

Impact of Adverse Event Solicitation on the Safety Profile of SQ House Dust Mite Sublingual Immunotherapy Tablet



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What is already known about this topic? Adverse events (AEs) collected by intentional solicitation or questionnaires may enhance detection of a safety signal, but may also lead to bias and inflated AE reporting rates.

What does this article add to our knowledge? Solicitation of prespecified AEs via a questionnaire did not alter the safety profile of SQ house dust mite sublingual immunotherapy (SLIT)-tablet, but did result in higher frequencies of some AEs versus unsolicited AE monitoring.

How does this study impact current management guidelines? Implementing a uniform solicitation of specific local application site reactions may improve and harmonize the surveillance and reporting of the safety of SLIT.

BACKGROUND: It has been recommended that sublingual immunotherapy (SLIT) safety be assessed using solicited adverse event (AE) collection methods.

OBJECTIVES: The objectives of this study were to describe the impact on the safety profile of SQ house dust mite (HDM)

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SLIT-tablet (12 SQ-HDM dose) when prespecified local application site reactions were solicited versus unsolicited, and discuss ramifications of AE solicitation.

METHODS: Subjects were randomized to daily 12 SQ-HDM or placebo for up to 52 weeks in 4 double-blinded, multicenter trials. In one trial (NCT01700192; N = 1272), subjects documented daily the presence or absence of 15 World Allergy Organization-defined local application site reactions using a structured questionnaire of closed-ended questions (solicited AEs). Subjects in the other trials were not asked about specific AEs (unsolicited AEs), and AE data were pooled (N = 1287). Analysis was limited to adults aged 18 to 65 years.

RESULTS: Whether AEs were solicited or unsolicited, the most common AEs leading to study discontinuation with 12 SQ-HDM were throat irritation and oral pruritus. Approximately 95% of treatment-related AEs were mild to moderate. Placebo-subtracted frequencies of local application site reactions associated with 12 SQ-HDM were higher when solicited versus unsolicited (ie, throat irritation, 46% vs 13%, respectively; oral pruritus, 47% vs 17%; ear pruritus, 40% vs 4%; mouth swelling, 8% vs 2%; tongue ulceration, 10% vs 0%; mouth ulceration, 7% vs <1%).

CONCLUSIONS: Qualitatively, the safety profile of 12 SQ-HDM was similar when AEs were solicited versus unsolicited; hence, solicitation did not alter the safety profile. Higher observed frequencies of local application site reactions with AE solicitation may be partly due to suggestive reporting bias, as observed in placebo-treated subjects. © 2018 ALK Abelló A/S. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2018;6:2081-6)

Key words: Adverse events; Questionnaire; Monitoring; SLIT; Allergy immunotherapy; Solicit

Abbreviations used

AE- Adverse event
AR/C- Allergic rhinitis with or without conjunctivitis
FDA- Food and Drug Administration
HDM- House dust mite
SLIT- Sublingual immunotherapy
WAO- World Allergy Organization

Reporting of adverse events (AEs) is a critical component of drug development and regulatory approval, as well as safety surveillance and benefit-risk assessment. In clinical trials, AE data are generally collected as part of organized data collection systems that can involve structured questionnaires with or without specifying individual AEs, or open-ended questioning of AEs in general without specifying individual AEs. In the context of the current analysis, solicited AEs refer to AEs collected via a structured questionnaire regarding specific AEs, whereas unsolicited AEs refer to open-ended questioning of AEs in general without specifying individual AEs. Both methods of AE collection have potential strengths and weaknesses. Unsolicited data capture is the simplest and most cost-effective method of AE collection; however, it may lead to underreporting due to hesitancy by the patient to report an AE, or forgetting that a specific AE occurred.¹ In contrast, AEs collected by structured questionnaires may enhance detection of a safety signal, but may also lead to inflated reporting rates due to the suggestive nature of questioning the presence of an AE.¹ Indeed, studies have demonstrated that the number of events for solicited AEs collected either by a data collection system or by structured questionnaire is generally several fold higher compared with unsolicited AEs.¹⁻³

The reporting and description of sublingual immunotherapy (SLIT) local application site reactions have been criticized, and it has been difficult to compare the reporting among studies. Therefore, the World Allergy Organization (WAO) proposed a grading system of predefined local application site reactions based on the use of the Medical Dictionary for Regulatory Activities.⁴ The approach has been recommended by the US Food and Drug Administration (FDA) with a further request to collect local application site reactions daily by a structured questionnaire with 15 predefined AEs, with the goal to enhance detection of a potential safety signal.

SQ house dust mite (HDM) SLIT-tablets (ALK, Hørsholm, Denmark) are indicated for the treatment of allergic rhinitis with or without conjunctivitis (AR/C), and outside of North America, they are also indicated as an add-on treatment for allergic asthma.⁵ In general, the most frequent AEs associated with SLIT are local application site reactions, such as oral pruritus and throat irritation.⁶ The tolerability of SQ HDM SLIT-tablet has been demonstrated in multiple trials.⁷⁻¹¹ One of the trials solicited specific AEs via a daily questionnaire per WAO and FDA recommendations and had notably higher frequencies of some of the local application site reactions in both placebo and active treatment groups compared with previous trials.⁹ In the previous trials, AEs were unsolicited, meaning subjects did not report AEs through a structured questionnaire and were not questioned regarding the presence or absence of specific AEs, but only questioned generally at each visit regarding the occurrence of any AEs. The objectives of this report were to describe the safety

profile of SQ HDM SLIT-tablet (12 SQ-HDM dose) when prespecified AEs in clinical trials were assessed via a structured questionnaire (solicited) versus only general questioning regarding AEs (unsolicited), and discuss overall ramifications of solicited AE reporting.

METHODS**Trial descriptions**

Four phase 2 and phase 3 randomized, double-blinded, placebo-controlled trials of HDM SLIT-tablets were conducted as previously described.^{7,9-11} In 3 of the 4 trials, all AEs were collected unsolicited. These 3 trials were a 24-week environmental chamber trial (P003; NCT01644617) conducted in European subjects aged ≥ 18 years with HDM AR/C with or without mild allergic asthma,¹⁰ a 52-week trial (MT-06; NCT01454544) conducted in European subjects aged ≥ 18 years with HDM AR/C with or without allergic asthma,⁷ and an 18-month trial (MT-04; NCT01433523) conducted in European subjects aged ≥ 18 years with HDM allergic asthma and AR/C.¹¹ In the fourth trial, a trial of up to 52 weeks (P001; NCT01700192) conducted in North American subjects aged ≥ 12 years with HDM AR/C with or without allergic asthma⁹; specific AEs were actively solicited. All other AEs were collected unsolicited. Subjects received daily placebo or SQ HDM SLIT-tablet (12 SQ-HDM dose in all trials and 6 SQ-HDM dose in all but P001). The 12 SQ-HDM dose contains approximately 15 mcg group 1 allergens (Der f 1 and Der p 1 combined) and approximately 15 mcg group 2 allergens (Der f 2 and Der p 2 combined) for a total of approximately 30 mcg major allergen content, which according to the current FDA standard is estimated to be a total of 5300 allergen units of mixed mites *Dermatophagoides pteronyssinus* and *D. farinae*.¹² Institutional review boards or ethics committees approved the protocols, and written informed consent was obtained from the subject or the subject's legal representative.

Safety data collection and analysis

In all 4 trials, investigators collected AE information by a general question for the subject at each visit regarding whether or not they had experienced AEs since the last visit.

Per the trial protocol, in addition to routine safety monitoring in trial P001, reporting of local application site reactions was solicited daily in a structured questionnaire for the first approximately 28 days of treatment using closed-ended questions regarding specific local application site reactions identified by the WAO.^{4,13} Subjects noted daily whether or not each of 15 local application site reactions occurred within the first 60 minutes after dosing.

The frequency of treatment-emergent AEs was calculated from data pooled for the 12 SQ-HDM dose in the 3 trials that did not solicit AEs and compared with the frequency of AEs for the 12 SQ-HDM dose in the trial that solicited AEs. The analysis was limited to reporting for adults aged 18 to 65 years.

RESULTS

In all, 1287 subjects were in the data pool from the trials with unsolicited AEs ($n = 639$, 12 SQ-HDM; $n = 648$, placebo) and 1272 were in the trial with solicited AEs ($n = 638$, 12 SQ-HDM; $n = 634$, placebo). Demographics and baseline characteristics were similar between the solicited and unsolicited AE trial populations, with the exception of a higher percentage of patients with asthma in the unsolicited AE trials (31% vs approximately 57%, respectively).

TABLE I. Treatment-emergent AEs reported in $\geq 5\%$ of subjects in one or more treatment groups

Adverse event, % of subjects	Trial with AEs solicited			Trials with AEs unsolicited (pooled data)		
	12 SQ-HDM (n = 638)	Placebo (n = 634)	Ratio Active/placebo	12 SQ-HDM (n = 639)	Placebo (n = 648)	Ratio Active/placebo
Throat irritation*	68	22	3:1	15	3	5:1
Oral pruritus*	62	15	4:1	20	3	7:1
Ear pruritus*	52	13	4:1	5	<1	NC
Lip swelling*	19	3	6:1	3	<1	NC
Swollen tongue*	16	2	8:1	2	<1	NC
Glossodynia*	15	3	5:1	2	<1	NC
Pharyngeal edema*	14	2	7:1	2	0	NC
Nausea*	16	7	2:1	2	1	2:1
Oral paraesthesia	10	3	3:1	6	<1	NC
Tongue ulceration*	13	3	4:1	0	0	0
Upper abdominal pain*	11	5	2:1	1	<1	NC
Mouth swelling*	10	2	5:1	2	0	NC
Mouth ulceration*	11	4	3:1	<1	<1	NC
Palatal swelling*	11	1	11:1	0	0	0
Dysgeusia*	10	4	2.5:1	1	0	NC
Upper respiratory tract infection	9	10	1:1	5	5	1:1
Nasopharyngitis	9	8	1:1	16	15	1:1
Diarrhea*	7	4	2:1	2	1	2:1
Tongue pruritus	5	1	5:1	5	1	5:1
Pharyngitis	1	1	1:1	6	5	1:1
Mouth edema*	<1	0	NC	9	<1	NC

AE, Adverse event; HDM, house dust mite; NC, not calculable.

*Indicates AEs that were included on the local site reaction reporting form.

The qualitative AE profile was overall similar between the trials with unsolicited AEs and the trial that solicited AEs. Throat irritation and oral pruritus were the 2 most common treatment-emergent AEs (both $>15\%$) in subjects treated with 12 SQ-HDM regardless of the method of AE collection (Table I). In the trials with unsolicited AEs, overall 7.7% of subjects treated with 12 SQ-HDM discontinued because of AEs and 9.8% treated with 12 SQ-HDM discontinued because of AEs in the trial that solicited AEs. The most common AEs ($\geq 1\%$) that led to study discontinuation in subjects treated with 12 SQ-HDM, regardless of whether AEs were solicited or unsolicited, were throat irritation, oral pruritus, ear pruritus, and mouth swelling. Approximately 95% of treatment-related AEs were mild to moderate regardless of the method of AE collection; thus, the frequencies of severe treatment-related AEs were similar when AEs were solicited versus unsolicited.

The placebo-subtracted frequencies of local application site reactions associated with 12 SQ-HDM treatment were notably higher when the reactions were solicited versus unsolicited (Fig 1). The incidence ratios between active treatment and placebo were lower for the top 2 most common AEs (throat irritation and oral pruritus) when solicited versus unsolicited, but higher or equivalent (when calculable, eg, for nonzero frequencies) for nearly all the remaining most common AEs when solicited versus unsolicited (Table I).

The frequencies of mouth (11%) and tongue (13%) ulceration associated with SQ HDM SLIT-tablet were notably higher when solicited in P001 than the frequencies associated with timothy grass SLIT-tablet (both 0.1%) and ragweed SLIT-tablet

(0.2% and 0.1%, respectively) when unsolicited in pivotal North American trials.¹⁴ However, a cognitive study of the structured questionnaire in untreated individuals suggested that subjects may have misinterpreted the question (“have you experienced mouth ulcer/sore in the mouth?” or “have you experienced tongue ulcer/sore on the tongue?”) as mouth/tongue pain rather than an actual ulcer.¹³ Of the 15 adults, adolescents, and children in the cognitive study, 4 patients characterized a hypothetical “sore in the mouth” and “sore on the tongue” event as “feeling sore.” When describing the hypothetical event in their own words, 4 patients described the event as being “sore,” 3 as “painful,” 1 as “uncomfortable,” and 1 as “bothersome.” Misinterpretation of questions is a disadvantage of solicited AE reporting. Additional advantages and disadvantages of solicited and unsolicited AE reporting in SLIT-tablet trials are listed in Table II.

Because the trial that solicited AEs was conducted only in North American subjects and the trials that did not specifically solicit AEs were all in European subjects, it was possible that the observed differences in AE frequencies were a regional variation rather than due to the method of AE reporting. To examine this possibility, data from timothy grass SLIT-tablet trials that did not specifically solicit AEs were evaluated in trials conducted in either North America or Europe. Grass SLIT-tablet data collected on different continents showed generally similar AE frequencies (relative to the large differences in frequencies observed between solicited and unsolicited AE collection), with some frequencies higher in Europe and some frequencies higher in North America (see Table E1 in this article’s Online

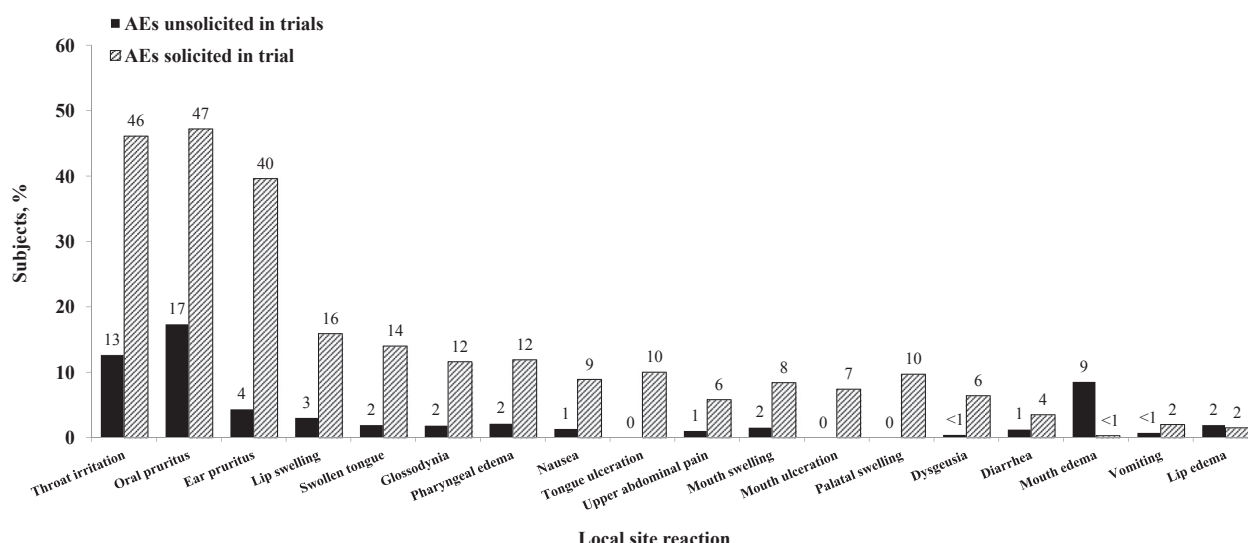


FIGURE 1. Placebo-subtracted frequencies of local site reactions in trials that solicited or did not solicit the daily occurrence of each reaction. *AE*, Adverse event.

TABLE II. Advantages and disadvantages of solicited and unsolicited AE collection in SLIT-tablet trials

Unsolicited AE collection	Solicited AE collection
Advantages 1. Avoids suggestion 2. Highlights severe AEs as they are likely more memorable to patients than mild-to-moderate AEs 3. Required by most regulatory agencies Disadvantages 1. Does not fully elicit percentage of mild-to-moderate AEs because they may be forgotten by patients	Advantages 1. Uniform nomenclature for AEs 2. Avoids hesitancy to report and forgetting by time of reporting Disadvantages 1. Misinterpretation of structured questions as indicated by reports of tongue (13%) and mouth (11%) ulceration with HDM SLIT-tablet, some of which were probably only soreness 2. High rate of AEs in the placebo-treated group (throat irritation [22%], oral pruritus [15%], and ear pruritus [13%]) 3. AE profile not comparable to trials using the unsolicited AE collection method

AE, Adverse event; *HDM*, house dust mite; *SLIT*, sublingual immunotherapy.

Repository at www.jaci-inpractice.org). These data indicate that there is no consistent regional difference in AE reporting for SLIT-tablets.

DISCUSSION

The method of collecting AE data in clinical trials can affect the reported AE frequency and profile related to a therapeutic treatment.³ Because the North American P001 trial was the first AIT trial to actively solicit AEs, the purpose of the current analysis was to examine the safety profile of SQ HDM SLIT-tablet when specific AEs defined by WAO were solicited versus unsolicited in clinical trials. The most common AEs, the AEs resulting in trial discontinuation, and the severity of AEs were similar when AEs were solicited versus unsolicited. Thus, the safety profile of SQ HDM SLIT-tablet was qualitatively unchanged by the method of AE reporting. In contrast, a higher frequency of some local application site reactions was observed in the trial that solicited specific AEs versus the other 3 trials that did not solicit specific AEs.

Regardless of the method of AE collection, the AE profile for SQ HDM SLIT-tablet was similar to that of other SLIT products in that local application site reactions were the most common AEs.⁶ Furthermore, nearly all of the AEs were mild to moderate in intensity. Studies have demonstrated that the local application site reactions with SQ HDM SLIT-tablet generally occur for 1 day and last less than 45 minutes.^{9,15} Therefore, the local application site reactions could be considered more a tolerability issue than a safety issue.

With unsolicited AE collection in clinical trials, subjects may be hesitant to report an AE or forget to report a specific AE at the time of the office visit, resulting in underreporting or underappreciation of the variability of AEs.¹ Therefore, the purpose of soliciting AEs is to enhance signal detection. In the current analysis, it was not clear that solicitation of events led to a greater ability to detect drug-placebo differences. The placebo rates were higher with solicited versus unsolicited AEs, which is an indicator of reporting bias with AE solicitation. Furthermore, the incidence ratios between SQ HDM SLIT-tablet and placebo were lower for the top 2 most common AEs when they were

solicited versus unsolicited, which indicates more noise than actual signal enhancement with AE solicitation. Compared with grass and ragweed SLIT-tablets, an enhanced frequency of mouth and tongue ulceration was observed; however, the qualitative study used to create the structured questionnaire indicated that subjects may have misinterpreted the term mouth or tongue “sore” as a physical feeling of pain or discomfort rather than an ulceration. The frequency of palatal swelling was also higher when solicited versus unsolicited. The reason for this potential higher frequency is unknown, but palatal swelling was not objectively confirmed on physical examination. Misinterpretation by subjects of any of the terms in the questionnaire is a potential limitation of this analysis and supports the importance of conducting appropriate focus group and questionnaire validation studies before implementing new patient questionnaires for general use.

Generally, there is no consensus on the best method to capture AE data from clinical trials and regulatory authorities do not provide any specific guidance for general AE data collection.¹⁶ However, the Center for Biologics Evaluation and Research within the US FDA has recently requested that SLIT-tablet trials use active solicitation to assess local application site reactions as defined by the WAO. Active solicitation of specific AEs is common in vaccine trials and is particularly useful to rapidly determine the safety of a seasonal vaccine (ie, influenza) by comparing the AE frequency of the new vaccine with historical controls.¹⁷ Furthermore, there is increasing interest in actively collecting specific AE data from patients receiving oncology treatments to determine AE profiles and help in the selection of tolerable dose levels and schedules.¹⁸ However, bias could be introduced by leading questions that solicit specific AEs because subjects may be more likely to report an AE merely by the suggestion that a specific AE could occur. Studies have shown that when physicians inform patients of specific AEs known to be associated with a treatment, patients are more likely to report experiencing the specific AE (ie, the placebo effect).¹⁹ For example, in a study of subjects prescribed beta-blockers, one third of the patients were not informed of the identity of the drug or potential for erectile dysfunction, another third were informed of the identity of the drug, but not the possibility of erectile dysfunction, whereas the last third of patients were informed about the identity of the drug and the potential for erectile dysfunction.²⁰ After 90 days, the incidence of erectile dysfunction was reported by 3%, 16%, and 31% in the 3 groups, respectively. Thus, differences in information provided to subjects appeared to have biased subjects' reports of a specific AE. Considering that in the current analysis the frequency of AEs with placebo was higher when AEs were solicited versus unsolicited, the overall increased frequency of specific AEs with solicitation was likely due to a similar effect. It is possible that overreporting of adverse effects could be mitigated, while still potentially enhancing signal detection, by providing subjects with a comment card or daily diary for general collection of AEs without soliciting for specific AEs.

The terms on the questionnaire were worded to be less clinical and better understood by patients,¹³ which did not always match terms used by investigators for unsolicited reporting. Thus, not all terms were directly comparable and potentially led to misinterpretation by patients. Furthermore, the reported AEs were not confirmed clinically by a physician as this would require daily inspection by a clinician; hence, the structured questionnaire

may rather be considered a subjective and perhaps more sensitive patient screening tool of local AEs than an objective validation of the actual occurrence of AEs.

CONCLUSIONS

AE assessment of SQ HDM SLIT-tablet was qualitatively similar when AEs were unsolicited versus solicited. Hence, solicitation did not enhance safety signal detection. However, the frequency of some local application site reactions increased when specific AEs were solicited. The higher frequency of local application site reactions observed with AE solicitation may be due to a suggestive effect leading to reporting bias. The solicited collection of data for predefined AEs of clinical interest for SLIT treatment per WAO recommendation may allow comparison of selected local application site reactions of SLIT across trials. However, the collection method must be standardized. The AE collection method used in SLIT trials should be further investigated as it is not clear that solicitation leads to better AE signal detection and it could bias subject reporting of AEs. As a result, there could be a perception of a less favorable drug profile compared with trials using the traditional unsolicited AE collection method.¹ On the basis of the current analysis, we suggest that AEs in SLIT trials be collected by open-ended questioning without specifying individual AEs (eg, unsolicited AE collection). However, there are other products for which solicited AE collection may be beneficial, particularly regarding AEs that subjects may be reluctant to report (eg, sexual dysfunction). Thus, the method of AE collection should be carefully considered for each product.

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TABLE E1. Grass SLIT-tablet treatment-emergent AE frequency in $\geq 5\%$ of subjects in either trial between North America and Europe (all unsolicited data collection)

AE, % of subjects	North American Adult Subjects*		European Adult Subjects*	
	Grass SLIT -tablet (n = 213)	Placebo (n = 225)	Grass SLIT-tablet (n = 316)	Placebo (n = 318)
Oral pruritus	35	3	46	4
Throat irritation	30	5	9	1
Ear pruritus	20	1	12	1
Upper respiratory tract infection	18	11	5	3
Oral paraesthesia	14	2	5	1
Nasopharyngitis	8	13	15	19
Mouth edema	8	<1	18	1
Stomatitis†	8	<1	<1	0
Pharyngeal edema	7	0	3	<1
Headache	7	7	3	6
Eye pruritus	5	4	4	5
Swollen tongue	5	0	1	<1
Pruritus	5	3	2	3
Dyspepsia	5	1	2	1
Oropharyngeal pain	5	5	4	5
Influenza	1	4	7	8

AE, Adverse event; SLIT, sublingual immunotherapy.

*Data are from 2 randomized, multicenter, double-blind, placebo-controlled studies in which North American or European subjects received grass SLIT-tablet (ALK, Hørsholm, Denmark) treatment or placebo daily. Data are for the 2800 bioequivalent allergen units/75,000 SQ-T dose.^{E1,E2}

†Indicates mild erythema and not ulcerations or infection.

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