excel spreadsheets. The three-physician panel of Allergy specialists independently reviewed the events and then held regular meetings to review each case, maintaining a blind to the subjects' treatment (active or placebo) during the case review process. The physicians considered co-reported AEs, temporal relationship and time to onset of AEs, seriousness of the event (i.e., requiring hospitalization), investigator-assessed severity of the AEs, any action taken (i.e., discontinued trial drug), AE duration, and the outcome of the event (i.e., resolved, not resolved). There was approximately 95% agreement among the physicians on the initial

categorization of each case. A consensus on each event was reached and each case was categorized as 1) local AEs, 2) mild to moderate systemic reaction, or 3) anaphylaxis (a severe or life-threatening systemic reaction), and while still blinded to subject treatment allotment, the categorized case was further categorized by the authors as "unrelated" or "related" to treatment. Local AEs were defined as AEs around the SLIT-tablet administration site, specifically ear, eye, rhinitis symptoms, or cough. During the case review process, the physicians decided to consider cough as a local AE for cases where the constellation of events in addition to local AEs and cough did not include any other MedDRA preferred terms from the cardio-respiratory or cutaneous organ class. The decision was further supported by a blinded analysis of treatment-emergent AEs reported as "cough" in the dataset, which found that cough was reported at a similar frequency in SLIT-tablet-treated (4.8%) and placebo-treated (5.1%) subjects. Five cases were removed from the analysis based on the revised cough criteria. Itching of the throat or neck was considered by the physicians as a local AE due to the nature of the typical side effects of SLIT being anatomically at the application site, throat, and neck and because it was within one dermatome. Mild-to-moderate systemic reactions were defined as cases constituting multiple events involving 2 or more organ systems, such as local AEs plus a skin reaction and/or respiratory or cardiovascular AEs (i.e., dyspnea or chest discomfort), but that were not considered medically severe. Anaphylaxis was identified as a case that, in addition to local AEs with or without cutaneous reactions, also included investigator-assessed severe respiratory or cardiovascular compromise that had the potential to be life-threatening (i.e., deterioration and high likelihood of rapid progression to respiratory or cardiac failure and death).

Analysis

The treatment allotment was unblinded after the physician expert panel review of each case. The number of potential anaphylactic reactions categorized as anaphylaxis (related or unrelated), mild to moderate systemic reaction (related or unrelated), or local AEs (related or unrelated) for each of the SLIT-tablets and placebo were analyzed descriptively. The proportion of each category for SLIT-tablet and placebo was calculated as the number of cases divided by the number of subjects treated. International regulatory authority cutoffs for frequency terminology were used and "rare" was defined as <1/1,000. In the SLIT-tablet trials and according to regulatory safety guidance documents, "life-threatening" was defined a priori as "immediate risk of death" and "severe" was defined as "incapacitating with inability to do normal activities or significant effect on clinical status, and warranted intervention".

Results

In all, 8200 subjects in the analysis received SLIT-tablet treatment and 7033 received placebo.

SMQ search results

SMQ searches tend to identify a very large array of events with high sensitivity and low specificity, and the events identified were only signs and symptoms potentially indicative of anaphylactic reactions. Using the SMQ search tool, 15 potential unconfirmed anaphylaxis cases were identified by the narrow search (criteria 1) and, as expected, a much larger number of potential unconfirmed cases (336) were identified by the broad search (criteria 2; **Table II**). After subsequent blinded medical review, 10 cases of anaphylaxis in 10 subjects were identified across the entire database; 2 were considered related to SLIT-tablet treatment, 1 was related to placebo, 5 were considered unrelated to treatment, and 2 were unable to be classified. The proportion of treatment-related anaphylaxis was 1 case/3984 subjects (0.03%) with grass SLIT-tablet (**Figure 1**) and 1 case/1570 subjects (0.06%) with ragweed SLIT-tablet (**Figure 2**). The case of anaphylaxis related to grass SLIT-tablet occurred within minutes of treatment on day 1 and was treated with epinephrine. The case related to ragweed SLIT-tablet occurred on day 6 within minutes of administration, and the subject self-administered epinephrine. These 2 anaphylaxis cases were not life-threatening. Details of the treatment-related anaphylaxis cases are shown in **Table III**. There were no identified cases of treatment-related anaphylaxis with the HDM SLIT-tablet (**Figure 3**) or tree SLIT-tablet (**Figure 4**). Therefore, based on the SMQ search criteria and medical review, the overall proportions of treatment-related anaphylaxis in SLIT-tablet- and placebo-treated subjects were 0.02% (2 cases/8200 subjects) and 0.01% (1 case/7033 subjects), respectively. None of the cases were reported as late occuring anaphylaxis (>60 minutes after treatment exposure).

The cases that after medical review were not considered anaphylaxis were designated as local AEs or mild-to-moderate systemic reactions (**Figures 1-4**). The overall proportions of treatment-related mild-to-moderate systemic reactions in SLIT-tablet- and placebo-treated subjects were 0.5% (43 cases/8200 subjects) and 0.2% (11 cases/7033 subjects), respectively.

MedDRA "Hypersensitivity" search results

Using the MedDRA preferred term "hypersensitivity", 80 potential unconfirmed cases of anaphylaxis were identified (**Supplemental Table EII**). After subsequent blinded medical review, 1 case of anaphylaxis was identified across the entire database and was considered related to treatment. The proportion of treatment-related anaphylaxis was 1 case/3984 subjects (0.03%) with grass SLIT-tablet (**Supplemental Figure E1**). The anaphylaxis case related to the grass SLIT-tablet occurred within 5 minutes of treatment on day 1, was treated with epinephrine, and was not life-threatening (**Table III)**. There were no identified cases of treatment-related anaphylaxis with the ragweed (**Supplemental Figure E2**), HDM (**Supplemental Figure E3**), or tree SLIT-tablets (**Supplemental Figure E4**). Therefore, based on the MedDRA "hypersensitivity" search method and medical review, the overall proportions of treatment-related anaphylaxis in SLIT-tablet- and placebo-treated subjects were 0.01% (1 case/8200 subjects) and 0% (0 cases/7033 subjects), respectively.

The remaining cases were categorized as local AEs or mild-to-moderate systemic reactions (**Supplemental Figures E1-E4**). The overall proportions of treatment-related mild-to-moderate systemic reactions in SLIT-tablet- and placebo-treated subjects were 0.2% (13 cases/8200 subjects) and 0.01% (1 case/7033 subjects), respectively. Eleven of the 13 cases of mild-to-moderate systemic reactions with SLIT-tablet treatment were related to ragweed SLIT-tablet

treatment; 10 of these 11 cases were in a single subject and were experienced daily from day 6 through day 26.

Epinephrine administrations

There were 40 intramuscular epinephrine administrations captured in the database (**Table IV**); 34 of these administrations have been previously described in an analysis published in 2017.[8] There have since been 6 new epinephrine administrations in the SLIT-tablet clinical trials conducted after 2017. Of these 6, 5 were in grass SLIT-tablet trials. Of these 5, 3 cases were unrelated to treatment and were used in response to food allergy, laryngotracheitis, and vocal cord disorder. The remaining 2 new administrations were for anaphylaxis events that were also identified in either the SMQ search or the MedDRA "hypersensitivity" search and are described in **Table III**. The 6th new epinephrine administration was in a ragweed SLIT-tablet trial and was administered in a subject on placebo in response to urticaria unrelated to treatment. Of the 40 epinephrine administrations, 17 were related to SLIT-tablet treatment, for an administration rate per subject of 17/8200 (0.2%), and 2 were in placebo-treated subjects, for an administration rate per subject of 2/7033 (0.03%; **Table IV**). Of the 17 epinephrine administrations related to SLIT-tablet treatment, 13 occurred in North America where self-injectable epinephrine was provided to most trial subjects, 4 occurred in Europe (all administered under medical supervision), and 0 occurred in Japan. The clinical rationale for epinephrine administration was not adjudicated by medical review.

There was no overlap between the potential cases of anaphylaxis identified by the SMQ and MedDRA "hypersensitivity" searches. Of the 17 epinephrine administrations related to SLIT-tablets, 9 were cases that also appeared in the SMQ or MedDRA "hypersensitivity" searches, of

312 which 3 were the identified anaphylaxis cases (**Table III**) and 3 were for mild-to-moderate
313 systemic allergic reactions.

314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330

Discussion

There is no universal consensus method for identifying anaphylaxis. Because of the variable clinical presentation of these reactions, incidence reporting of anaphylaxis is not aligned in clinical studies. After an extensive evaluation of the data, we determined that it was not possible to directly apply the well-known NIAID criteria[4] for anaphylaxis to clinical trial safety data for SLIT because the NIAID criteria are not described in MedDRA preferred terms, which is the method of AE reporting in clinical trials. Furthermore, the expert panel producing the NIAID definition did not specifically consider systemic allergic reactions associated with SLIT. Most problematic are the frequent local site application reactions (i.e., swollen lips and tongue) associated with SLIT that are typically self-limited and mild to moderate in severity.[9] Local site application reactions were not considered in the current analysis as a criterion for anaphylaxis. The proposed SMQ anaphylaxis search criteria uses objective MedDRA preferred terms adapted from NIAID criteria,[4] combined with knowledge of the safety profile of SLIT, to deliver results that are tailored to SLIT. The expert panel then distinguished anaphylaxis from less serious systemic reactions by the presence of clinically meaningful respiratory symptoms and/or hypotension. This method to identify potential cases of anaphylaxis can be applied to SLIT trials and possibly to real-world data. When the SMQ anaphylaxis search criteria were applied to a large, comprehensive database of clinical trial data for SLIT-tablets and potential cases were reviewed by medical experts, two SLIT-tablet related events of anaphylaxis were identified.

The SMQ and preferred term “hypersensitivity” searches allowed data from thousands of subjects to be screened for potential unconfirmed anaphylaxis and systemic allergic reactions. Many potential cases were expected to be identified given the broad spectrum of selected signs and symptoms that spanned multiple system organ classes. The SMQ narrow search specifically

was more successful than the broad search in identifying the anaphylaxis cases; after blinded medical review by the authors, none of the cases in the narrow search were categorized as local AEs. In contrast, the broad SMQ search did not identify any anaphylaxis cases, only cases that after medical review were categorized as local AEs or mild-to-moderate systemic reactions. These findings indicate that the medical review was a critical component of the analysis. Indeed, many of the potential unconfirmed anaphylaxis cases identified in the searches were only a constellation of local AEs. This is because by definition the algorithm flagged all treatment-emergent AEs that occurred on the same day with terms from ≥ 2 or more body systems (i.e., respiratory, cutaneous, cardiovascular), and the respiratory and cutaneous body systems both contained preferred terms that are well known local AEs with SLIT-tablets (e.g., throat tightness, lip swelling). Itching of neck and throat were decided to be local AEs based on their proximity to the SLIT-tablet administration site and occurrence within one dermatome. Cough, on one hand, is a commonly reported symptom of anaphylaxis, including anaphylaxis to SCIT.[10, 11] The WAO considers cough a symptom of a systemic reaction to SCIT.[5] On the other hand, cough can be unspecific with a broad etiology such as normal response, infection, allergy, asthma, or postnasal drip. It could also be an irritant effect elicited by dissolved granules/fragments of the SLIT-tablet. In a survey of systemic reactions to allergy immunotherapy, cough occurred in 15 systemic reactions to SCIT and only 1 systemic reaction to SLIT.[10] Furthermore, the WAO also does not include cough that is unrelated to bronchospasm in their definition of a systemic reaction for SLIT.[6] Finally, in the current analysis, the rate of treatment-emergent cough was similar between SLIT-tablet treatment and placebo (4.8% vs 5.1%, respectively). Therefore, the authors decided to exclude cough as a systemic AE provided no other systemic AEs were present. The WAO uses a similar modification when considering gastrointestinal symptoms in

the systemic reaction grading system for SLIT.[6] Gastrointestinal symptoms are considered as local AEs if the only other AEs are oromucosal and as systemic AEs if other systemic AEs are also present.[6]

Application of the SMQ anaphylaxis search criteria to a large dataset and subsequent blinded medical review indicated that anaphylaxis was rare for all the evaluated SLIT-tablets. It was of interest to note that no reports of late occurring anaphylaxis were identified. The few cases that were identified were severe systemic reactions but were not life-threatening events as defined by regulatory authorities. Larger data sets are needed to determine if the modality of administration could impact the speed and risk of near-fatal and fatal anaphylaxis. The limited number of epinephrine administrations indicated that the low rate of anaphylaxis was not simply due to treatment of reactions with epinephrine. This finding suggests that the need for epinephrine prescriptions in patients receiving SLIT-tablet treatment should be based on physician judgment and shared decision making.

A limitation of the analysis is that a lack of sufficient investigator-input to support appropriate MedDRA preferred term coding led to cases that were unable to be classified or that did not meet the constellation of symptoms. Timing of the events in relation to SLIT-tablet administration was not always precisely recorded, which also limited interpretation of relatedness for some cases. Another limitation of the analysis is that medication use other than epinephrine to treat events was not used in the evaluation of potential anaphylaxis cases because this information was not captured consistently among the clinical trials.

The proposed SMQ search met its purpose as an apparently sensitive standardized method for identifying potential anaphylaxis cases, although it was not entirely specific for clinically meaningful anaphylaxis, which required final expert review. In a large database of subjects

participating in SLIT-tablet trials, anaphylaxis was rare for all the evaluated SLIT-tablets when using the proposed SMQ search criteria and after medical expert review. No fatalities were reported. Preliminary application of the SMQ search tool followed by expert medical review may be a useful tool in the safety evaluation of future SLIT products that may be used to harmonize consistent anaphylaxis reporting across allergy immunotherapy formulations.

Acknowledgments

Medical writing and editorial assistance were provided by Erin P. Scott, PhD, of Scott Medical Communications, LLC. This assistance was funded by ALK-Abelló, Hørsholm, Denmark.

References

1. Calderon MA, Simons FE, Malling HJ, Lockey RF, Moingeon P, Demoly P. Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. Allergy. 2012;67:302-11.

2. Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J. 2014;7:6.

3. Epstein TG, Calabria C, Cox LS, Dreborg S. Current Evidence on Safety and Practical Considerations for Administration of Sublingual Allergen Immunotherapy (SLIT) in the United States. J Allergy Clin Immunol Pract. 2017;5:34-40.e2.

4. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

5. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol. 2010;125:569-74, 74 e1-74 e7.

6. Cox LS, Sanchez-Borges M, Lockey RF. World Allergy Organization Systemic Allergic Reaction Grading System: Is a Modification Needed? J Allergy Clin Immunol Pract. 2017;5:58-62.e5.

7. Introductory guide for Standardised MedDRA Queries (SMQs) Verison 22.1 [Internet]. ICH; 2019 [cited 2020 December 16]. Available from: https://admin.new.meddra.org/sites/default/files/guidance/file/000356_smq_intguide_22_1.pdf.

8. Nolte H, Casale TB, Lockey RF, Fogh BS, Kaur A, Lu S, et al. Epinephrine use in clinical trials of sublingual immunotherapy tablets. J Allergy Clin Immunol: In Practice. 2017;5:84-9.

9. Bernstein DI, Bardelas JA, Jr., Svanholm Fogh B, Kaur A, Li Z, Nolte H. A practical guide to the sublingual immunotherapy tablet adverse event profile: implications for clinical practice. Postgrad Med. 2017:1-8.

10. Calderon MA, Vidal C, Rodriguez Del Rio P, Just J, Pfaar O, Tabar AI, et al. European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a real-life clinical assessment. Allergy. 2017;72:462-72.

11. Grabenhenrich LB, Dölle S, Moneret-Vautrin A, Köhli A, Lange L, Spindler T, et al. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. J Allergy Clin Immunol. 2016;137:1128-37.e1.

443

444 **Table I.** Search strategies to identify potential anaphylaxis in the clinical development program
445 of the timothy grass, ragweed, house dust mite, and tree sublingual immunotherapy tablets.

Search Strategy	Potential Anaphylaxis Events
SMQ	
Criteria 1, narrow search	All treatment-emergent adverse events with narrow terms of the SMQ Anaphylactic Reaction
Criteria 2, broad search	All treatment-emergent adverse events that occurred on the same day with terms from at least 2 body systems - A term from category including respiratory terms (e.g., cough or dyspnea) AND a term from category including cutaneous terms (e.g., angioedema/urticaria/pruritus/flush) - A term from category including cardiovascular terms (e.g., hypotension) AND a term from category including respiratory terms (e.g., cough or dyspnea) OR a term from category including cutaneous terms (e.g., angioedema/urticaria/pruritus/flush)
Preferred term "hypersensitivity"	All treatment-emergent adverse events identified by the MedDRA preferred term "hypersensitivity"
Epinephrine administration	All events of epinephrine administration

446 MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardized MedDRA Query.

447

448

449

450

451

452

453

454

Table II. Potential anaphylaxis and systemic allergic reaction cases identified by the SMQ search criteria.

			SMQ Narrow Search Results, Number of Cases (Proportion*)								SMQ Broad Search Results, Number of Cases (Proportion*)					
			Local AE		Mild-Moderate Systemic Reaction			Anaphylaxis			Local AE		Mild-Moderate Systemic Reaction		Anaphylaxis	
	Total Subjects, N	Total Number of Cases	Related	Unrelated	Related	Unrelated	UTC†	Related	Unrelated	UTC†	Related	Unrelated	Related	Unrelated	Related	Unrelated
Grass SLIT-Tablet Trials																
Grass SLIT-tablet	3984	101	0	0	2 (0.05%)	0	2 (0.05%)	1 (0.03%)	0	1 (0.03%)	54 (1.4%)	12 (0.3%)	15 (0.4%)	14 (0.4%)	0	0
Placebo	2743	29	0	0	0	0	0	0	0	1 (0.04%)	9 (0.3%)	14 (0.5%)	4 (0.1%)	1 (0.04%)	0	0
Ragweed SLIT-Tablet Trials																
Ragweed SLIT-tablet	1570	57	0	0	0	0	0	1 (0.06%)	1 (0.06%)	0	40 (2.5%)	4 (0.3%)	8 (0.5%)	3 (0.2%)	0	0
Placebo	1266	17	0	0	0	0	0	1 (0.08%)	0	0	6 (0.5%)	9 (0.7%)	0	1 (0.08%)	0	0
HDM SLIT-Tablet Trials																
HDM SLIT-tablet	2166	102	0	0	0	0	0	0	1 (0.05%)	0	84 (3.9%)	1 (0.05%)	15 (0.7%)	1 (0.05%)	0	0
Placebo	2548	17	0	0	0	1 (0.04%)	0	0	2 (0.08%)	0	8 (0.3%)	0	3 (0.1%	3 (0.1%)	0	0
Tree SLIT-Tablet Trials																
Tree SLIT-tablet	480	21	0	0	0	0	0	0	0	0	17 (3.5%)	1 (0.2%)	3 (0.6%)	0	0	0
Placebo	476	7	0	0	0	0	0	0	1 (0.2%)	0	0	0	4 (0.8%)	2 (0.4%)	0	0

AE, adverse event; HDM, house dust mite; MedDRA, Medical Dictionary for Regulatory Activities; SLIT, sublingual immunotherapy; SMQ, standardized MedDRA query; UTC, unable to classify relatedness.

*Number of cases per total subjects.

†Cases were identified by the narrow search but could not be classified as related or unrelated to treatment.

Table III. Details of treatment-related anaphylaxis cases.

Treatment	Method of Case Identification	Day of Onset	Case Description	Investigator Assessed Severity	Action Taken	Administered Treatment	Outcome
Grass SLIT-tablet	SMQ search criteria	1*	Subject experienced itching in mouth, tongue, lips and pharynx within 1 minute of first SLIT-tablet intake, followed by swelling of pharynx and tongue and difficulty breathing. The subject also had an acute asthma attack with wheezing and prolonged expiration.	Severe	Treatment discontinued	Epinephrine, beta-agonist, prednisolone	Recovered
Grass SLIT-tablet	MedDRA "hypersensitivity" search	1*	Subject experienced dysphagia, respiratory distress, and hypotension 5 minutes after first SLIT-tablet intake.	Severe	Hospitalization and treatment discontinued	Epinephrine, antihistamine, beta-agonist, corticosteroids	Recovered
Ragweed SLIT-tablet	SMQ search criteria	6†	Subject had developed local applications site reactions starting at Day 1. The events persisted with subsequent study drug administrations and on Day 6, the subject developed local symptoms within 5 minutes of study drug administration followed by swelling in the throat, shortness of breath, nausea, and light-headedness 30 minutes after dosing. The subject self-administered epinephrine and proceeded to an emergency department where he received antihistamine therapy and corticosteroids.	Severe	Treatment discontinued	Epinephrine, antihistamine, corticosteroids	Recovered
Placebo	SMQ search criteria	1*	Subject developed urticaria within 5 minutes of first tablet intake. The subject was treated with an antihistamine. Within 1 hour the subject developed cough, dyspnea, pharyngeal pruritus, and thoracic	Severe	Treatment discontinued	Epinephrine, antihistamine, corticosteroids, beta-agonist	Recovered

			pain which were assessed as an anaphylactic reaction. Epinephrine was given by the doctor and subject was transferred to the emergency room, where she received antihistamine, corticosteroids, and salbutamol. En route to the emergency facility, the subject was administered epinephrine (due to a bronchospasm). The subject stayed under observation for about 7 hours and was not hospitalized.				

AE, adverse event; HDM, house dust mite; MedDRA, Medical Dictionary for Regulatory Activities; SLIT, sublingual immunotherapy; SMQ, standardized MedDRA query.

*1st dose of SLIT-tablet.

†6th dose of SLIT-tablet.

Table IV. Summary of epinephrine administrations.

	N, subjects		Epinephrine Administrations, n		Epinephrine Administrations Investigator-assessed as Related, n	
SLIT-Tablet Trials	**Active**	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**
Grass SLIT-tablet	3984	2743	14	4	10	0
Ragweed SLIT-tablet	1570	1266	6*	3	3	2
HDM SLIT-tablet	2166	2548	8	5	4	0
Tree SLIT-tablet	480	476	0	0	0	0
TOTAL	**8200**	**7033**	**28**	**12**	**17 (0.2%†)**	**2 (0.03%†)**

HDM, house dust mite; N, number of total subjects; n, number of administrations; SLIT, sublingual immunotherapy.

*A epinephrine administration at a dose (6 Amb-a 1-U) lower than the approved dose (12 Amb-a 1-U) has also previously described.[8]

†Number of administrations per total subjects.

Figure Legends

Figure 1. SMQ search criteria results for the grass SLIT-tablet. Percentages are the number of cases per total subjects. *Cases identified by the narrow search that could not be classified as related or unrelated to treatment during the blinded medical review. MedDRA, Medical Dictionary for Regulatory Activities; N, number of total subjects; n, number of cases; SLIT, sublingual immunotherapy; SMQ, standardized MedDRA query; UTC, unable to classify for relatedness.

Figure 2. SMQ search criteria results for the ragweed SLIT-tablet. Percentages are the number of cases per total subjects. MedDRA, Medical Dictionary for Regulatory Activities; N, number of total subjects; n, number of cases; SLIT, sublingual immunotherapy; SMQ, standardized MedDRA query.

Figure 3. SMQ search criteria results for the HDM SLIT-tablet. Percentages are the number of cases per total subjects. HDM, house dust mite; MedDRA, Medical Dictionary for Regulatory Activities; N, number of total subjects; n, number of cases; SLIT, sublingual immunotherapy; SMQ, standardized MedDRA query.

Figure 4. SMQ search criteria results for the tree SLIT-tablet. Percentages are the number of cases per total subjects. MedDRA, Medical Dictionary for Regulatory Activities; N, number of total subjects; n, number of cases; SLIT, sublingual immunotherapy; SMQ, standardized MedDRA query.