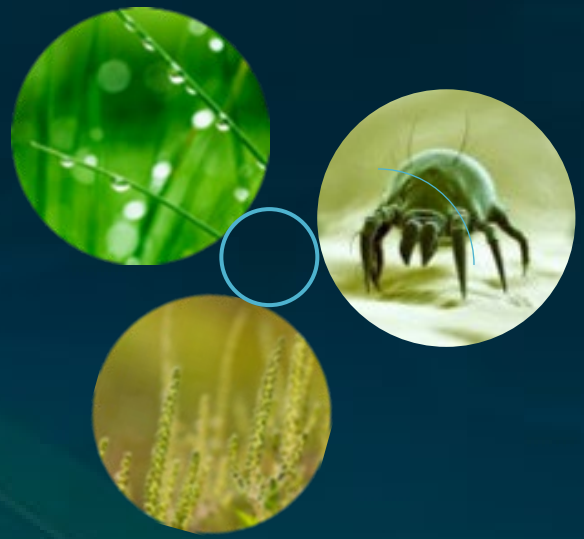
ALK Abstracts & Posters

AAAAI ANNUAL MEETING 2021



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The 12 SQ-HDM SLIT-Tablet Shows Similar Safety and Efficacy Across Geographies, Ethnic and Age Groups

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Tokyo, Japan; [5]ALK, Hørsholm, Denmark

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Introduction

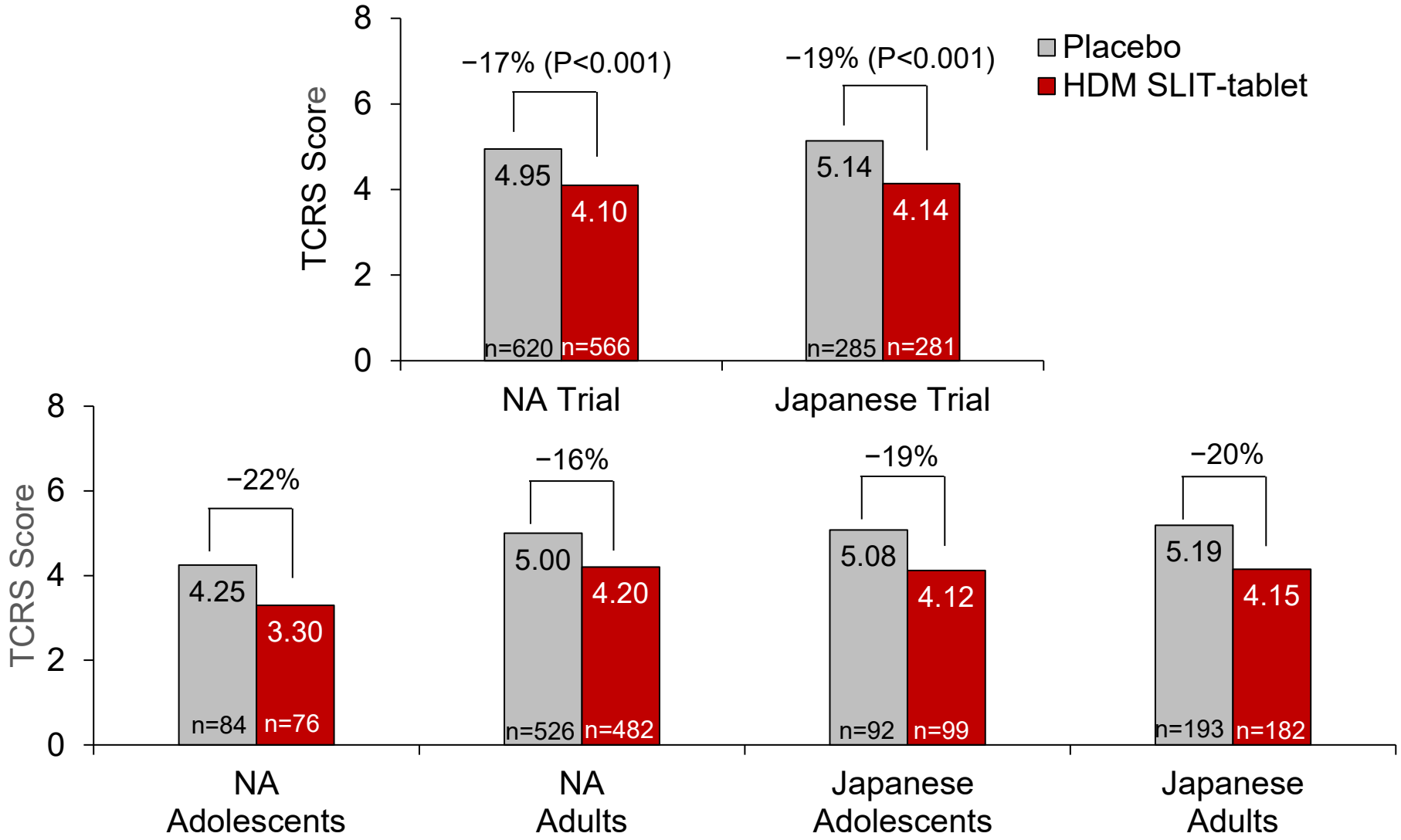
- House dust mite (HDM) sublingual immunotherapy (SLIT)-tablets have been evaluated in large clinical trials of adolescents and adults with allergic rhinoconjunctivitis in North America and Japan[1,2]
- Because of the diversity of participants in the trials and the large sample sizes, it is possible to assess safety and efficacy across age groups and ethnic/world regions

Methods

- Data from 2 randomized, double-blind, placebo-controlled phase III clinical trials (NCT01700192 [12 SQ-HDM, n=741; placebo, n=742] and JapicCTI-121848 [12 SQ-HDM, n=314; placebo, n=319]) [1,2] with 12 SQ-HDM were analysed by:
  - Age groups: adolescents (12-17 years) and adults (18-64 years)
  - Ethnicity/region (Japan/North America [NA])
- Trials had similar design, medical practice, target population, eligibility criteria, efficacy and safety monitoring
  - Primary endpoint: Total combined rhinitis score (TCRS; sum of rhinitis daily symptom score and daily medication score: max=24) during the 8-week efficacy assessment period

1. Nolte H, et al. *J Allergy Clin Immunol* 2016; 138:1631-1638.
2. Okubo K, et al. *J Allergy Clin Immunol* 2017; 139:1840-1848.e1810.

TCRS is comparable across ethnic/world regions and age



NA, North America; TCRS=sum of rhinitis daily symptom score and daily medication score

Safety is comparable across ethnic/world regions and age

- HDM SLIT-tablet was well-tolerated and safety profile was generally similar in NA and Japanese populations
- In total, 4 events of epinephrine use due to treatment-related events – all were in NA adults*

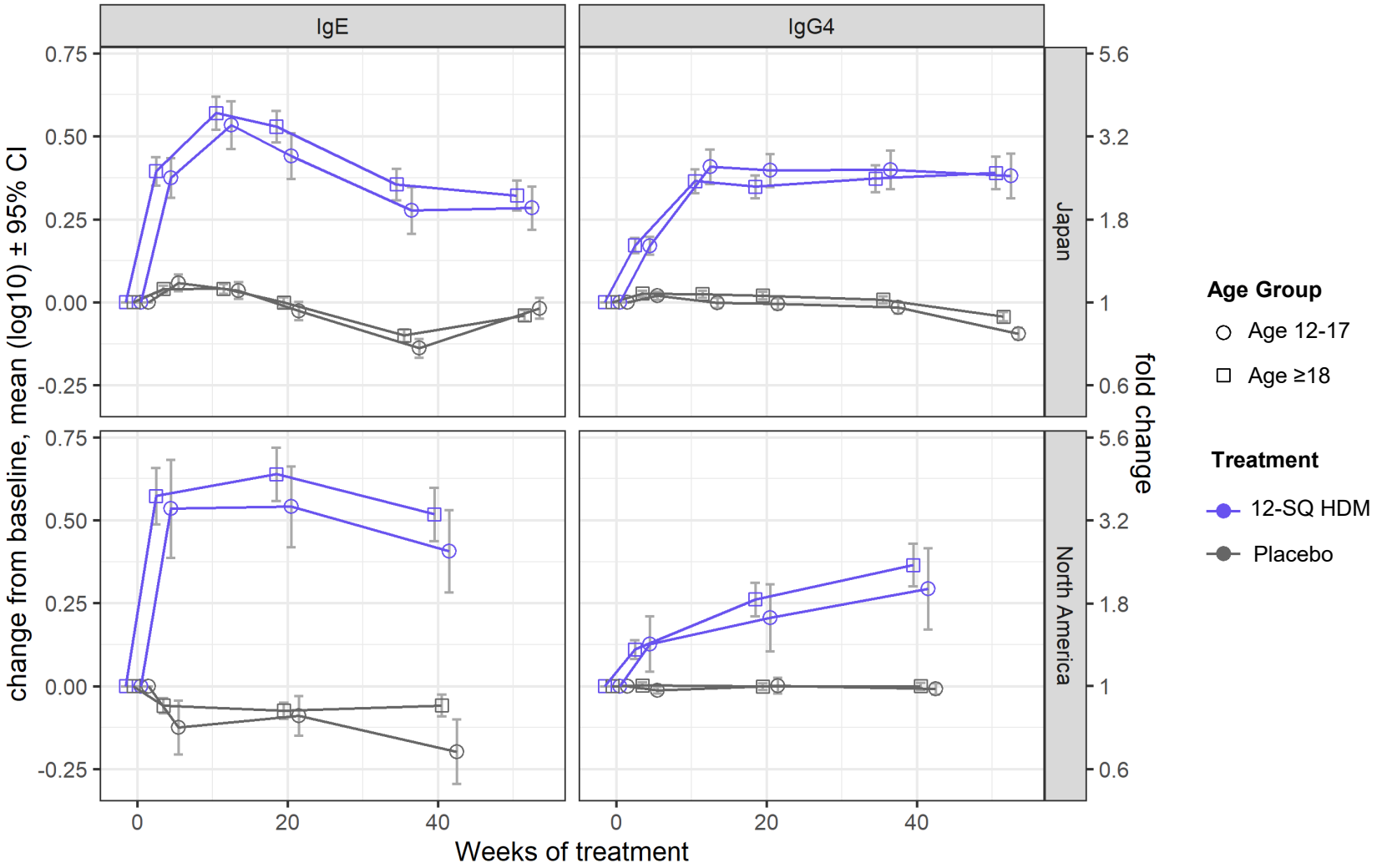
	NA Population					
	Adolescents			Adults		
	12 SQ-HDM (n=94)	PBO (n=95)	PBO-subtracted Rate†, %	12 SQ-HDM (n=649)	PBO (n=643)	PBO-subtracted Rate†, %
Any TEAE	95%	79%	16%	89%	74%	15%
Any TRAE	93%	47%	45%	80%	39%	41%
Any TRAE leading to study discontinuation	10%	0%	10%	6%	1%	5%
	Japanese Population					
	Adolescents			Adults		
	12 SQ-HDM (n=107)	PBO (n=99)	PBO-subtracted Rate†, %	12 SQ-HDM (n=207)	PBO (n=220)	PBO-subtracted Rate†, %
Any TEAE	93%	83%	10%	89%	79%	10%
Any TRAE	66%	19%	47%	62%	16%	46%
Any TRAE leading to study discontinuation	2%	2%	0%	1%	2%	0%

PBO, placebo; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

*Epinephrine co-prescription was required by the FDA in the North American trial. The Japanese trial had no requirement for epinephrine co-prescription.

†Placebo-subtracted rate = proportion of subjects in 12 SQ-HDM group minus proportion of subjects in placebo group

HDM IgE and IgG_4 responses are comparable across ethnic/world regions and age



Impact of age and region on immune responses to allergy immunotherapy

#411

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Introduction

- Allergy immunotherapy (AIT) can treat allergic disease by modifying the adaptive immune system,[1] similar to anti-pathogen vaccines, supporting the concept of AIT as an "allergy vaccination"
- Some anti-infectious vaccines, e.g. influenza, pneumococcal pneumoniae, are administered globally with the same dose for all age groups

Objective

- The aim of this study was to determine if the same dose of sublingual immunotherapy (SLIT) across regions and age groups induce similar immunologic changes in IgE and IgG_4 to support the goal of using the same dose and formulation worldwide

Methods

Literature search

- PubMed was searched for relevant human trials published in English from 01/01/2000 to 04/01/2020 evaluating age and regional factors related to dosage and immunologic response to AIT or anti-pathogen vaccines to elucidate similarities and differences
  - Search terms were related to ethnicity, region/geography, age factors, safety, efficacy, immunology, IgA, IgG, IgE, and treatment dose
  - Preventative vaccine articles were limited to hepatitis A, influenza, and pneumococcal pneumoniae
  - AIT articles involving fungi- and food allergy, simultaneous administration of omalizumab, cancer therapy and comparisons of sublingual/subcutaneous immunotherapy efficacy were excluded

Clinical trial data

- Immunologic data from 12 completed multi-national randomized, double-blind, placebo-controlled pivotal trials of birch, timothy grass, ragweed, and house dust mite SLIT-tablet (N=5645) were analysed post-hoc by age and region

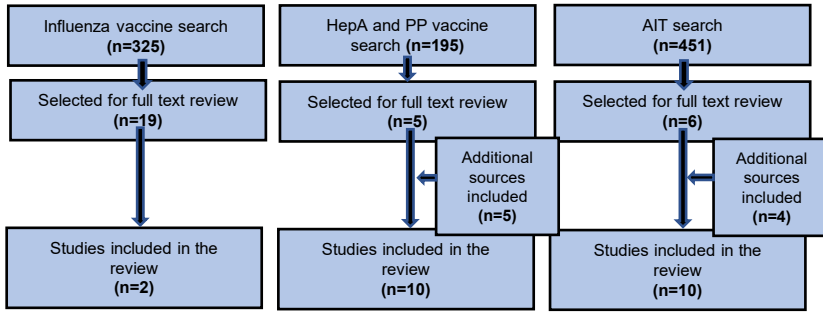
Funding: Studies included in this analysis were funded by ALK, Hørsholm, Denmark, Torii Pharmaceuticals Co., Ltd., Tokyo, Japan, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Results

Literature search

- In all, 971 articles met the inclusion criteria (AIT, n=451; anti-pathogen vaccines, n=520); 22 articles were ultimately reviewed (**Figure 1**)
- The literature search did not reveal conclusive data supporting a universal AIT dosage
- Published data indicated that age and other host factors can influence anti-pathogen vaccine immunogenicity

Figure 1. Flowchart of AIT and anti-pathogen vaccine literature search.



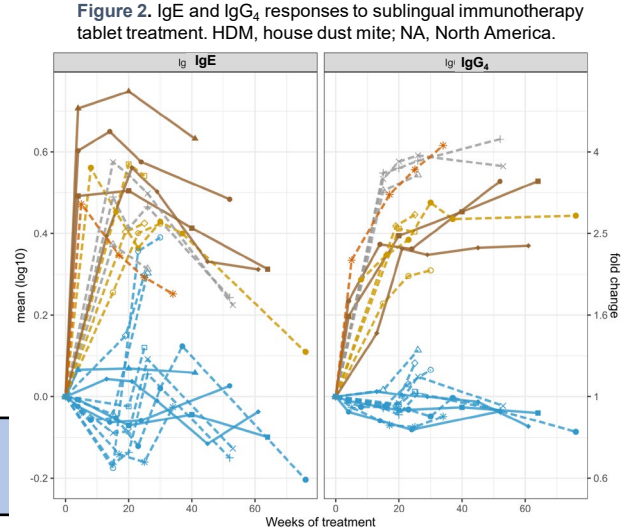
Clinical trial data

- Serum samples from 5645 subjects were analyzed for immunologic responses (**Table 1**)
- SLIT-tablets induced a significant immunologic response compared with placebo shortly after initiation (**Figure 2**)
- The pattern and magnitude of the response to SLIT-tablet for both IgE and IgG_4 were similar across allergen species, regions, and age (**Figure 2**)

Table 1. Number of subject serum samples per allergen species SLIT-tablet by region.

Region	House Dust Mite	Timothy Grass	Ragweed	Tree	Placebo
Japan	314	NA	NA	NA	319
Europe	297	387	93	316	1081
North America	743	348	323	NA	1424

Figure 2. IgE and IgG_4 responses to sublingual immunotherapy tablet treatment. HDM, house dust mite; NA, North America.



Reference

1. Jutel M and Akdis CA. *Allergy*. 2011;66(6):725-732.

Disclosure of presenting author: J. Nolte has nothing to disclose.

Conclusion

The results indicate that the overall immunologic responses to SLIT-tablet are insensitive to region and age

#410

No severe anaphylaxis in clinical trials of house dust mite sublingual immunotherapy tablet using a standardized identification algorithm

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Introduction

- Anaphylaxis can potentially occur with any administration of allergy immunotherapy
- Lack of a universally accepted standardized definition for anaphylaxis in clinical trials is an unmet need for safety reporting of allergy immunotherapy products
- Standardized MedDRA Queries (SMQs) are standardized and validated groupings of MedDRA terms that relate to a defined medical condition or area of interest[1]
  - Narrow terms indicate high certainty of the condition
  - Broad terms are less specific and require further evaluation and interpretation
- SMQs are used as tools in drug safety monitoring

Objective

- An algorithm in the SMQ Anaphylactic Reaction was used to identify anaphylaxis in house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet clinical trials

Methods

- Criteria 1 of the algorithm was all treatment-emergent AEs with the narrow terms of the SMQ Anaphylactic Reaction
- Criteria 2 was all treatment-emergent AEs with broad terms from ≥2 of 3 categories (respiratory, cutaneous, and cardiovascular) occurring on the same day (**Table 1**)
- The criteria were applied to a pooled dataset of all subjects treated with HDM SLIT-tablet (12 SQ-HDM dose) in randomized clinical trials and after treatment interruptions of 12 SQ-HDM of any duration for any reason
- All identified cases were reviewed by a medical professional

Disclosure of presenting author: V. Hulstrøm was an employee of ALK, Hørsholm, Denmark, at the time of this analysis.

Table 1. Standardized MedDRA Query (SMQ) searches to identify potential anaphylaxis in the clinical development program of the house dust mite sublingual immunotherapy tablet (12 SQ-HDM dose).

Criteria	SMQ Search
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 ≥ 2 or more 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)

Results

12 SQ-HDM pooled dataset (N=2166 subjects)

- Criteria 1 identified one event (**Table 2**)
  - This event occurred at first dose and was considered non-treatment-related (food-related allergic reaction)
- Criteria 2 identified 101 potential cases in 77 subjects (**Table 2**)
- Most events were mild-to-moderate local allergic reactions
- Medical review identified 1 systemic allergic reaction (facial flushing, itchy palms, swollen throat)
  - This event occurred at first dose and was assessed as moderate

Treatment interruption dataset (300 interruptions in 207 subjects)

- No events were identified by criteria 1 (**Table 2**)
- Criteria 2 identified 5 potential cases in 3 subjects (**Table 2**)
- After medical review, none of the events met the criteria for anaphylaxis

Table 2. Potential anaphylaxis events identified by Standardized MedDRA Query searches.

	Pooled 12 SQ-HDM Dataset (N=2166 subjects)		Pooled Treatment Interruption Dataset (N=207 subjects)	
Criteria	Subjects	Cases	Subjects	Cases
Criteria 1, narrow search	1*	1*	0	0
After medical review	0	0	0	0
Criteria 2, broad search	77	101	3	5
After medical review	1	1	0	0

*Non-treatment-related food-related allergic reaction.

Conclusion

In clinical trials, there was no severe anaphylaxis with the HDM SLIT-tablet with or without SLIT-tablet interruption using the SMQ algorithm

Reference

1. Introductory guide for Standardised MedDRA Queries (SMQs) Version 22.1. https://admin.new.meddra.org/sites/default/files/guidance/file/000356_smq_intguide_22_1.pdf. Accessed December 16, 2020.

Funding: Studies included in this analysis were funded by ALK, Hørsholm, Denmark, Torii Pharmaceuticals Co., Ltd., Tokyo, Japan, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.