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

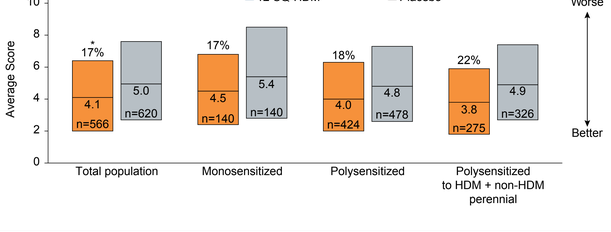
- Overall, the adverse event profile was not qualitatively different between the monosensitized and polysensitized subgroups

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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