Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber

Hendrik Nolte, MD, PhD,[a] Jennifer Maloney, MD,[a] Harold S. Nelson, MD,[b] David I. Bernstein, MD,[c] Susan Lu, PharmD,[a] Ziliang Li, PhD,[a] Amarjot Kaur, PhD,[a] Petra Zieglmayer, MD,[d] René Zieglmayer, Dipl Ing,[d] Patrick Lemell, PhD,[d] and Friedrich Horak, MD[d] *Kenilworth, NJ, Denver, Colo, Cincinnati, Ohio, and Vienna, Austria*

Background: The magnitude of effect of sublingual immunotherapy for house dust mite (HDM)–induced allergic rhinitis with or without conjunctivitis is uncertain, partly because there are few well-controlled trials with well-defined doses.

Objective: We sought to determine the dose-related efficacy and onset of action of the HDM sublingual immunotherapy tablet MK-8237 (Merck/ALK-Abelló) using the Vienna Challenge Chamber.

Methods: In this randomized, double-blind, single-site trial, adults with HDM-induced allergic rhinitis with or without conjunctivitis and with or without asthma (n = 124) received 12 developmental units (DU) of MK-8237, 6 DU of MK-8237, or placebo daily for 24 weeks. Subjects underwent 6-hour exposure challenges at screening and weeks 8, 16, and 24. The total nasal symptom score (TNSS) during chamber challenge at week 24 was the primary end point. The TNSS was the sum of 4 nasal symptom scores (maximum = 12). Total ocular symptom scores (TOSSs; 2 symptoms; maximum = 6) and total symptom scores (TSSs; TSS = TNSS plus TOSS; maximum = 18) were secondary end points.

Results: Dose- and time-dependent improvements with MK-8237 versus placebo were observed. At week 24, TNSS improvement relative to placebo was 48.6% (95% CI, 35.3% to 60.2%) with 12 DU of MK-8237 and 26.6% (95% CI, 11.2% to 39.6%) with 6 DU of MK-8237. Statistically significant improvements for TNSSs were also observed at weeks 8 (12 DU of MK-8237) and 16 (6 and 12 DU of MK-8237) and for TOSSs and TSSs by both doses at week 24. MK-8237 was well tolerated. No investigator-assessed anaphylactic allergic reactions or reactions requiring epinephrine were observed.

Conclusions: MK-8237, 12 DU, reduced nasal and ocular symptoms and exceeded World Allergy Organization–established clinical efficacy criteria (≥20% improvement vs placebo). The onset of action for 12 DU of MK-8237 was week 8. MK-8237, 12 DU, is appropriate for further evaluation to determine the magnitude of effect in an uncontrolled allergen exposure environment. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Allergen immunotherapy, allergic rhinoconjunctivitis, house dust mite, sublingual immunotherapy tablet, dose response, dose related, onset of action, environmental exposure chamber, nasal symptoms, ocular symptoms*

Subcutaneous immunotherapy (SCIT) has been demonstrated to decrease symptoms associated with house dust mite (HDM)–induced allergic rhinitis (AR).[1-3] However, SCIT requires frequent office visits, which might be inconvenient for many patients. Indeed, inconvenience is the most common reason for a patient to discontinue or reject SCIT.[4] Alternatively, sublingual immunotherapy (SLIT) has been investigated as a simple and favorable form of immunotherapy with a potentially more benign safety profile.[5] However, a review of HDM SLIT studies concluded that reported results have been variable, partly because of insufficient treatment exposure, and there is a need for more rigorous studies that assess standardized efficacy outcomes, treatment duration, and dose.[6] Few dose-finding or onset-of-action studies have been conducted for perennial allergens in general, let alone HDM.[7] Thus, there is limited knowledge regarding dose responses and onset of action with HDM SLIT.

The magnitude of the efficacy of immunotherapy is related to environmental allergen exposure; when allergen exposure is high, a greater treatment effect with SLIT is observed.[8] The environmental exposure chamber (EEC) provides an efficient method to optimize exposure and reduce confounding from nonspecific triggers or overlapping allergens.[9,10] Thus, compared with field trials, EEC studies allow for a better assessment of the dose response, onset of action, and potentially the optimal magnitude of the treatment effect of immunotherapy products. Because of the controlled environment of the EEC, there is very low variability in outcomes, which can lead to highly significant results with a smaller sample size than what is required for field studies.[9] Furthermore, a strong correlation between symptoms experienced during controlled exposure and in-field allergen exposure has been demonstrated.[11] As such, an EEC study was conducted to determine the appropriate dose for further field trial evaluation of the rapidly dissolving (within seconds) HDM SLIT tablet

From [a]Merck & Co, Kenilworth; [b]the Department of Medicine, Division of Allergy and Immunology, National Jewish Health, Denver; [c]the Bernstein Allergy Group and the Division of Allergy and Immunology, University of Cincinnati, Cincinnati; and [d]Vienna Challenge Chamber, Vienna.

Supported by Merck & Co.

Disclosure of potential conflict of interest: This study was funded by Merck & Co. H. Nolte is employed by Merck, as is J. Maloney, S. Lu, Z. Li, and A. Kaur. H. S. Nelson has received consulting fees or honorariums from Merck, as well as consultancy fees from Circassia, from which he has also received or has grants pending. D. I. Bernstein has received consultancy fees from Merck and Circassia, as well as payment for delivering lectures from Merck, and has received or has grants pending from Merck and Circassia. F. Horak holds several international patents from Europe, Canada, and the United States, pertaining to a fundamental technique of the allergen challenge chamber. The rest of the authors declare that they have no relevant conflicts of interest.

ClinicalTrials.gov identifier: NCT01644617.

Received for publication September 22, 2014; revised November 25, 2014; accepted for publication December 16, 2014.

Corresponding author: Hendrik Nolte, MD, PhD, Merck & Co, 1 Merck Dr, Whitehouse Station, NJ 08889. E-mail: Hendrik.nolte@merck.com.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2014.12.1911

Abbreviations used

AAR: Active anterior rhinomanometry
AE: Adverse event
AR: Allergic rhinitis
AR/C: Allergic rhinitis with or without conjunctivitis
DU: Developmental units
EEC: Environmental exposure chamber
HDM: House dust mite
MID: Minimally important difference
RQLQ(S)12+: Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities for subjects ≥12 years old
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
TNSS: Total nasal symptom score
TOSS: Total ocular symptom score
TSS: Total symptom score
VAS: Visual analog scale
VCC: Vienna Challenge Chamber

MK-8237 (Merck & Co, Kenilworth, NJ, and ALK-Abelló, Hørsholm, Denmark). Prior dose-escalation safety and tolerability trials with MK-8237 tested up to 32 developmental units (DU) per dose and demonstrated that doses of up to 12 DU of HDM SLIT tablet were tolerated and thus suitable for further clinical efficacy evaluations.[12]

The primary objective was to characterize the dose-related efficacy of MK-8237 versus placebo based on the total nasal symptom score (TNSS) at week 24 in subjects with HDM-induced allergic rhinitis with or without conjunctivitis (AR/C) and with or without asthma. Onset of action was a key secondary objective.

METHODS

Study design

This was a randomized, placebo-controlled, double-blind, dose-ranging, onset-of-action, single-site trial (Vienna Challenge Chamber [VCC] Site, Vienna, Austria) conducted between October 29, 2012, and August 27, 2013. The challenge sessions during the trial were conducted outside of the regional tree and grass pollen seasons to avoid having subjects who were symptomatic to other environmental allergens at the time of the efficacy assessments. The clinicaltrials.gov identifier was NCT01644617.

The VCC is a 54-m^3 sealed room in which a precisely defined and monitored airborne concentration of HDM allergen (approximately 0.3 g of material per hour) was administered to subjects continuously and maintained over a period of 6 hours per challenge visit. The VCC was charged with 100% fresh air which was cleaned, cooled, dried, and then loaded with the qualitatively and quantitatively determined HDM allergen load. The house dust material was a 10:10:1 mixture of *Dermatophagoides pteronyssinus* whole bodies, *Dermatophagoides farinae* whole bodies, and feces from both species, which reflects the composition of mite material during natural exposure.[13,14] Challenge visits occurred during the screening period and at weeks 8, 16, and 24 of treatment. Office visits without exposure challenge occurred at weeks 4, 12, 20, and 26 (Fig 1).

This study was conducted in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by an independent ethics committee, and written informed consent was obtained from each subject before the study.

Treatment

Adults with a history of HDM-induced AR/C with or without asthma were randomized 1:1:1 according to a computer-generated randomization schedule to 12 DU of MK-8237, 6 DU of MK-8237, or placebo daily for approximately 24 weeks (Fig 1). Randomization numbers were assigned to subjects by providing the next available number and kit (ordered sequentially). Placebo and MK-8237 were identical in appearance, smell, taste, and packaging to ensure treatment blinding was maintained. The sponsor, investigator, study personnel, and study subjects were blind to treatment. DU is a measure of the potency of the tablet based on an in-house reference used to standardize the HDM extracts during development of MK-8237. In Europe the DU is referred to as the SQ-HDM. MK-8237 contains a 1:1 mixture of *D pteronyssinus* and *D farinae* characterized by a constant ratio between the 4 major allergens: *D pteronyssinus* group 1 and group 2 allergens and *D farinae* group 1 and group 2 allergens. The first dose was self-administered on site, and subjects were monitored for 30 minutes after tablet intake. Subsequent doses were self-administered at home. The tablet was to be placed under the tongue and allowed to remain for a few seconds until dissolved. Subjects were advised not to swallow during the first minute after administration. Treatment compliance was assessed by subject-reported compliance and inspection of study drug at monthly visits and was calculated as the number of days on the study drug divided by the number of expected days on the study drug. A washout period of 3 days before randomization and before each exposure challenge was required for antihistamines and decongestants; the use of oral, nasal, or ocular corticosteroids was not permitted during the trial. Self-injectable epinephrine is not a requirement for SLIT studies in Europe and was therefore not prescribed.

Key inclusion and exclusion criteria

Subjects eligible for inclusion in the trial were men and women aged 18 years or older with HDM-induced AR/C of 1 year or longer in duration with or without asthma. Subjects were required to have a TNSS of 6 or more of a possible 12 within the first 2 hours of the screening exposure challenge; a positive skin prick test response (wheal diameter ≥3 mm larger than saline control) to *D pteronyssinus*, *D farinae*, or both at screening; a serum specific IgE level (≥0.7 kU/L equivalent to RAST class 2 or greater) to *D pteronyssinus*, *D farinae*, or both at screening; and an FEV_1 of 70% of predicted value or greater (according to reference values of the European Coal and Steel Community) at screening and randomization. Subjects were excluded from the trial if they had unstable, uncontrolled/partially controlled, or severe asthma as judged by the investigator; asthma requiring medium- or high-dose inhaled corticosteroids within the last 12 months before screening; or HDM immunotherapy within the past 3 years. Key discontinuation criteria were as follows: a life-threatening treatment-related adverse event (AE); a decrease in FEV_1 of 20% or peak expiratory flow of 25% less than prechallenge values during the exposure challenge; a late-phase asthmatic reaction temporally associated with exposure challenge that required treatment and, per the investigator's discretion, necessitated discontinuation; poor asthma control despite titration of inhaled corticosteroids based on the investigator's assessment; and a treatment-related acute severe asthmatic reaction or anaphylactic reaction.

Study assessments

Symptoms were scored every 15 minutes during exposure challenges and recorded directly in an electronic database. It was expected that symptoms during exposure challenges would plateau after about 2 hours.[15,16] Thus, data collected from the last 4 hours of each 6-hour challenge were used to derive the symptom-based efficacy end points. A total of 9 nasal, ocular, and asthma symptoms were evaluated, and each was scored as 0 (no symptoms), 1 (mild symptoms), 2 (moderate symptoms), or 3 (severe symptoms, see Table E1 in this article's Online Repository at www.jacionline.org). Nasal symptoms were runny nose, blocked nose, sneezing, and itchy nose; ocular symptoms were gritty/red/itchy eyes and watery eyes; and asthma symptoms were cough, wheeze, and dyspnea.

The primary efficacy end point was the average TNSS at week 24. The TNSS was the sum of the 4 nasal symptoms, with a maximum score of 12 (see Table E1). Key secondary efficacy end points were the average TNSS at weeks 8 and 16 and the average total symptom score (TSS) at week 24. The TSS was the sum of the 4 nasal symptoms and 2 ocular symptoms, with a maximum