



Major allergen content consistency of SQ house dust mite sublingual immunotherapy tablets and relevance across geographic regions

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ABSTRACT

Background: Consistency in composition and potency, particularly regarding major allergens, is crucial for the quality of extracts for allergen immunotherapy.

Objective: To characterize the major allergen composition of house dust mite (HDM) extracts commercially available in the United States and the SQ HDM sublingual immunotherapy (SLIT) tablet, and to relate the composition to patient sensitization patterns.

Methods: Der 1/Der 2 ratios were determined in 10,000- and 30,000-AU/mL HDM extracts from 5 US companies and the SQ HDM SLIT-tablet. Allergen content was analyzed by enzyme-linked immunosorbent assay and compared with an in-house reference. Sensitivity toward Der p 1, Der p 2, and Der p 10 was determined in serum from randomly selected subgroups of 220 individuals from North American and European SQ HDM SLIT-tablet trials.

Results: Mean Der 1/Der 2 ratios in US HDM extracts ranged from 0.4 to 20.5. For the SQ HDM SLIT-tablet (20 batches), variability did not exceed 12% regarding content of Der f 1 (SD, 11.9%; 95% confidence interval [CI], 0.94–1.06), Der p 1 (SD, 6.1%; 95% CI, 0.97–1.03), and combined Der 2 allergen (SD, 6.4%; 95% CI, 0.97–1.03), indicating a consistent Der 1/Der 2 ratio. High allergen sensitivity frequencies toward Der p 1 and Der p 2 were observed regardless of geographic region. Efficacy of the SQ HDM SLIT-tablet has been demonstrated in 5 clinical trials.

Conclusion: The SQ HDM SLIT-tablet has efficacy potential for a broad range of patients because it includes a consistent 1:1 ratio of the 2 major HDM allergens to which individuals were most frequently sensitized across geographic regions. Efficacy has been demonstrated.

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Introduction

Sensitization to house dust mite (HDM) is common in many countries worldwide at a prevalence of approximately one-quarter to one-third of the general population^{1–5} and half of the population with allergic rhinitis.⁶ HDM allergy immunotherapy (AIT) modulates basic immunologic mechanisms of allergic disease and is

recognized as the only treatment with the potential to alter the natural course of the disease. With the recent accumulation of statistically robust efficacy and safety data from large, double-blinded, placebo-controlled (DBPC) clinical trials, HDM AIT has re-emerged as an attractive treatment option for HDM rhinoconjunctivitis and asthma. *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* are the most common HDM species found in bedding and mattresses throughout the world⁷ and are generally considered the most relevant for HDM AIT. The major allergens for *D pteronyssinus* and *D farinae* belong to groups 1 and 2.⁸ The group 1 and 2 allergens are considered major allergens based on studies that found that 63% to 100% of patients allergic to HDM in Europe, North America, and Japan and up to 81% of children with asthma are strongly sensitized to Der p 1 and/or Der p 2.^{9–12} A number of other allergens are known, but sensitivity is less

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frequent. For example, approximately 15% of patients allergic to HDM are sensitized to Der p 10.^{9,13} Sensitization to Der 10 (tropomyosin) causes cross-reactivity and is a potential cross-sensitizing allergen to shellfish, cockroach, and other insects.

The extracts for HDM AIT are made by growing *D pteronyssinus* and *D farinae* in pure cultures, which typically contain proteins from mite bodies and mite fecal particles, and culture medium. HDM fecal particles contain high amounts of group 1 allergen, whereas mite bodies are the primary source for group 2.¹⁴ The manufacturing process among HDM AIT formulations varies, with differences in culture media and extraction processes and with limited possibility of adjusting the composition. Studies have found that the composition and content among HDM extracts from various manufacturers in Europe and the United States highly differ.^{15–18}

As part of the standardization program of allergen extracts, the US Food and Drug Administration (FDA) assigns the strengths of HDM extracts by comparison with the FDA reference standard in an IgE antigen-binding competition enzyme-linked immunosorbent assay (ELISA) using a human IgE serum pool provided by the FDA.¹⁹ The results of a manufacturer's product are then expressed in allergy units (AU) per milliliter relative to the FDA reference standard,²⁰ although this does not indicate the composition or allergen content of the extract.²¹ Because extract production processes differ among manufacturers, FDA-standardized HDM extracts (as defined by AU per milliliter) may contain various amounts of any allergen and, most importantly, differing amounts and ratios of major allergens. Consistency in total allergenic potency and composition of the AIT extracts, particularly regarding major allergens, will affect the clinical efficacy of the product and is crucial for safety. Recognition of the need for consistency of the extracts, which was previously largely missing from available AIT products, prompted the development of sublingual immunotherapy (SLIT) tablets that are manufactured in a consistent, characterized process. SQ HDM SLIT-tablets (MK-8237; Merck & Co Inc, Kenilworth, New Jersey, and ALK, Hørsholm, Denmark) contain extracts that are produced by a controlled process that allows for the use of body and fecal fractions of *D farinae* and *D pteronyssinus* to achieve a 1:1:1:1 ratio between Der f 1/2 and Der p 1/2 allergens.²² In addition to an equal and controlled ratio of the 4 major allergens, the controlled use of body and fecal particles ensures a content with the broadest possible range of HDM allergens in each tablet. The objectives of this report are to describe the results of studies assessing the major allergen composition of HDM extracts commercially available in the United States and the SQ HDM SLIT-tablet, and to relate the composition to patient sensitization patterns.

Methods

HDM Extracts

Standardized HDM extracts commercially available for diagnostic purposes and subcutaneous immunotherapy from 5 US manufacturers (ALK-Abelló Inc, Greer, Allergy Labs, Antigen Labs, and Hollister-Stier) were assessed. All the extracts had labeled specific activities of 10,000 or 30,000 AU/mL as determined by the FDA.

Potency and Allergen Content

IgE-binding potency of 20 batches of the SQ HDM SLIT-tablet was determined using an automated ADVIA Centaur assay (Siemens, Ballerup, Denmark).²³ Measured potency was determined relative to an in-house (ALK) reference preparation that was based on histamine equivalent potency determined by skin prick test.

The absolute values of major allergen content may depend on the assays used. Concentrations of Der p 1, Der f 1, and Der 2

Table 1

Levels of Der 1 and Der 2 for *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* in Commercially Available US House Dust Mite Extracts

Manufacturer, AU/mL	Der 1, μ g/mL	Der 2, μ g/mL	Der 1/Der 2 ratio
<i>D pteronyssinus</i>			
ALK, 10-year average, 10,000 AU/mL ^a	66	64	1.0
Greer, 10,000 AU/mL	58	51	1.1
Greer, 10,000 AU/mL	60	25	2.4
Greer, 30,000 AU/mL	127	61	2.1
Jubilant Hollister Stier, 10,000 AU/mL	27	17	1.6
Jubilant Hollister Stier, 10,000 AU/mL	19	10	1.9
Jubilant Hollister Stier, 30,000 AU/mL	85	48	1.8
Allergy Labs, 10,000 AU/mL	64	61	1.0
Antigen Labs, 10,000 AU/mL	42	38	1.1
<i>D farinae</i>			
ALK, 10-year average, 10,000 AU/mL ^a	84	92	0.9
Greer, 10,000 AU/mL	80	73	1.1
Greer, 10,000 AU/mL	144	73	2.0
Greer, 10,000 AU/mL	79	34	2.3
Greer, 30,000 AU/mL	266	54	4.9
Jubilant Hollister Stier, 10,000 AU/mL	41	2	20.5
Jubilant Hollister Stier, 10,000 AU/mL	26	5	5.2
Jubilant Hollister Stier, 30,000 AU/mL	103	14	7.4
Jubilant Hollister Stier, 30,000 AU/mL	109	8	13.6
Allergy Labs, 10,000 AU/mL	40	95	0.4
Antigen Labs, 10,000 AU/mL	100	95	1.1

Abbreviation: AU, allergy units.

^aExtract is different than that manufactured by ALK, Inc, for HDM sublingual immunotherapy tablet. Value reported is the mean from every batch manufactured from 2002 to 2012; lots from the other manufacturers were measured during this same period.

in the standardized HDM extracts and the SQ HDM SLIT-tablet were analyzed by validated sandwich ELISA methods and compared with an in-house reference. The ELISA for Der 2 used a monoclonal antibody with a similar reactivity to Der p 2 and Der f 2. Every batch of SQ HDM SLIT-tablet manufactured between 2002 and 2012 (20 batches) was tested. Lots from the standardized HDM extracts were measured during this same 10-year period.

Sensitization Patterns

Sensitivity toward Der p 1, Der p 2, and Der p 10 allergens was determined for individuals who participated in a North American or European SQ HDM SLIT-tablet phase 3 trial. Details of these trials have been previously described.^{24,25} Serum samples were collected at baseline, and the sera from 110 individuals in the North American trial were then randomly selected as a subset. This subset was compared with the remaining cohort and found to be comparable in regional distributions and IgE class division to the remaining cohort. There was no significant difference in the mean HDM specific IgE values for *D pteronyssinus* and *D farinae* between the subset and the remaining cohort; therefore, the subset was considered to

Table 2

Batch-to-Batch Consistency of SQ HDM SLIT-Tablet^a

Assessment	Normalized mean (SD) [95% CI]
IgE-binding potency	1.000 (0.045) [0.98–1.02]
Der f 1 major allergen	1.000 (0.119) [0.94–1.06]
Der p 1 major allergen	1.000 (0.061) [0.97–1.03]
Der 2 major allergen	1.000 (0.064) [0.97–1.03]

Abbreviations: CI, confidence interval; HDM, house dust mite; SLIT, sublingual immunotherapy.

^aTwenty batches were analyzed. All parameters were normally distributed. Data were normalized relative to mean. Reproduced with permission from Henmar et al.²²

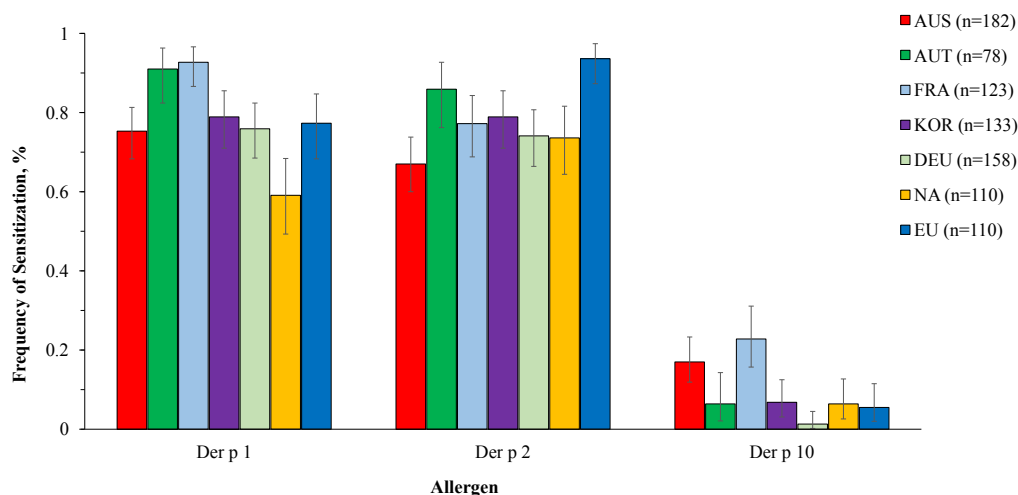


Figure 1. Prevalence of sensitivity toward Der p 1, Der p 2, and Der p 10 among house dust mite allergic populations.^{11,24,25,27–30} The KOR study investigated the profiles to Der f 1, Der f 2, and Der f 10, which are representative of Der p 1, Der p 2, and Der p 10. Error bars indicate 95% confidence intervals. AUS, Australia; AUT, Austria; DEU, Germany; EU, Europe; FRA, France; KOR, Korea; NA, North America.

be representative of the remaining cohort. The samples came from 22 states across the United States and 2 Canadian regions. Similarly, 110 baseline serum samples from the European HDM study were selected randomly as a subset and were compared with the remaining cohort. Using the same measures as described for the North American subset, the 110 samples were considered representative of the remaining cohort. The samples came from 13 European countries across the continent.

Analysis of serum specific IgE to *D pteronyssinus* extract, *D farinae* extract, Der p 1, Der p 2, and Der p 10 was performed using the ImmunoCAP 250 immunofluorimetric assay (Thermo Fisher Scientific, Waltham, Massachusetts) with a commercially available instrument and reagents. A cut-off value of 0.7 kU_A/L was applied as the threshold for positive test result.

The relative specificity distribution was calculated to compare the magnitude of IgE binding of Der p 1 and Der p 2 relative to the magnitude of total IgE binding toward Der p extract in the North American and European SQ HDM SLIT-tablet trial populations. These calculations were made by normalizing the mean kU_A/L IgE

concentration for each of the individual allergens and the *D farinae* extract to the mean kU_A/L IgE concentration of the *D pteronyssinus* extract.

The distribution of sensitivity toward *D farinae* and *D pteronyssinus* across North America was examined using the baseline serum specific IgE values of a subset of the randomized patients in the North American SQ HDM SLIT-tablet trial.²⁵

Literature Search for Sensitivity Profile Comparison

Studies in the literature that provided patient sensitization patterns for Der 1, Der 2, and Der 10 were identified for comparison with the North American and European SQ HDM SLIT-tablet trial populations. The cut-off values used as the threshold for positive serum specific IgE positivity in the cited studies varied. For some of the studies, a detection limit of 1.0 kU_A/L was applied, and in some of the studies there was no information disclosed regarding the cut-off value. In addition, the methods used for determination of the levels of serum-specific IgE differed from study to study.

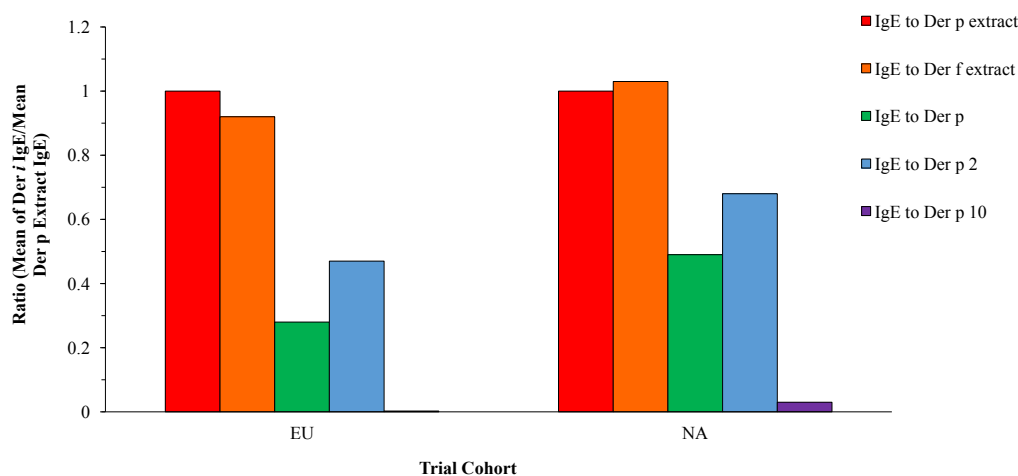


Figure 2. Relative specificity distribution of IgE reactivity against HDM allergens from North American and European SQ HDM SLIT-tablet trial populations (subset of 110 individuals per trial).^{24,25} Der i represents *D pteronyssinus* extract, *D farinae* extract, Der p 1, Der p 2, and Der p 10. HDM, house dust mite; SLIT, sublingual immunotherapy.

Table 3Baseline IgE Levels to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* Across North America From a SQ HDM SLIT-tablet Trial Population²⁵

State or province, No. of participants	<i>D pteronyssinus</i> IgE, mean, kU _A /L	<i>D farinae</i> IgE, mean, kU _A /L
Virginia, 21	27.11	34.92
Iowa, 9	33.06	33.53
Vermont, 21	24.04	23.72
Maine, 6	26.39	23.68
Michigan, 13	21.82	21.28
Rhode Island, 18	21.54	20.84
Arkansas, 9	16.82	19.09
California, 127	21.17	18.72
Maryland, 18	15.31	18.54
Kansas, 10	10.97	18.46
Pennsylvania, 53	14.63	16.85
South Carolina, 22	15.39	16.70
New Jersey, 65	12.78	15.70
North Carolina, 18	18.10	15.05
Minnesota, 16	14.50	14.98
New York, 28	16.19	14.64
Ontario, 189	12.03	14.13
Illinois, 10	15.03	13.77
Ohio, 67	12.24	13.71
Oregon, 45	16.49	13.38
Nebraska, 8	8.47	13.18
Oklahoma, 13	11.09	12.99
Massachusetts, 22	10.81	11.88
Quebec, 20	9.43	11.86
Wisconsin, 32	11.67	11.78
Alabama, 18	10.23	11.68
Georgia, 9	8.70	9.40
Texas, 96	8.67	9.22
Washington, 22	9.50	7.21
Florida, 3	9.01	6.86
Missouri, 43	3.64	5.08
Kentucky, 4	4.70	4.15
Utah, 4	4.52	3.72
Tennessee, 1	1.70	1.14
Indiana, 1	1.10	0.70
Total, 1061	13.98	14.80

Abbreviations: HDM, house dust mite; SLIT, sublingual immunotherapy.

Results

Der 1 and Der 2 Content of Available HDM Products in the United States

Differences in the content of Der 1 and Der 2 in the commercially available HDM extracts were observed despite equivalent concentration labeling (Table 1). The mean Der 1/Der 2 ratio ranged from 0.4 to 20.5.

Potency and Allergen Content of SQ HDM SLIT-Tablet

Analysis of 20 batches of SQ HDM SLIT-tablet yielded a normalized mean (SD) of IgE-binding potency of 1.000 (0.045; 95% confidence interval [CI], 0.98–1.02) (Table 2). Variability (as determined by SD) did not exceed 12% with regard to content of Der f 1, Der p 1, and combined Der 2 allergen (Table 2), indicating a consistent Der 1/Der 2 ratio. Other HDM allergens were also present (data not shown).

The absolute amount of major allergen in the SQ HDM SLIT-tablet was approximately 0.6 µg per major allergen per SQ HDM unit. For the 12 SQ HDM SLIT-tablet, which was investigated in a chamber provocation study,²⁶ in 2 large phase 3 trials in individuals with allergic rhinitis with or without conjunctivitis caused by HDM,^{24,25} and in a large trial of patients with allergic asthma caused by HDM,²⁷ this corresponds to roughly 15 µg of Der 1 (Der f 1 and Der p 1 combined) and 15 µg of Der 2 (Der f 2 and Der p 2 combined) per 12 SQ HDM SLIT-tablet (marketed dose in Europe).²²

Sensitization Patterns

The results regarding the frequency of serum specific IgE toward major allergens Der p 1 and Der p 2, as well as the minor allergen Der p 10, from the European and North American SQ HDM SLIT-tablet trials were compared with results reported in the literature. The cited literature studies cover Australia,²⁸ Austria,²⁹ France,³⁰ Korea,³¹ and Germany.¹¹ The data reveal variations within (as indicated by the 95% CIs) and between data sets, but a general pattern can be recognized (Fig 1). Sensitization toward the major Der p 1 and Der p 2 allergens occurred with high frequency in all the geographic regions, with the frequency being greater than 70% in all but the North American trial population. Sensitization to Der p 2 is more frequent than sensitization to Der p 1 for the North American and European trials. In contrast, the frequency of sensitization to Der p 10 was very low for all the studies.

The relative specificity distribution revealed that the relative magnitudes of *D pteronyssinus* and *D farinae*, Der p 1, and Der p 2 IgE, respectively, were generally comparable between the North American and European populations in the SQ HDM SLIT-tablet trials (Fig 2).

Sensitization to *D pteronyssinus* and *D farinae* across North America was examined in the North American SQ HDM SLIT-tablet clinical trial.²⁵ The highest IgE level to *D pteronyssinus* was 33.06 kU_A/mL, and the highest IgE level to *D farinae* reached 34.92 kU_A/mL. IgE levels for *D pteronyssinus* and *D farinae* were similar within each state or Canadian province (Table 3).

Clinical Trial Outcome Summary for SQ HDM SLIT-Tablet

A summary of efficacy results from all the phase 2 and phase 3 DBPC SQ HDM SLIT-tablet clinical trials is given in Table 4. All 5 trials met their primary efficacy end point. The trials revealed that the SQ HDM SLIT-tablet significantly improved rhinitis symptoms vs placebo and improved asthma outcomes.

Discussion

Substantial differences in major allergen content were observed in HDM extracts labeled with identical AU/mL as determined by the FDA reference standards. By comparison, the SQ HDM SLIT-tablet contained equal and consistent amounts of Der 1 and Der 2 from *D pteronyssinus* and *D farinae*, the HDM species to which humans are most commonly exposed. Furthermore, the 1:1:1:1 ratio of Der p 1, Der f 1, Der p 2, and Der f 2 content in the SQ HDM SLIT-tablet was consistent, with SDs of less than 12% among 20 different batches. Data from clinical trials and published literature confirmed that a high percentage of HDM allergic patients are sensitized to the major allergens Der 1 and Der 2, and the sensitization patterns are comparable across geographic regions. Together these data indicate that the SQ HDM SLIT-tablet contains, in a consistent lot-to-lot manner, the major allergens needed to effectively treat patients with HDM allergy across various geographic regions. This premise is supported by the efficacy results from 5 clinical trials conducted in Europe and North America, which revealed significant improvement in allergic rhinoconjunctivitis symptoms or asthma outcomes with SQ HDM SLIT-tablet treatment vs placebo.^{24–27,32}

The differences in Der 1 and Der 2 content among the standardized HDM extracts indicate that the in vitro AU/mL standardization method does not reflect a standardization of allergen content. A lack of Der 1 and/or Der 2 in HDM extracts could have an impact on AIT efficacy. The standardization of HDM extracts as determined by the FDA is based on the overall IgE-binding potency, but if comparable potencies of different extracts have different allergen composition as demonstrated in the current analysis, then the variability in allergen composition could pose a safety hazard. Furthermore, the ability to effectively treat HDM allergy may be

Table 4

Efficacy Results From All the Phase 2 and Phase 3 Randomized, Double-Blinded, Placebo-Controlled SQ HDM SLIT-Tablet Clinical Trials

Trial (protocol; registration No.)	No. of patients randomized	Population	Age, y	Primary outcome	Primary outcome results	Baseline serum specific IgE, mean, kU _A /L ^a
Nolte et al (P003; NCT01644617) ^{26,b}	124	AR/C with/without asthma	≥18	Mean TNSS at week 24	49% improvement vs placebo (12 SQ-HDM dose); mean difference, −3.62 ($P < .001$)	<i>D farinae</i> = 23.7 <i>D pteronyssinus</i> = 20.4
Nolte et al (P001; NCT01700192) ²⁵	1,482	AR/C with/without asthma	≥12	TCRS during approximately the last 8 weeks of treatment	17% improvement vs placebo (12 SQ-HDM dose); mean difference, −0.80 ($P < .001$)	<i>D farinae</i> = 15.0 <i>D pteronyssinus</i> = 14.1
Demoly et al (MERIT; NCT01454544) ²⁴	992	AR/C with/without asthma	18–65	TCRS during approximately the last 8 weeks of treatment	18% improvement vs placebo (12 SQ-HDM dose); mean difference, −1.22 ($P = 0.001$)	<i>D farinae</i> = 29.9 <i>D pteronyssinus</i> = 28.6
Virchow et al (MITRA; NCT01433523) ²⁷	834	AR/C with asthma not well controlled by medium-high dose ICS	≥18	Time to first asthma exacerbation during ICS reduction period	34% reduced risk in time to first asthma exacerbation vs placebo (12 SQ-HDM dose); HR = 0.66, $P = .02$	<i>D farinae</i> = 43.9 <i>D pteronyssinus</i> = 50.1
Mosbech et al (MT-02; NCT00389363) ³²	604	AR/C with asthma	≥14	Reduction in ICS dose from baseline	42% reduction (6 SQ-HDM dose); $P = .001$ vs placebo	<i>D farinae</i> = 27.2 <i>D pteronyssinus</i> = 34.2

Abbreviations: AR/C, allergic rhinitis with or without conjunctivitis; HDM, house dust mite; HR, hazard ratio; ICS, inhaled corticosteroid; SLIT, sublingual immunotherapy; TCRS, total combined rhinitis score (sum of rhinitis symptom and medication scores); TNSS, total nasal symptom score (sum of 4 nasal symptoms).

^aAll randomized subjects.

^bP003 was an environmental exposure chamber trial.

hampered. This variability suggests that clinical trials with all commercially available HDM extracts should be conducted to confirm the adequacy of the material for AIT. Data surrounding this issue are just beginning to emerge. So far, only 2 randomized DBPC trials have evaluated the efficacy of HDM AIT in the United States. The first trial ($n = 31$) used FDA-standardized HDM extract as sublingual drops (Greer), and no significant difference in total symptom scores or symptom-relieving medication use was observed with the high- or low-dose treatment vs placebo after 12 months.³³ The second trial ($n = 1,482$) used the SQ HDM SLIT-tablet (12 SQ-HDM dose) and found a significant improvement in total combined rhinitis symptom and medication scores vs placebo after a median treatment duration of 271 days.²⁵ There are no North American trial data available for HDM subcutaneous immunotherapy using current commercially available US extracts.

The need for standardization of allergen content is recognized, and a European panel ("Development of certified reference materials for allergenic products and validation of methods for their quantification," CREATE) has attempted to develop international allergen standards to unify allergen measurements.^{21,34} However, these standards have yet to be developed and adopted for HDM, and analysis of commercially available HDM extracts available in Europe has revealed variability of Der 1 and Der 2 content.^{15,16,18} In the current analysis, SQ HDM SLIT-tablets had a 1:1 ratio of Der 1 and Der 2. This ratio was intentional and is a result of the production process based on separation of HDM source material into body and fecal fractions. The process enables control of precise dosing of the major Der 1 and Der 2 allergens and ensures the best possible coverage of HDM allergens in general. This coverage includes minor allergens that are likely to provide a broader specificity beyond the 4 major allergens.^{22,35}

The prevalence of sensitization to the major Der p 1 and Der p 2 allergens and minor allergen Der p 10 was very similar among the populations in the North American and European trials and other geographic regions reported in the published literature. These results confirm that Der 1 and Der 2 are important HDM allergens and are in agreement with those obtained from an analysis of 1,302 North American, European, and Japanese adults and children allergic to HDM, which determined that the IgE sensitization to the group 1 and group 2 allergens was highly prevalent, and the sensitization patterns for HDM allergens overall were highly comparable among

these populations.¹² The minor differences among the studies may be attributable to differences in the study designs, such as the number of included patients and variation in the analytical methods used for determination of specific IgE. In the current analysis, the relative specificity distribution revealed the comparability of the sensitization patterns between the North American and European SQ HDM SLIT-tablet trial populations. Together, the data indicate that the composition of the SQ HDM SLIT-tablet is relevant for treatment of HDM allergic populations across a broad geographic area, including North America, Europe, and Asia.

Der 1 and Der 2 are major HDM allergens worldwide, and the content of these allergens varies in standardized HDM extracts commercially available in the United States. The clinical relevance of the observed variation is unknown because there are no clinical studies with FDA-standardized HDM extracts that document their efficacy. The unique manufacturing process of the SQ HDM SLIT-tablet enables separate control of each major allergen and results in a consistent formulation that contains equal strength from both mite species, as well as a consistent and equivalent content of Der 1 and Der 2. The SQ HDM SLIT-tablet has efficacy potential for a broad range of patients because it includes a consistent 1:1 ratio of the 2 major HDM allergens to which individuals were most frequently sensitized across geographic regions. The composition of the SQ HDM SLIT-tablet results in clinical efficacy as revealed in multiple clinical trials.

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