Poster # 192

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Duration and Recurrence of Local Site Reactions Associated with SQ House Dust Mite Sublingual Immunotherapy Tablet Treatment

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Introduction

- Mild to moderate local application site reactions are the most frequent adverse events associated with sublingual immunotherapy (SLIT)
- Approximately 5% of subjects discontinue due to AEs in SLIT clinical trials[1,2]
  - The local site reactions are expected since the high-dose allergen can elicit IgE-mediated responses[3]
- SQ house dust mite (HDM) SLIT-tablet has beneficial effects on allergic rhinitis with or without conjunctivitis (AR/C) and allergic asthma,[4-8] and consistent with other SLIT treatments, is associated with local site reactions
- Information regarding the duration and recurrence of local site reactions may improve patient acceptability and adherence to SLIT treatment

Objective

- To report the duration and recurrence of local site reactions to SQ HDM SLIT-tablet using pooled data from 4 trials

Methods

Trials included in pooled analysis

- Adverse event (AE) data from four phase 2 and phase 3 randomized, double-blinded, placebo-controlled trials were pooled
  - P003 was a 24-week environmental chamber trial (NCT01644617) conducted in European subjects aged ≥18 years with HDM AR/C[7]
  - P001 was a trial of up to 52-weeks (NCT01700192) conducted in North American subjects aged ≥12 years with HDM AR/C[6]
  - MT-06 was a 52-week trial (NCT01454544) conducted in European subjects aged ≥18 years with HDM AR/C[4]
  - MT-04 was an 18-month trial (NCT01433523) conducted in European subjects aged ≥18 years with HDM allergic asthma and AR[8]
- Subjects received daily SQ HDM SLIT-tablet (MK-8237; Merck & Co., Inc., Kenilworth, NJ, USA/ALK, Hørsholm, Denmark; 12 SQ-HDM dose in all trials and 6 SQ-HDM dose in all trials except P001) or placebo
  - The 12 SQ-HDM dose contains ≈15 mcg HDM group 1 allergens (Der f 1 and Der p 1 combined) and ≈15 mcg HDM group 2 allergens (Der f 2 and Der p 2 combined) for a total of 30 mcg major allergen content,[9] estimated to be approximately 5,300 allergen units
- Institutional review boards or ethics committees approved the protocols and written informed consent was obtained from the subject or subject's legal representative

Safety data collection and analysis

- In P001, reporting of local AEs was solicited daily for the first ≈28 days of treatment using closed-ended questions regarding local AEs identified by the World Allergy Organization[10]
  - AE reporting in the other three trials was unsolicited
- Data on duration in minutes on the first day of treatment was collected for local site reactions
- Data on the number of days each local site reaction recurred was analyzed
- AE data from the 12 SQ-HDM dose in the 4 trials were pooled

Results

- In all, 1,383 subjects treated with 12 SQ-HDM and 1,540 treated with placebo were included in the pooled analysis
- The incidence of treatment-emergent AEs was 83% with 12 SQ-HDM and 64% with placebo
  - The incidence of treatment-related AEs was 69% with active treatment and 28% with placebo
  - The percentage of subjects who discontinued due to treatment-related AEs was 7% with 12 SQ-HDM and 1% with placebo
- The treatment-related local site reactions reported at an incidence of >10% with 12 SQ-HDM were throat irritation, oral pruritus, ear pruritus, and lip swelling (**Table 1**)
- Approximately 95% of the local site reactions were assessed as mild-to-moderate in severity
- Median duration of the most common treatment-related local site reactions in minutes on first day of treatment is shown in **Table 2**
- Median recurrence of the most common treatment-related local site reactions in days is shown in **Table 3**

Table 1. Treatment-related AEs reported in ≥5% of subjects in one or more treatment groups

Adverse event, % of subjects	12 SQ-HDM (N=1,383)	Placebo (N=1,540)
Throat irritation	43	12
Oral pruritus	43	8
Ear pruritus	29	6
Lip swelling	11	1
Swollen tongue	10	1
Glossodynia	9	2
Pharyngeal edema	9	1
Nausea	8	2
Oral paraesthesia	7	2
Tongue ulceration†	7	1
Upper abdominal pain	6	2
Mouth swelling	6	1
Mouth ulceration†	6	1
Palatal swelling	6	1
Dysgeusia	5	2

HDM, house dust mite.
†Not directly observed by the investigator and a cognitive debriefing suggests that ulceration was often misinterpreted by subjects as pain rather than an actual ulcer.

Table 2. Median duration (minutes) of local site reactions

Adverse event	12 SQ-HDM (N=1,383)	Placebo (N=1,540)
Throat irritation		
Median (range), min	42 (1–870)	45 (1–810)
No. of subjects with data	460	94
Oral pruritus		
Median (range), min	30 (1–826)	60 (1–1149)
No. of subjects with data	414	62
Ear pruritus		
Median (range), min	30 (1–624)	60 (5–600)
No. of subjects with data	289	30
Lip swelling		
Median (range), min	60 (10–864)	15 (15–15)
No. of subjects with data	49	4

HDM, house dust mite.

Table 3. Median recurrence† (days) of local site reactions

Adverse event	12 SQ-HDM (N=1,383)	Placebo (N=1,540)
Throat irritation		
Median (range), days	12 (1–377)	3 (1–384)
No. of subjects with data	596	189
Oral pruritus		
Median (range), days	12 (1–532)	3 (1–464)
No. of subjects with data	588	128
Ear pruritus		
Median (range), days	10 (1–376)	3 (1–313)
No. of subjects with data	411	93
Lip swelling		
Median (range), days	3 (1–379)	3 (1–144)
No. of subjects with data	184	23

HDM, house dust mite.
†Does not imply a continuous duration, but rather a recurrence on subsequent days.

Conclusions

- The discontinuation rate due to treatment-related AEs was similar to the rate in trials of timothy grass and ragweed SLIT-tablets
- The median duration of the most common local site reactions associated with 12 SQ-HDM was 30 to 60 minutes, and the recurrence was less than 2 weeks
  - The duration and recurrence of local site reactions associated with 12 SQ-HDM were similar to those associated with timothy grass and ragweed SLIT-tablet
- These data should reassure patients that local site reactions to SQ HDM SLIT-tablet are typically mild-to-moderate, often transient, and that most decrease with continued treatment

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Disclosures

Q. Li and H. Nolte are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. H.H. Villesen is an employee of ALK. D.I. Bernstein has received consulting fees from Merck & Co., Inc., Kenilworth, NJ, USA, Circassia, Teva, and Sanofi Aventis, received grant support from Merck & Co., Inc., Kenilworth, NJ, USA, Circassia, Stallergenes Greer, Teva, GSK, Pfizer, Amgen, Pearl, Genentech, Allergy Therapeutics, Boehringer Ingelheim, and AstraZeneca, and received lecture fees from Merck & Co., Inc., Kenilworth, NJ, USA and AstraZeneca. H.S. Nelson has received consulting fees from Merck & Co., Inc., Kenilworth, NJ, USA and Circassia and has received grant support from Circassia. J. Kleine-Tebbe is a paid board member of ALK, Novartis, Leti, and Bencard Advisory boards, has served as a consultant for Merck & Co., Inc., Kenilworth, NJ, USA and Circassia, has received grant support from Circassia, and has received payment for lectures from Allergopharma, ALK, Bencard, HAL Allergy, LETI, Lofarma, Novartis, and Stallergenes Greer.

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Poster # 198

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

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Introduction

- The most frequent adverse events (AEs) associated with sublingual immunotherapy (SLIT) are local application site reactions[1]
- The safety of SQ house dust mite (HDM) SLIT-tablet has been demonstrated in multiple trials,[2-6] however, one of the trials had notably higher frequencies of some of the local site reactions compared with previous trials[4]
- The collection of AE data is generally either intentionally solicited (meaning that the data are part of the uniform collection of information in the registry) or unsolicited (meaning that the AE information is volunteered or noted in an unsolicited manner and not as a required data element through a case report form)
- AEs collected by solicitation are expected to lead to higher reporting rates[7]

Objective

- To describe the safety profile of SQ HDM SLIT-tablet (12 SQ-HDM dose) when AE reporting is solicited vs unsolicited

Methods

Trial descriptions

- Four phase 2 and phase 3 randomized, double-blinded, placebo-controlled trials were conducted
- Trial with solicited AE reporting per World Allergy Organization (WAO) modified questionnaire:
  - P001 was a trial of up to 52 weeks (NCT01700192) conducted in North American subjects aged ≥12 years with HDM allergic rhinitis with or without conjunctivitis (AR/C)[4]
- Trials with unsolicited AE reporting (spontaneous reporting):
  - P003 was a 24-week environmental chamber trial (NCT01644617) conducted in European subjects aged ≥18 years with HDM AR/C[5]
  - MT-06 was a 52-week trial (NCT01454544) conducted in European subjects aged ≥18 years with HDM AR/C[2]
  - MT-04 was an 18-month trial (NCT01433523) conducted in European subjects aged ≥18 years with HDM allergic asthma and AR[6]
- Subjects received daily SQ HDM SLIT-tablet (MK-8237; Merck & Co., Inc., Kenilworth, NJ, USA/ALK, Hørsholm, Denmark; 12 SQ-HDM dose in all trials and 6 SQ-HDM dose in all but P001) or placebo
  - The 12 SQ-HDM dose contains ≈15 mcg group 1 allergens (Der f 1 and Der p 1 combined) and ≈15 mcg group 2 allergens (Der f 2 and Der p 2 combined) for a total of 30 mcg major allergen content,[8] estimated to be approximately 5,300 allergen units
- Institutional review boards or ethics committees approved the protocols and written informed consent was obtained from the subject or subject's legal representative

Methods (continued)

Safety data collection and analysis

- In addition to routine safety monitoring in trial P001, reporting of local site reactions was solicited daily for the first ≈28 days of treatment using closed-ended questions regarding local site reactions identified by the WAO[9]
  - Subjects indicated whether or not each of 15 local site reactions occurred within the first 60 minutes after dosing (**Table 1**)
- AE reporting in the other three trials was unsolicited and data from the 12 SQ-HDM dose were pooled
- The current analysis was limited to adults aged 18 to 65 years

Table 1. Local site reaction reporting form used in trial P001

	Day _____	
	Month/day/year	
	Yes	No
Did you take the study tablet today?		
Side Effect	**Yes**	**No**
Taste alteration/food tastes different		
Mouth ulcer/sore in the mouth		
Swelling of the uvula/back of the mouth		
Itching in the mouth		
Itching in the ear		
Swelling of the lips		
Swelling of the tongue		
Tongue pain		
Tongue ulcer/sore on the tongue		
Throat irritation/tickle		
Throat swelling		
Stomach pain		
Nausea		
Diarrhea		
Vomiting		
	Yes	**No**
Did you take a medication for any of the above side effects?		
If yes, please list them for each day		

Results

- Throat irritation and oral pruritus were the two most common AEs (both >15%) in subjects treated with 12 SQ-HDM regardless of whether AEs were solicited or unsolicited (**Table 2**)
  - The most common AEs (≥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 whether AEs were solicited or unsolicited
- The placebo-subtracted frequencies of local site reactions associated with 12 SQ-HDM treatment were notably higher when solicited vs unsolicited (**Figure 1**)
  - Throat irritation, 46% vs 12%, respectively
  - Oral pruritus, 47% vs 17%
  - Ear pruritus, 39% vs 4%
  - Mouth swelling, 8% vs 2%
  - Tongue ulceration, 10% vs 0%
  - Mouth ulceration, 7% vs <1%
    - The incidences of mouth and tongue ulceration were higher in P001 (solicited) than in the pivotal North American timothy grass and ragweed SLIT-trials (unsolicited), but a cognitive debriefing study 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
- Except for mouth and tongue ulceration (which may be a result of misinterpretation), it is not clear that solicitation of events led to a greater ability to detect drug-placebo differences (**Figure 1**)

Figure 1. Placebo-subtracted frequencies of local site reactions in trials that solicited or did not solicit daily occurrence of each reaction

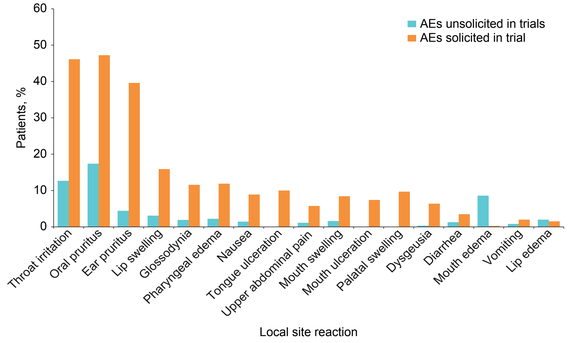

Table 2. AEs reported in ≥5% of subjects in one or more treatment groups

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

HDM, house dust mite.
†Indicates AEs that were included on the local site reaction reporting form.

Conclusions

- Qualitatively, the safety profile of 12 SQ-HDM was similar when AEs were solicited vs unsolicited
- Active solicitation is a likely cause of the higher frequency of local site reactions in the North American trial versus the other three trials
- The AE collection method (solicited vs unsolicited) 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, resulting in a perception of a less favorable drug profile compared with trials using the traditional unsolicited AE collection method

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Disclosures

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Poster # 610

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Biomarkers of SQ House Dust Mite Sublingual Immunotherapy (SLIT)-Tablet Treatment After Nasal Allergen Challenge

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Introduction

- Treatment with SQ house dust mite (HDM) sublingual immunotherapy (SLIT) tablet:
  - Improves allergic rhinoconjunctivitis symptoms
  - Improves time to first moderate or severe asthma exacerbation during inhaled corticosteroid reduction
  - Increases antibodies with the capacity to compete with IgE (including allergen-specific IgG_4 and functional blocking capacity measured as IgE blocking factor [BF])[1,2]
- There have been difficulties in establishing accurate, reliable biomarkers to assess allergy immunotherapy treatment response and little work surrounding the pharmacodynamics and biomarkers for HDM immunotherapy
- Nasal allergen challenge (NAC) allows the delivery of a controlled allergen stimulus to the nasal mucosa to evaluate the effects of immunotherapy on clinical symptoms and local nasal immune responses

Methods

Study design

- This was an exploratory, phase 1b, randomized, placebo-controlled, double-blind study (NCT01852825) conducted across two sites
- Adults with a clinical history of allergic rhinitis to HDM with demonstrable sensitization were randomized in a 2:1 ratio to receive daily 12 SQ-HDM (MK-8237, Merck & Co., Inc., Kenilworth, NJ, USA/ALK, Hørsholm, Denmark) or placebo for 12 weeks
- NAC was conducted at 2 weeks pre-treatment, week 8, and week 12 (**Figure 1**)
  - Nasal Pfeiffer Bidose applicator (Aptar Pharma, Milton Keynes, UK) was used to administer a challenge of 900 SQ-U HDM allergen extract (Aquagen, *D pteronyssinus*; ALK, Hørsholm, Denmark) per nostril
- Total nasal symptom score (TNSS) was assessed by a visual analog scale (VAS) from 0 (absent) to 100 (severe) for each symptom of nasal congestion, rhinorrhea, itching, and sneezing (total possible 400)
- TNSS and peak nasal inspiratory flow (PNIF) were recorded before NAC, every 15 minutes in the first hour, at 90 minutes, and hourly for 6 hours
- Nasal mucosal lining fluid (MLF) was collected using synthetic absorptive membranes by nasosorption, and concentrations of IL-5, IL-13, and TARC in MLF determined using singleplex immunoassays
- Nasal scrapes were collected using nasal curettes from the inferior side of the inferior turbinate at 1 hour pre-NAC and 6.5 hours post-NAC, and nasal mRNA assessed
- Serum for measurement of IgE-BF and IgG_4 were analyzed using validated immunoassays

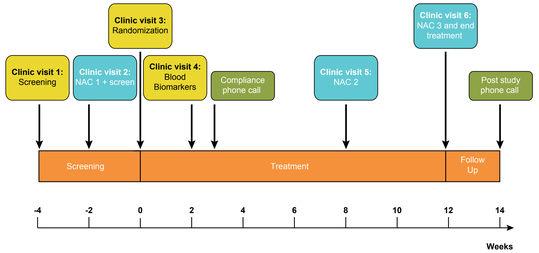
Endpoints

- Primary endpoints were the change induced by 12 SQ-HDM from baseline in HDM-specific IgG_4 and IgE-BF antibodies at week 12
- Secondary endpoints were changes in nasal MLF IL-5 concentration in response to NAC after treatment, and changes in time-weighted average TNSS during NAC for early phase (baseline to 1 hour post NAC) and peak (15 minutes post NAC) responses

Methods (continued)

Figure 1. A) Study design; B) sampling schedule at weeks −2, 8, and 12. NAC, nasal allergen challenge.

A)



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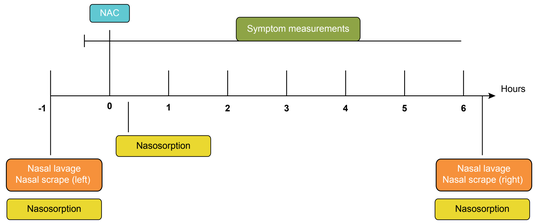


Results

- A total of 23 subjects were randomized (n=16, 12 SQ-HDM; n=7, placebo) and 21 subjects completed the study
- HDM-specific IgG_4 significantly increased from baseline with 12 SQ-HDM versus placebo, increasing at week 8 and increasing further by week 12 (**Figure 2**)
- IgE-BF significantly increased with 12 SQ-HDM versus placebo at both weeks 8 and 12 (**Figure 2**)
- In comparison to baseline NAC, treatment with 12 SQ-HDM reduced early symptoms by 43% at week 8 and 57% at week 12 (**Figure 3**)
- In comparison to baseline NAC, treatment with 12 SQ-HDM reduced peak symptoms (15 minutes post NAC) by 36% at week 8 and 52% at week 12

Results (continued)

Figure 2. IgG_4 and IgE-BF. *P<0.05 for difference in ratio of geometric mean (IgG_4) or change from baseline (IgE-BF) vs placebo determined by constrained longitudinal data analysis (cLDA) model. HDM, house dust mite.

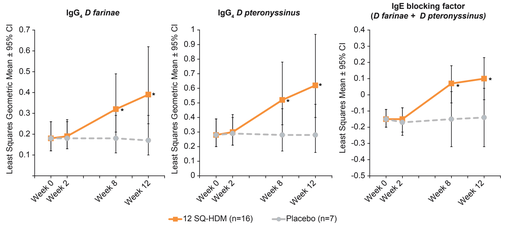
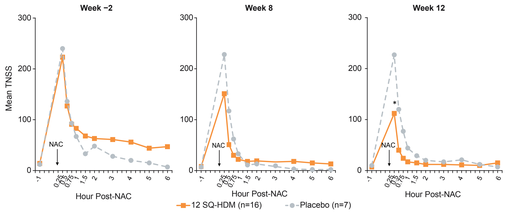
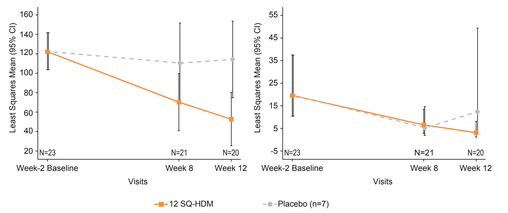


Figure 3. Nasal symptoms. TNSS during A) NAC and B) early and late phases of NAC at weeks −2, 8, and 12. Percentages indicate changes in time-weighted score from baseline. *P≤0.05 for change from baseline vs placebo using cLDA model. HDM, house dust mite; NAC, nasal allergen challenge.

A)

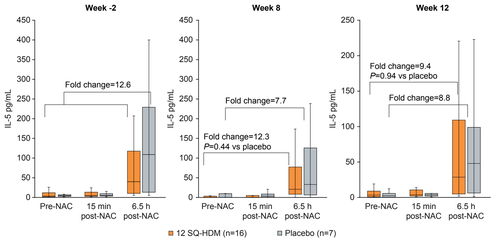


B)



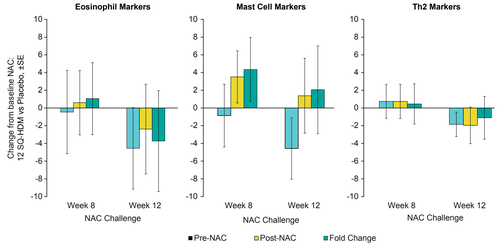
- There was no significant difference between the 12 SQ-HDM group and placebo in change from baseline for PNIF during any NAC challenge
- No significant differences from baseline NAC or in fold changes from −1 hour pre NAC to 6.5 hours post NAC between 12 SQ-HDM and placebo were observed for IL-5 at any timepoint (**Figure 4**)
  - There were also no significant differences for IL-13 or TARC

Figure 4. Nasal concentrations of IL-5 in mucosal lining fluid at weeks −2, 8, and 12 NAC. Box plots indicate medians and quartiles. Error bars indicate minimum and maximum values. Fold changes are estimated and the fold change at baseline is assumed to be the same for both treatment groups. P values were determined using the cLDA model. HDM, house dust mite; NAC, nasal allergen challenge.



- There was a good correlation between absolute values for known mRNA markers of mast cells, IL-5 and IL-13, and eosinophils with most r values ≥0.90
- A trend toward reduction in eosinophil, mast cell, and Th2 inflammation markers from baseline in 12-SQ HDM treated group versus placebo was observed, but did not reach statistical significance (**Figure 5**)
  - There were no consistent correlations found between these markers and VAS symptoms across all the NAC timepoints, either with placebo or 12 SQ-HDM

Figure 5. Change from baseline NAC in eosinophil, mast cell, or Th2 inflammation mRNA markers before and after week 8 and week 12 NAC, and fold change from baseline NAC.



- No serious AEs, systemic allergic events, or epinephrine administrations were reported
- The most frequent AEs were upper respiratory tract infection, throat irritation, tongue pruritus, mouth swelling, and oral paresthesia
- Two events of mild local hypersensitivity reactions were reported

Conclusions

- Induction of HDM-specific IgG_4 and IgE-BF by 12 SQ-HDM, along with significant improvement in early phase NAC-induced nasal symptoms, suggests that IgE-BF generation may contribute to the mechanism of action of 12 SQ-HDM during the first 12 weeks of treatment primarily affecting the early allergic response
- In this study there was no significant effect on mucosal IL-5 and IL-13, or eosinophil-associated gene expression demonstrated
- Treatment was well tolerated and the AE profile was consistent with that reported in large clinical trials of 12 SQ-HDM[1,2]

Acknowledgments

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Disclosures

Q. Zhao, K. Tsai, D. Selverian, L.N. Carayannopoulos, and H. Nolte are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. K. Lund is an employee of ALK. N.C. Gunawardana has nothing to disclose. T.T. Hansel is establishing a company called Mucosal Diagnostics. G.W. Clarke was an employee of Quintiles IMS, Reading, UK, and T. Mant is a current employee of Quintiles IMS, which provides consulting services for Merck Sharp & Dohme Corp.

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Poster # 609

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March 3-6, 2017

Efficacy of SQ House Dust Mite Sublingual Immunotherapy Tablet in Monosensitized and Polysensitized Subjects

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Introduction

- The majority of patients with allergic rhinitis with/without conjunctivitis (AR/C) are sensitized to multiple allergens
- Efficacy of timothy grass and ragweed sublingual immunotherapy (SLIT)-tablets has been demonstrated in monosensitized and polysensitized subjects[1,2]
- House dust mite (HDM) allergy immunotherapy trials often exclude patients co-sensitized to other relevant allergens or with clearly confounding symptoms

Objective

- To compare the efficacy of SQ HDM SLIT-tablet (12 SQ-HDM dose) in monosensitized and polysensitized subjects with HDM AR/C and no history of confounding non-HDM allergy symptoms during an 8 week efficacy assessment period

Methods

Trial design

- Randomized, double-blinded, multicenter trial conducted in North America from January 2013 to April 2015 (P001; clinicaltrials.gov identifier NCT01700192)[3]
- Subjects received daily SQ HDM SLIT-tablet (MK-8237; Merck & Co., Inc., Kenilworth, NJ, USA/ALK, Hørsholm, Denmark; 12 SQ-HDM dose) or placebo for up to approximately 52 weeks, preceded by a run-in phase of up to 6 weeks when subjects were not allowed to use anti-allergy medications
- Institutional review boards approved the protocol and written informed consent was obtained from the subject or subject's legal representative

Treatment

- The 12 SQ-HDM dose contains ≈15 mcg HDM group 1 allergens (Der f 1 and Der p 1 combined) and ≈15 mcg HDM group 2 allergens (Der f 2 and Der p 2 combined) for a total of 30 mcg major allergen content,[4] estimated to be approximately 5,300 allergen units
- Open-label symptom-relieving medications were provided approximately 1 month before the 8-week efficacy assessment period
- A total symptom score of ≥4, or persistent eye symptoms, were required before permission was given to use symptom-relieving medications

Key inclusion and exclusion criteria

- Inclusion criteria
  - ≥12 years of age
  - HDM-induced AR/C of ≥1 year's duration, with or without asthma requiring ARC medication and, at most, a daily medium dose of an inhaled corticosteroid
  - Forced expiratory volume in 1 second (FEV_1) predicted ≥80%
  - *Dermatophagoides (D.) pteronyssinus* and/or *D. farinae* skin prick test wheal size ≥5 mm larger than normal saline control
  - *D. pteronyssinus* and/or *D. farinae* serum-specific IgE ≥0.7 kU_A/L
  - Total rhinitis daily symptom score of ≥6, or ≥5 with 1 symptom being severe, on 5 of 7 consecutive days without the use of symptom-relieving medications before randomization

Methods (continued)

- Exclusion criteria
  - History of symptomatic perennial (animal dander, molds, and/or cockroach present in home, job, daycare, etc.) or seasonal AR/C to an allergen which potentially overlapped with run-in and efficacy assessment periods
  - Unstable or severe asthma

Assessments

- Average total combined rhinitis score (TCRS) during the last 8 weeks of treatment was the primary endpoint
  - TCRS is the sum of rhinitis daily symptom score (DSS) and rhinitis daily medication score (DMS; **Table 1**)
- Pretreatment IgE sensitization was determined by serum-specific IgE (≥0.35 kU_A/L) to a region-specific panel of common inhalant allergens
- Safety endpoints
  - Reporting of local AEs was solicited daily for the first ≈28 days of treatment using closed-ended questions regarding local AEs identified by the World Allergy Organization[5]
  - General safety assessment throughout the study period

Statistical analysis

- Efficacy analyses were evaluated on all randomized subjects who took ≥1 dose of study medication (full analysis set); for symptom endpoints based on diary subjects, ≥1 e-diary entry during the efficacy assessment period was required
- Between-treatment comparisons performed using the Wilcoxon Rank Sum test
  - Hodges-Lehmann estimate of treatment difference calculated
- Percentage treatment difference relative to placebo: (12 SQ-HDM – placebo)/placebo x 100

Table 1. Symptom and medication scoring measures

	Rhinitis DSS	Rhinitis DMS	TCRS
Runny nose	0–3		0–3
Stuffy nose	0–3		0–3
Sneezing	0–3		0–3
Itchy nose	0–3		0–3
Loratadine 10 mg tablet†		0 or 4	0 or 4
Mometasone furoate nasal spray 50 µg‡		0–8	0–8
Total	0–12	0–12	0–24

DSS=daily symptom score; DMS=daily medication score; TCRS=total combined rhinitis score.
†One tablet gave a score of 4 when taken for rhinitis symptoms
‡One puff/nostril gave a score of 2

Results

Subjects

- In all, 1,482 subjects were randomized; median treatment duration was 271 days
  - 79% of subjects completed the trial
- Approximately three quarters of the randomized subjects were polysensitized (**Table 2**)

Table 2. Baseline characteristics and demographics (randomized subjects)

	12 SQ-HDM (n=741)	Placebo (n=741)
Women, %	60	58
Mean age±SD (range), y	35±14 (12–77)	35±14 (12–85)
White, %	77	76
Subjects with asthma, %	31	31
ICS use, %†	29	27
Mean FEV_1 % predicted±SD†	98.3±16.7	97.2±11.1
Mean duration of AR/C±SD, y	18±13	19±13
IgE sensitization type, %		
HDM only (monosensitized)	25	23
HDM and other allergens (polysensitized)	75	77
HDM and other perennial allergens‡§	37	44
HDM and no other perennial allergens‡	20	21
Not sensitized to HDM¶	0.3	0.4

AR/C=allergic rhinitis with or without conjunctivitis; FEV_1=forced expiratory volume in 1 second; HDM=house dust mite; ICS=inhaled corticosteroid.
†Of subjects with asthma.
‡Of total subjects. A subject was considered to have sensitization to other perennial allergens if the IgE to cat or dog dander was ≥0.35 kU_A/L at Screening.
§Includes subjects with and without sensitivity to seasonal allergens.
¶Protocol violators.

Efficacy

- In the total trial population, mean TCRS difference with 12 SQ-HDM was −0.8 (**Table 3**) vs placebo, corresponding to an improvement of 17% (**Figure**)
- In monosensitized subjects, mean TCRS difference was −0.9 (**Table 3**) vs placebo, corresponding to a 17% improvement (**Figure**)
- In polysensitized subjects, mean TCRS difference was −0.8 (**Table 3**) vs placebo, corresponding to an 18% improvement (**Figure**)
- In subjects polysensitized to non-HDM perennial allergens (cat/dog), mean TCRS difference was −1.0 (**Table 3**) vs placebo, corresponding to a 22% improvement (**Figure**)

Safety

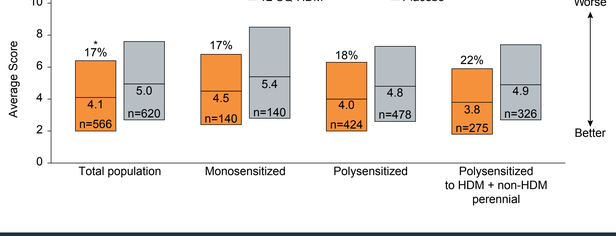
- Overall, the adverse event profile was not qualitatively different between the monosensitized and polysensitized subgroups

Table 3. Treatment difference in average TCRS during approximately the last 8 weeks of treatment with SQ HDM SLIT-tablet versus placebo (full analysis set) in monosensitized and polysensitized subjects

Treatment	Baseline TCRS Mean (SD)	Average TCRS During the Last 8 Weeks of Treatment Median (Lower, upper quartiles)
Total population		
12 SQ-HDM (n=566)	7.9 (1.7)	4.1 (2.0, 6.4)
Placebo (n=620)	7.9 (1.8)	5.0 (2.7, 7.6)
Hodges-Lehmann Estimate of Shift (95% CI)		−0.8 (−1.2, −0.4)*
% Improvement From Placebo (95% CI)		17% (10%, 25%)
Monosensitized subpopulation		
12 SQ-HDM (n=140)	7.7 (1.6)	4.5 (2.4, 6.8)
Placebo (n=140)	7.7 (1.7)	5.4 (2.8, 8.5)
Hodges-Lehmann Estimate of Shift (95% CI)		−0.9 (−1.7, −0.1)
% Improvement From Placebo (95% CI)		17%
Polysensitized subpopulation		
12 SQ-HDM (n=424)	8.0 (1.8)	4.0 (2.0, 6.3)
Placebo (n=478)	8.0 (1.8)	4.8 (2.6, 7.3)
Hodges-Lehmann Estimate of Shift (95% CI)		−0.8 (−1.2, −0.3)
% Improvement From Placebo (95% CI)		18%
Polysensitized to non-HDM perennial allergens		
12 SQ-HDM (n=275)	8.1 (1.8)	3.8 (1.8, 5.9)
Placebo (n=326)	8.1 (1.8)	4.9 (2.7, 7.4)
Hodges-Lehmann Estimate of Shift (95% CI)		−1.0 (−1.6, −0.5)
% Improvement From Placebo (95% CI)		22%

HDM, house dust mite; TCRS, total combined rhinitis score.
*P<0.001

Figure. TCRS for total and sensitization populations during approximately the last 8 weeks of treatment. Plots indicate median values and upper and lower quartiles for the average scores. Percentages indicate the improvement in scores relative to placebo. *P value <0.001 vs placebo. HDM, house dust mite; TCRS, total combined rhinitis score.



Conclusions

- Treatment with 12 SQ-HDM was similarly effective and well tolerated in monosensitized and polysensitized subjects with HDM AR/C

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Disclosures

Z. Li, S. Lu, and H. Nolte are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. H.S. Nelson has received consulting fees from Merck & Co., Inc., Kenilworth, NJ, USA and Circassia and has received grant support from Circassia. D.I. Bernstein has received consulting fees from Merck & Co., Inc., Kenilworth, NJ, USA, Circassia, Teva, and Sanofi Aventis, received grant support from Merck & Co., Inc., Kenilworth, NJ, USA, Circassia, Stallergenes Greer, Teva, GSK, Pfizer, Amgen, Pearl, Genentech, Allergy Therapeutics, Boehringer Ingelheim, and AstraZeneca, and received lecture fees from Merck & Co., Inc., Kenilworth, NJ, USA and AstraZeneca. J. Kleine-Tebbe is a paid board member of ALK, Novartis, Leti, and Bencard Advisory boards, has served as a consultant for Merck & Co., Inc., Kenilworth, NJ, USA and Circassia, has received grants support from Circassia, and has received payment for lectures from Allergopharma, ALK, Bencard, HAL Allergy, LETI, Lofarma, Novartis, and Stallergenes Greer.

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Poster # 190

American Academy of Allergy, Asthma, & Immunology Annual Meeting
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Consistent Efficacy and Safety of SQ House Dust Mite Sublingual Immunotherapy Tablet Among Subgroups with Allergic Rhinoconjunctivitis

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Introduction

- Allergic rhinitis with/without conjunctivitis (AR/C) is a ubiquitous disease, affecting people throughout the world regardless of age, gender, or race; therefore, it is important that AR/C treatments be efficacious in various subpopulations
- The efficacy and safety of SQ house dust mite (HDM) sublingual immunotherapy (SLIT) tablet has been demonstrated in multiple clinical trials[1-5]
- Although a SLIT-tablet for timothy grass is efficacious for AR/C in subpopulations including polysensitized and asthmatic patients, data regarding the efficacy of SQ HDM SLIT-tablet in subpopulations of interest are lacking

Objective

- To examine the consistency of efficacy and safety across subgroups of interest in subjects with HDM AR/C

Methods

Trial design

- Two randomized, double-blinded, multicenter trials were conducted (NCT01700192, NCT01454544), one in North America (P001)[3] and one in Europe (MT-06)[1]
- Subjects received daily SQ HDM SLIT-tablet (MK-8237; Merck & Co., Inc., Kenilworth, NJ, USA/ALK, Hørsholm, Denmark; 12 SQ-HDM dose) or placebo for up to approximately 52 weeks
  - The 6 SQ-HDM dose was also evaluated in MT-06
- Institutional review boards or ethics committees approved the protocols and written informed consent was obtained from the subject or subject's legal representative

Treatment

- The 12 SQ-HDM dose contains ≈15 mcg HDM group 1 allergens (Der f 1 and Der p 1 combined) and ≈15 mcg HDM group 2 allergens (Der f 2 and Der p 2 combined) for a total of 30 mcg major allergen content, estimated to be approximately 5,300 allergen units
- Open-label symptom-relieving medications were provided

Key inclusion and exclusion criteria

- Inclusion criteria
  - ≥12 years of age (P001) or ≥18 years of age (MT-06)
  - HDM-induced AR/C of ≥1 year's duration, with or without asthma requiring AR/C medication and, at most, a daily medium dose of an inhaled corticosteroid
  - Forced expiratory volume in 1 second (FEV_1) predicted ≥80% (P001) or ≥70% (MT-06)
  - *Dermatophagoides (D.) pteronyssinus* and/or *D. farinae* skin prick test wheal size ≥5 mm (P001) or ≥3 mm (MT-06) larger than normal saline control
  - *D. pteronyssinus* and/or *D. farinae* serum-specific IgE ≥0.7 kU_A/L
  - Total rhinitis daily symptom score of ≥6, or ≥5 with 1 symptom being severe, on 5 of 7 consecutive days (P001) without the use of symptom-relieving medications before randomization or ≥8 days (MT-06) out of the 15-day baseline period with use of symptom-relieving medications
- Exclusion criteria
  - History of symptomatic perennial or seasonal AR/C to an allergen which potentially overlapped the efficacy assessment period
  - Unstable or severe asthma (P001) or uncontrolled asthma (MT-06)

Methods (continued)

Assessments

- Average total combined rhinitis score (TCRS) during the last 8 weeks of treatment was the primary endpoint in both trials
  - TCRS is the sum of rhinitis daily symptom score (DSS) and rhinitis daily medication score (DMS; **Table 1**)
- Safety assessment
  - Safety data were pooled from P001 and MT-06, as well as an asthma trial (MT-04, NCT01433523)[5] and an environmental chamber trial (NCT01644617)[4] that evaluated 12 SQ-HDM safety
  - In P001, reporting of local AEs was solicited daily for the first ≈28 days of treatment using closed-ended questions regarding local AEs identified by the World Allergy Organization
  - AE reporting in the other three trials was unsolicited

Statistical analysis

- In P001, pre-specified between-treatment comparisons were performed using the Wilcoxon Rank Sum test and the Hodges-Lehmann estimate of treatment difference calculated
- In MT-06, pre-specified between-treatment comparisons were performed using a linear mixed effects model, with the square root transformed average TCRS as response, the square root transformed AR symptom score at baseline as a fixed effect, and country as a random effect and adjusted for different error variation for each treatment group
- TCRS data for the 12 SQ-HDM dose were pooled post-hoc for subgroup analysis based on age, gender, race, baseline asthma status, and allergen sensitization
- Pooled TCRS data were analyzed post-hoc by analysis of covariance with square root transformed values as response, trial, treatment, subgroup, treatment-by-subgroup interaction and baseline asthma status (except in asthma subgroup analysis) as fixed effects and square root transformed baseline value as a covariate, and adjusted for different error variation for each treatment group
- Percentage treatment difference relative to placebo:
  (12 SQ-HDM – placebo)/placebo x 100

Table 1. Symptom and medication scoring measures

	Rhinitis DSS	Rhinitis DMS	TCRS
Runny nose	0–3		0–3
Stuffy nose	0–3		0–3
Sneezing	0–3		0–3
Itchy nose	0–3		0–3
Loratadine or desloratadine tablet†		0 or 4	0 or 4
Mometasone furoate or budesonide nasal spray‡		0–8	0–8
Total	0–12	0–12	0–24

DSS=daily symptom score; DMS=daily medication score; TCRS=total combined rhinitis score.
†One tablet gave a score of 4 when taken for rhinitis symptoms
‡One puff/nostril gave a score of 2

Results

- In all, 2,138 subjects were included in the efficacy analysis and 2,923 were included in the safety analysis
- In the two individual trials, treatment with 12 SQ-HDM improved TCRS 17% and 18%, respectively, vs placebo (**Figure 1**)
- Across the subgroups there were consistent trends of numeric superiority with 12 SQ-HDM vs placebo (**Figure 2**)
- The lowest observed TCRS improvement was 15% in subjects without asthma, and the greatest improvement was 25% in subjects aged 12 to 17 years (**Figure 2**)
- The AE profile was generally similar within subgroups, although the incidence of treatment-related AEs in the 12 SQ-HDM and placebo-treated groups appeared numerically higher in subjects aged 12 to 17 years vs 18 to 49 years (**Table 2**)

Figure 1. TCRS for total populations during approximately the last 8 weeks of treatment in P001 and MT-06. Plots indicate average score medians for P001 and least square means for MT-06. Percentages indicate the improvement in scores relative to placebo. *P value ≤0.001 vs placebo. HDM, house dust mite; TCRS, total combined rhinitis score.

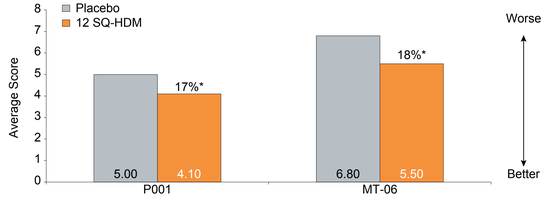

Figure 2. Treatment difference in average TCRS during approximately the last 8 weeks of treatment in various subpopulations. HDM, house dust mite; TCRS, total combined rhinitis score.

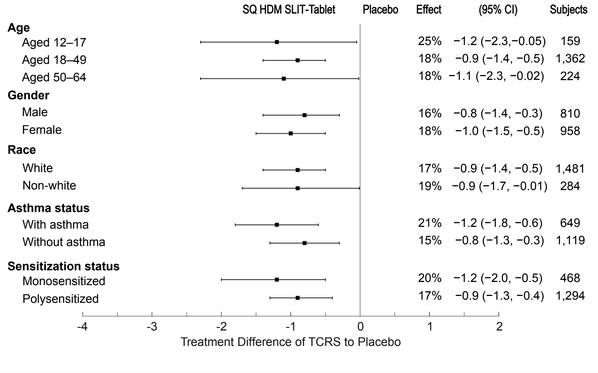

Table 2. Summary of adverse events in subpopulations

Subpopulation	Any TEAE, %	Any TRAE, %	Serious TRAE, %	Discontinued Due to TRAE, %
Total population				
12 SQ-HDM (n=1383)	83	69	0.2†	7
Placebo (n=1540)	64	28	0.1	1
Aged 12 to 17				
12 SQ-HDM (n=95)	94	92	0	10
Placebo (n=106)	78	43	0	0
Aged 18 to 49				
12 SQ-HDM (n=1105)	82	68	0.2	7
Placebo (n=1247)	62	26	0.2	1
Aged 50 to 64				
12 SQ-HDM (n=169)	79	61	0.6	4
Placebo (n=164)	68	31	0	1
Male				
12 SQ-HDM (n=629)	80	64	0.2	5
Placebo (n=728)	60	23	0.1	1
Female				
12 SQ-HDM (n=754)	86	73	0.3	8
Placebo (n=812)	67	32	0.1	1
White				
12 SQ-HDM (n=1195)	82	68	0.2	7
Placebo (n=1347)	63	25	0.1	1
Non-white				
12 SQ-HDM (n=185)	86	76	0.5	6
Placebo (n=189)	71	45	0	0.5
With asthma				
12 SQ-HDM (n=686)	82	62	0.1	8
Placebo (n=825)	64	23	0.2	1
Without asthma				
12 SQ-HDM (n=697)	84	75	0.3	6
Placebo (n=715)	64	32	0	1
Monosensitized				
12 SQ-HDM (n=394)	78	64	0	5
Placebo (n=415)	56	23	0	1
Polysensitized				
12 SQ-HDM (n=987)	85	71	0.3	7
Placebo (n=1117)	66	29	0.2	1

HDM, house dust mite; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
†2 subjects had accidental overdose, considered serious per the study protocol, but did not meet International Conference on Harmonization criteria for seriousness.

Conclusions

- The 12 SQ-HDM SLIT-tablet consistently improved symptoms and was well tolerated in relevant subgroups of subjects with HDM AR/C defined by age, gender, race, asthma status, and sensitization to non-HDM aeroallergens

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Disclosures

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Poster # 194

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Atlanta, GA

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Safety of Year-Round Initiation with SQ House Dust Mite Sublingual Immunotherapy Tablet

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Introduction

- Most patients with allergic rhinitis with or without conjunctivitis (AR/C) are polysensitized to more than one allergen
- Sublingual immunotherapy (SLIT) tablets for seasonal allergies have a recommended initiation of treatment several weeks before pollen season, but SQ house dust mite (HDM) SLIT-tablet may be initiated at any time of year
- In polysensitized subjects, increased exposure to pollens or other allergens could impact the safety of treatment initiation with SQ HDM SLIT-tablet

Objective

- To evaluate the safety of year-round initiation of SQ HDM SLIT-tablet (6 and 12 SQ-HDM doses)

Methods

Trial descriptions

- Five phase 2 and phase 3 randomized, double-blinded, placebo-controlled trials were conducted
  - P001 was a trial of up to 52 weeks (NCT01700192) conducted in North American subjects aged ≥12 years with HDM AR/C[1]
  - P003 was a 24-week environmental chamber trial (NCT01644617) conducted in European subjects aged ≥18 years with HDM AR/C[2]
  - MT-02 was a 52-week trial (NCT00389363) conducted in European subjects aged ≥14 years with allergic asthma[3]
  - MT-06 was a 52-week trial (NCT01454544) conducted in European subjects aged ≥18 years with HDM AR/C[4]
  - MT-04 was an 18-month trial (NCT01433523) conducted in European subjects aged ≥18 years with HDM allergic asthma and AR[5]
- Subjects received daily SQ HDM SLIT-tablet (MK-8237; Merck & Co., Inc., Kenilworth, NJ, USA/ALK, Hørsholm, Denmark; 6 or 12 SQ-HDM dose [12 SQ-HDM dose only in P001; 1, 3, or 6 SQ-HDM doses in MT-02]) or placebo
- Institutional review boards or ethics committees approved the protocols and written informed consent was obtained from the subject or subject's legal representative

Safety data collection and analysis

- In trial P001, reporting of local site reactions was solicited daily for the first ≈28 days of treatment using closed-ended questions regarding local site reactions identified by the World Allergy Organization[6]
  - AE reporting in the other four trials was unsolicited
- Data on the proportion of subjects with any AE, treatment-related AEs, local site reactions, and asthma-related AEs were pooled for the 6 and 12 SQ-HDM doses and evaluated comparing the season when treatment was initiated with the season during which the AE started (up to 2 years after initiation)
  - Seasons were winter (December-February), spring (March-May), summer (June-August), and fall (September-November)

Results

- Overall, 72% of the 3,731 subjects included in the analysis were polysensitized
- The highest reported frequencies of any AEs, treatment-related AEs, and local site reactions were consistently reported in the same season in which SLIT-tablet treatment was initiated, and decreased with treatment (**Table 1**)
- Regardless of the season in which treatment was initiated, the placebo-subtracted frequencies of treatment-related AEs were generally similar and ranged from 33% to 45% during the initiating season (**Figure 1**)
- For polysensitized and monosensitized subjects initiating in spring and summer (pollen seasons), placebo-subtracted frequencies of treatment-related AEs in spring were 46% and 44%, respectively, and in summer were 44% and 49% (**Figure 2A-B**)
- Asthma-related AE frequency was ≤7% and similar across seasons (**Table 1**)

Table 1. Summary of adverse event frequency by season of SQ HDM SLIT-tablet initiation. The first column of data displayed for each initiating group is the initiating season. Columns to the right are the subsequent seasons of treatment. Teal indicates winter initiation, green indicates spring initiation, purple indicates summer initiation, and orange indicates fall initiation. Data from one full year is shown for each initiating group.

	Winter		Spring		Summer		Fall		Winter		Spring		Summer	
Season of Initiation	SQ-HDM SLIT-tablet	Placebo	SQ-HDM SLIT-tablet	Placebo	SQ-HDM SLIT-tablet	Placebo	SQ-HDM SLIT-tablet	Placebo	SQ-HDM SLIT-tablet	Placebo	SQ-HDM SLIT-tablet	Placebo	SQ-HDM SLIT-tablet	Placebo
Winter	N=470	N=539	N=449	N=533	N=420	N=511	N=383	N=461						
TEAE, %	59	30	46	31	33	23	35	25						
TRAE, %	50	10	30	7	17	5	13	5						
Local site reactions, %	43	5	24	3	12	1	8	1						
Asthma AEs, %	3	4	7	4	4	3	1	2						
Spring			N=695	N=768	N=608	N=733	N=563	N=694	N=539	N=654				
TEAE, %			84	49	50	31	44	34	45	37				
TRAE, %			79	33	32	9	20	6	16	4				
Local site reactions, %			75	27	26	5	15	3	12	2				
Asthma AEs, %			4	2	2	3	3	3	4	3				
Summer					N=120	N=121	N=109	N=113	N=104	N=103	N=94	N=94		
TEAE, %					88	50	66	44	53	56	30	35		
TRAE, %					87	42	47	22	19	13	10	4		
Local site reactions, %					83	34	46	16	16	7	6	4		
Asthma AEs, %					2	0	1	2	2	2	1	0		
Fall							N=97	N=112	N=95	N=112	N=91	N=109	N=89	N=107
TEAE, %							54	34	45	30	28	24	21	15
TRAE, %							40	7	27	7	17	4	11	1
Local site reactions, %							33	5	18	4	11	0	8	1
Asthma AEs, %							6	5	4	5	0	4	0	4

AE, adverse event; HDM, house dust mite; SLIT, sublingual immunotherapy; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Figure 1. Placebo-subtracted frequency of treatment-related AEs by season of SQ HDM SLIT-tablet initiation. AE, adverse event; HDM, house dust mite; SLIT, sublingual immunotherapy.

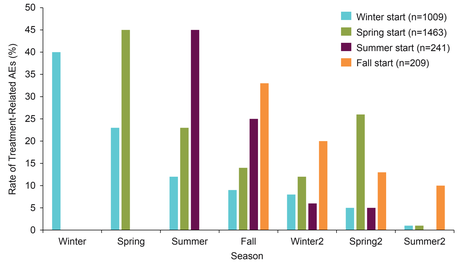
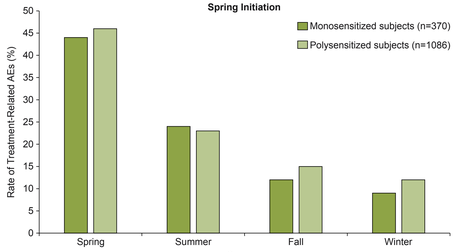
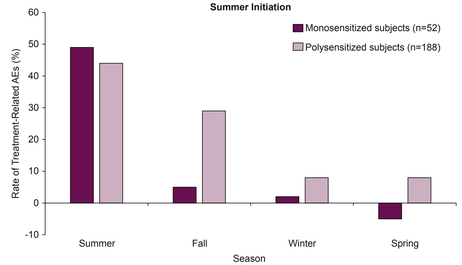


Figure 2. Placebo-subtracted frequency of treatment-related AEs among monosensitized and polysensitized subjects initiating in A) spring and B) summer. AE, adverse event; HDM, house dust mite; SLIT, sublingual immunotherapy.

A)



B)



Conclusions

- The highest AE frequency occurred within the same season in which treatment was initiated
- AEs did not appear to increase in polysensitized subjects who were initiated during pollen seasons
- The frequency of asthma-related AEs was not affected by the initiation season

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Disclosures

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