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.

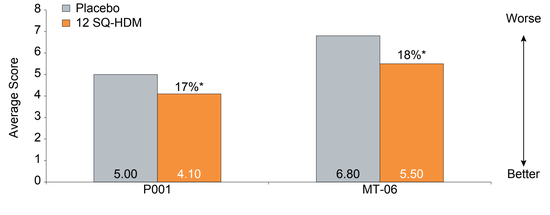

Figure 2. Treatment difference in average TCRS during approximately the last 8 weeks of treatment in various subpopulations. HDM, house dust mite; TCRS, total combined rhinitis score.

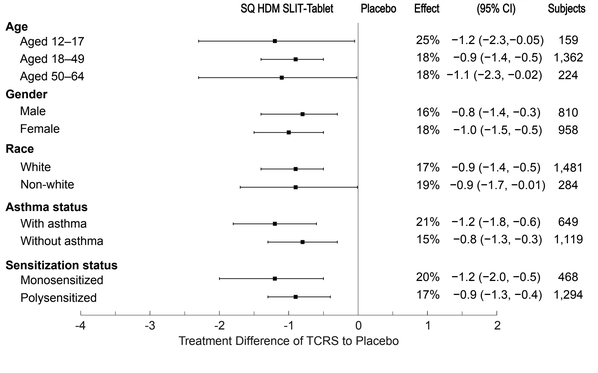

Table 2. Summary of adverse events in subpopulations

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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