1 TITLE PAGE

CLINICAL STUDY REPORT

Sponsor Name	Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc.
Compound Name	MK-8237
Protocol Title	A One-year Placebo-Controlled Study Evaluating the Efficacy and Safety of the House Dust Mite Sublingual Allergen Immunotherapy Tablet (SCH 900237/MK-8237) in Children and Adult Subjects With House Dust Mite-Induced Allergic Rhinitis/Rhinoconjunctivitis With or Without Asthma
CSR Identification	P001
Indication	Allergic Rhinitis/Rhinoconjunctivitis
Trial Design	Efficacy, safety, parallel assignment, randomized, double-blind, placebo-controlled treatment
Phase	III
Trial Initiation Date	24-JAN-2013 (first subject first visit)
Trial Early Termination Date	Not Applicable
Trial Completion Date	27-APR-2015 (last subject last visit)
Report Date	01-DEC-2015
Previous CSR Identification	Not applicable
Responsible Medical Officer	[redacted], PharmD
Investigator Name/Affiliation	Multicenter (182 trial sites)
GCP Compliance	Information regarding GCP compliance can be found in Section 5.2
Questions about the clinical study report should be directed to the individual listed on the accompanying correspondence.	

2 SYNOPSIS

SPONSOR:	**Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	MK-8237 12 development unit (DU); sublingual tablet	
INDICATION:	Allergic Rhinitis/Rhinoconjunctivitis	
PROTOCOL TITLE:	A One-year Placebo-Controlled Study Evaluating the Efficacy and Safety of the House Dust Mite Sublingual Allergen Immunotherapy Tablet (SCH 900237/MK-8237) in Children and Adult Subjects With House Dust Mite-Induced Allergic Rhinitis/Rhinoconjunctivitis With or Without Asthma	
TRIAL IDENTIFIERS:	Protocol Number:	P001
	Clinical Phase:	III
	EudraCT Number	Not applicable
TRIAL CENTERS:	This trial was conducted at 182 trial sites: 157 in the United States (US) and 25 in Canada.	

DESIGN:	This was a double-blind, randomized, placebo-controlled, multicenter trial of MK-8237 12 DU sublingual tablets in subjects, 12 years of age and older with a clinical history of house dust mite (HDM)-induced allergic rhinitis/rhinoconjunctivitis of 1 year duration or more, with or without asthma. Subjects were required to demonstrate a positive skin prick test wheal response (≥5 mm greater than saline control) and specific immunoglobulin E (IgE) reactivity to HDM (*Dermatophagoides* [*D.*] *pteronyssinus* and/or *D. farinae*) of at least 0.7 kU/L; forced expiratory volume in 1 second (FEV_1) >80% of predicted at screening, run-in, and randomization visits; and a rhinitis daily symptom score (DSS) of at least 6 (or a score of at least 5 with 1 symptom being severe) out of 12 on 5 of 7 consecutive calendar days before randomization. At selected sites pre-approved by the Sponsor, a rhinitis DSS of at least 6 of 12 of the total score possible assessed by an HDM environmental chamber challenge within the past 1 year before the Screening Visit was used to confirm positive allergy to HDM in lieu of the Run-in period. A subject receiving anti-allergy medication was required to washout of their medication prior to and during the Run-in period of the study until the required symptom threshold was met. The trial was designed to randomize a total of approximately 1500 subjects to receive (1:1) either MK-8237 12 DU or placebo once daily for up to 52 weeks. Randomization was stratified by asthma status (yes/no) and age (<18/≥18 years). Subjects were required to record rhinitis, conjunctivitis, and asthma symptom scores in an e-diary in the morning during the Run-in period and again from Visits 9 to 11. Rescue medications were provided to the trial sites to be given to the subjects as pre-defined, open-label medications to be taken in a step-wise fashion depending on the persistence, severity, and type of symptoms for allergic rhinoconjunctivitis during the last 12 weeks of the treatment period starting from Visit 9. Requirements for the start of rescue medication use included total symptom score of ≥4 (ie, for loratadine or mometasone furoate monohydrate nasal spray) and/or persistent eye symptoms (ie, for olopatadine hydrochloride ophthalmic solution). Efficacy was measured during approximately the last 8 weeks of the treatment period.	
	Planned duration of treatment phase:	up to 12 months
	Planned duration of Run-in phase:	up to 6 weeks
	Planned duration of extension phase:	Not applicable

Objectives	<u>Primary</u> 1. To evaluate the efficacy of MK-8237 compared to placebo in the treatment of HDM-induced allergic rhinitis/rhinoconjunctivitis based on the average total combined rhinitis score (TCRS) during the last 8 weeks of treatment. 2. To evaluate the safety and tolerability of MK-8237 administered sublingually once daily to subjects with a history of HDM-induced allergic rhinitis/rhinoconjunctivitis. <u>Key Secondary</u> To compare the following between the MK-8237 and placebo groups: 1. Average rhinitis daily symptom score (DSS) during the last 8 weeks of treatment; 2. Average rhinitis daily medication score (DMS) during the last 8 weeks of treatment; 3. Average total combined score (TCS) during the last 8 weeks of treatment; 4. Average allergic rhinitis/rhinoconjunctivitis symptoms assessed by Visual Analogue Scale (VAS) during the last 8 weeks of treatment.	
Hypotheses	<u>Primary</u> Administration of MK-8237 sublingual tablet (12 DU), compared with placebo, results in significant reduction in the average TCRS during the last 8 weeks of treatment. <u>Key Secondary</u> Administration of MK-8237 12 DU, compared with placebo, results in significant score reduction on the following endpoints: 1. Average rhinitis DSS during the last 8 weeks of treatment; 2. Average rhinitis DMS during the last 8 weeks of treatment; 3. Average TCS during the last 8 weeks of treatment; 4. Average allergic rhinitis/rhinoconjunctivitis symptoms assessed by VAS during the last 8 weeks of treatment.	
Treatments groups	MK-8237	MK-8237 12 DU sublingual tablet, once daily up to approximately 52 weeks 741 subjects
	Placebo	Placebo sublingual tablet, once daily up to approximately 52 weeks 741 subjects
Clinical Supplies Dispensed to Subjects	Study drug	Manufacturing Lot Numbers
	MK-8237 tablet (12 DU)	GL00002246, GL00002245, GL00003073, GL00003076

	MK-8237 matching-image placebo tablet	GL00002248, GL00003078

Endpoints and definitions	Primary endpoint	TCRS	Average TCRS during the last 8 weeks of treatment. The TCRS was the sum of rhinitis DSS and rhinitis DMS with a range of 0 to 24 points. Average TCRS was calculated based on non-missing TCRS values during the last 8 weeks of treatment.
	Key Secondary Endpoints	DSS	Average rhinitis DSS during the last 8 weeks of treatment. Rhinitis DSS was the sum of 4 nasal symptoms (runny nose, blocked nose, sneezing, itchy nose), each rated on a scale from 0 (no symptoms) to 3 (severe symptoms) with a range of 0 to 12 points. Average rhinitis DSS was calculated based on non-missing values during the last 8 weeks of treatment.
		DMS	Average rhinitis DMS during the last 8 weeks of treatment. Rhinitis DMS consists of rhinitis symptomatic medication scores with a range of 0 to 12. Average rhinitis DMS was calculated based on non-missing values during the last 8 weeks of treatment.
		TCS	Average TCS during the last 8 weeks of treatment. TCS was the sum of rhinoconjunctivitis DSS and the rhinoconjunctivitis DMS with a range of 0 to 38 points. Average TCS was calculated based on non-missing values during the last 8 weeks of treatment.

		VAS	Average allergic rhinitis/rhinoconjunctivitis VAS score during last 8 weeks of treatment. VAS was a weekly self-reported assessment on symptom severity with a range of 0 ("no symptoms") to 100 ("severe symptoms"). Average VAS was calculated based on non-missing values during the last 8 weeks of treatment.
	Safety	Overall Safety and Tolerability	General safety: Proportion of subjects with any adverse events (AEs), drug-related AEs, serious adverse events (SAEs), serious and drug-related AEs, discontinued due to an AE, upper respiratory viral infection, and who died. Tier 1: Proportion of subjects with pre-specified local application site reactions, proportion of subjects with anaphylaxis and/or systemic allergic reactions, and proportion of subjects with AEs treated with epinephrine.
Database lock	15-MAY-2015 (original); 16-OCT-2015 (database re-lock)	Trial status	24-JAN-2013 (first subject first visit) to 27-APR-2015 (last subject last visit) *trial was re-monitored from 05-AUG-15 through 08-OCT-15 which resulted in a re-lock of the database
RESULTS AND ANALYSIS:	The primary and key secondary efficacy and safety analyses were performed according to the protocol.		

Baseline and demographic characteristics were generally similar in the MK-8237 and placebo groups (Table 2-1). The majority of subjects (79.2%) completed the trial. There were more discontinuations in the MK-8237 group than in the placebo group, with AEs most notably contributing to the difference in rates of discontinuations.

Table 2-1 Subject Baseline Characteristics and Disposition

	MK-8237 12 DU n (%)	Placebo n (%)	Total n (%)
SUBJECTS NOT RANDOMIZED			3015
RANDOMIZED	741	741	1482
Gender			
Male	296 (39.9)	311 (42.0)	607 (41.0)
Female	445 (60.1)	430 (58.0)	875 (59.0)
Age (Years)			
Mean	34.9	35.2	35.1
Range	12 to 77	12 to 85	12 to 85
Baseline Asthma Status			
Subjects with Asthma	228 (30.8)	232 (31.3)	460 (31.0)
With ICS use	66 (28.9)	62 (26.7)	128 (27.8)
Without ICS use	162 (71.1)	170 (73.3)	332 (72.2)
Subjects without Asthma	513 (69.2)	509 (68.7)	1022 (69.0)
Allergen Sensitivity[†]			
Sensitized to HDM[‡] only	184 (24.8)	171 (23.1)	355 (24.0)
Multi-sensitized	555 (74.9)	567 (76 5)	1122 (75.7)
Not sensitized to HDM	2 (0.3)	3 (0.4)	5 (0.3)
COMPLETED	561 (75.7)	613 (82.7)	1174 (79.2)
DISCONTINUED	179 (24.2)	128 (17.3)	307 (20.7)
Adverse Event	73 (9.9)	18 (2.4)	91 (6.1)
Lost to Follow-up	42 (5.7)	29 (3.9)	71 (4.8)
Withdrawal by Subject	56 (7.6)	64 (8.6)	120 (8 1)

DU = development unit; HDM = house dust mite; ICS = inhaled corticosteroids.
For the ICS usage status, the denominator for the calculation of percentages was the number of Subjects with Asthma.
[†] Sensitization to HDM was determined by serum specific IgE testing and skin prick test. Sensitization to other allergens was determined by serum specific IgE testing.
[‡] *D. pteronyssinus* and/or *D. farinae*.

Analysis description	**Primary Analysis — TCRS** The primary efficacy endpoint was analyzed using the non-parametric approach where between-treatment difference was performed using the Wilcoxon Rank Sum Test with the p-value reported. The reported p-values for between-treatment differences were based on difference across 2 treatment arms for efficacy endpoints. The Hodges-Lehmann estimate of treatment difference and the corresponding 2-sided 95% confidence interval (CI) are presented. Also, the difference in medians between the treatment groups relative to the median of the placebo group is presented as a percentage with the corresponding 95% CI derived using the bootstrap method.
Analysis population and time point description	The analysis population for the primary efficacy analysis was the Full Analysis Set (FAS) population. The FAS population considered all randomized patients who had received at least 1 dose of study drug. Subjects were analyzed according to the treatment group to which they were randomized. The endpoint was assessed during approximately the last 8 weeks of treatment. A supportive analysis was performed in the Per Protocol (PP) population, which included all randomized subjects who did not have major pre-specified protocol violations.
Summary results of primary endpoint	For the primary endpoint the average TCRS was lower in the MK-8237 group compared with the placebo group in the last 8 weeks of treatment; the relative treatment difference between the groups was -17.2% (95% CI, -25.0%, -9.7%), and the between treatment difference was statistically significant ($p<0.001$) (Table 2-2).

Analysis description	**Secondary Efficacy Analyses** Secondary efficacy endpoints were analyzed in a similar fashion as the primary endpoint except for rhinitis DMS. Because of the large number of zeroes observed in the data, the zero-inflated log-normal model was used to analyze the average rhinitis DMS, as specified in the protocol.
Analysis population and time point description	The analysis population for the secondary efficacy analysis was the FAS population. The endpoints were assessed during approximately the last 8 weeks of treatment.

Summary results of key secondary endpoints	The first key secondary endpoint showed a lower average rhinitis DSS in the MK-8237 group compared with the placebo group with the difference relative to placebo of -15.5%; the difference between the groups was statistically significant (Table 2-2). The average rhinitis DMS was numerically lower in the MK-8237 group than in the placebo group; however, a statistically significant difference was not demonstrated. The average TCS and average rhinitis/rhinoconjunctivitis VAS were each lower in the MK-8237 group than in the placebo group. The nominal p-value for each difference was less than 0.001; however, these results cannot be considered as confirmatory due to the pre-specified multiplicity control strategy.

Table 2-2 Primary and Key Secondary Endpoints (Full Analysis Set)

Treatment	N	Mean (SD)	Median	Treatment Difference (%) Relative to Placebo (95% CI)	Treatment Difference (95% CI)	p-Value
Total Combined Rhinitis Score (TCRS) during last 8 weeks of Treatment (Primary Endpoint)						
MK-8237 12 DU	566	4.67 (3.55)	4.10	-17.2 (-25.0, -9.7)	-0.80 (-1.20, -0.40)	<0.001
Placebo	620	5.49 (3.82)	4.95			
Rhinitis Daily Symptom Score (DSS) during last 8 weeks of Treatment (Key Secondary Endpoint)						
MK-8237 12 DU	566	3.83 (2.64)	3.55	-15.5 (-24.4.-7.3)	-0.60 (-1.00, -0.30)	<0.001
Placebo	620	4.46 (2.80)	4.20			
Rhinitis Daily Medication Score (DMS) during last 8 weeks of Treatment (Key Secondary Endpoint)						
MK-8237 12 DU	566	0.84 (1.817)	0.65	-18.4 (-41, 4.3)	-0.15 (-0.35, 0.05)	0.154
Placebo	620	1.03 (2.074)	0.79			
Total Combined Rhinoconjunctivitis Score (TCS) during last 8 weeks of Treatment (Key Secondary Endpoint)						
MK-8237 12 DU	566	6.40 (5.16)	5.50	-16.7 (-24.6,-4.0)	-1.10 (-1.70, -0.60)	<0.001
Placebo	620	7.62 (5.48)	6.60			
Average Visual Analogue Scale (VAS) during last 8 weeks of Treatment (Key Secondary Endpoint)						
MK-8237 12 DU	540	42.29 (23.57)	41.40	-16.0 (-22.7, -8.3)	-6.10 (-9.10, -3.10)	<0.001
Placebo	585	47.96 (23.66)	49.30			

CI = confidence interval; DMS = Daily Medication Score; DSS = Rhinitis Daily Symptom Score; N = number of subjects included in the analysis; SD = standard deviation; TCRS = Total Combined Rhinitis Score (TCRS); TCS = Total Combined Score; VAS = Visual Analogue Scale.
Note: TCRS, Rhinitis DSS, and TCS were analyzed using a non-parametric approach where the treatment difference was performed using the Wilcoxon Rank Sum test. Rhinitis DMS was analyzed using a zero-inflated log-normal model.

Analysis description	**Safety and Tolerability Analyses** The general safety parameters were summarized by subject counts and percentages or descriptive statistics, as appropriate. The analysis of safety parameters followed a tiered approach. Tier 1 safety endpoints (pre-specified local application site reactions, anaphylactic reactions, and epinephrine use) were subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group differences, using the stratified Miettinen and Nurminen method with baseline asthma status (yes/no) and age group (<18/≥18) as stratification factors.

Analysis population and time point description	An All-Subjects-as-Treated (ASaT) population was used for safety analyses. The ASaT population included all randomized subjects who received at least 1 dose of study drug. Subjects were included in the treatment group corresponding to the study drug they actually received during the trial. Any subject randomized to the placebo group who took MK-8237 in error was included in the MK-8237 group, as pre-specified in the handling convention.
Summary	The majority of subjects (82.0%) reported at least 1 AE, irrespective of causality (Table 2-3). There were more subjects with AEs, drug-related AEs, discontinuations due to AEs, and discontinuations due to drug-related AEs in the MK-8237 group than in the placebo group. Of the subjects treated with MK-8237 who experienced at least 1 AE, the majority (92.2%) had AEs with maximal intensity of mild or moderate. There were no deaths. Serious adverse events were infrequently reported, and a similar percentage of subjects in the MK-8237 and placebo groups experienced SAEs. There were no drug-related SAEs in the MK-8237 group reported as life-threatening, resulted in persistent or significant disability/incapacity, resulted in or prolonged an existing inpatient hospitalization, was a congenital anomaly/birth defect or was considered by the Investigator to be an other important medical event. Two subjects reported overdoses (each subject took 1 extra tablet) with drug-related AEs (1 subject had 2 AEs, oral pruritus and throat irritation, and the other subject had an AE of oral pain). The Sponsor classified these overdoses with drug-related AEs as SAEs. All 3 AEs were assessed as mild in intensity by the Investigators and did not meet International Conference on Harmonisation (ICH) criteria for seriousness. There were no differences between the treatment groups with respect to the percentage of subjects with upper respiratory viral infections.

Table 2-3 Adverse Event Summary (All-Subjects-as-Treated)

	MK-8237 12 DU		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	743		738		1481	
with one or more adverse events	676	(91.0)	539	(73.0)	1215	(82.0)
with no adverse event	67	(9.0)	199	(27.0)	266	(18.0)
with drug-related † adverse events	624	(84.0)	301	(40.8)	925	(62.5)
with serious adverse events	11	(1.5)	7	(0.9)	18	(1.2)
with serious drug-related ‡ adverse events	2	(0.3)	0		2	(0.1)
who died	0		0		0	
discontinued† † due to an adverse event	73	(9.8)	19	(2.6)	92	(6.2)
discontinued due to a drug-related adverse event	62	(8.3)	6	(0.8)	68	(4.6)
discontinued due to a serious adverse event	3	(0.4)	1	(0.1)	4	(0 3)
discontinued due to a serious drug-related adverse event	0		0		0	

Every subject was counted a single time for each applicable row and column.

† Determined by the investigator to be related to the study drug.
‡ The occurrences of serious drug-related AEs were AEs associated with an overdose. These AEs did not meet ICH criteria for seriousness.
†† Study drug withdrawn.

Source: T14-03-01-01-AE-SUMM-ALL.sas, QUINTILES (US) 17-OCT-2015 13:41 DATA TRANSFER: 17OCT2015

The majority of subjects (81.2%) in the MK-8237 group reported at least 1 local application site reaction (Table 2-4); the majority of these AEs were assessed as drug related by the Investigator. The most frequently reported local application site reactions in the MK-8237 group, irrespective of causality, were throat irritation, oral pruritus, and ear pruritus.

The median time to onset of pre-specified local application site reactions in the MK-8237 treatment group ranged from 1 to 8 days. The median duration of local application site reactions occurred on Day 1 after treatment administration ranged from 14 to 67 minutes, all of which were assessed as mild or moderate in intensity by the Investigator. The median recurrence of all local application site reactions for all subjects as treated was 1 day.

Table 2-4 Pre-specified Local Application Site Reactions (All-Subjects-as-Treated), Irrespective of Causality

	MK-8237 12 DU		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	743		738		1481	
Subjects with 1 or more local application site reactions	603	81.2	242	32.8	845	57 1
Subjects with drug-related local application site reactions	595	80.1	228	30.9	823	55.6
Lip Swelling/Edema	151*	20.3	19	2.6	170	11.5
Mouth Swelling/Edema	75*	10.1	12	1.6	87	5.9
Palatal Swelling/Edema	89*	12.0	11	1.5	100	6.8
Swollen Tongue/Edema	133*	17.9	17	2.3	150	10 1
Oropharyngeal Swelling/Edema	1	0.1	0	0.0	1	0.1
Pharyngeal Edema/Throat Tightness	113*	15.2	24	3.3	137	9.3
Oral Pruritus	468*	63.0	109	14.8	577	39.0
Throat Irritation	506*	68.1	172	23.3	678	45.8
Tongue Pruritus	36*	4.8	7	0.9	43	2.9
Ear Pruritus	382*	51.4	92	12.5	474	32.0
* p < 0.0001 versus placebo.						

For sublingual immunotherapy, the events of clinical interest (ECI) are systemic allergic reactions; local allergic swelling of the mouth and/or throat of severe intensity; and events that are treated with epinephrine. Table 2-5 provides the frequency of each of these ECI categories.

Table 2-5 Frequency of Anaphylaxis and/or Systemic Reactions, Severe Local Swelling of the Mouth and/or Throat, and Events Treated with Epinephrine

	MK-8237 12 DU n (%)	Placebo n (%)	Total n (%)
Subjects in population	743	738	1481
Anaphylaxis and/or systemic allergic reactions	3 (0.4)	3 (0.4)	6 (0.4)
Severe local swelling or edema of the mouth and/or throat	2 (0.3)	0	2 (0.1)
Events treated with epinephrine	4 (0.5)	3 (0.4)	7 (0.5)

Every subject was counted a single time for each applicable row and column.

Anaphylactic and/or systemic allergic reactions were reported by a total of 6 subjects (3 subjects in the MK-8237 group and 3 subjects in the placebo group). One of the 3 subjects in the MK-8237 treatment group had an MK-8237-related systemic allergic reaction, which occurred on Day 1. Within minutes of the first dose of study drug, the subject had symptoms of itchy palms, facial flushing, shortness of breath, pre-syncope, and throat swelling. The event was assessed as non-serious and was considered moderate in intensity by the Investigator. The subject was treated with epinephrine by the Investigator and the event resolved.

Additionally, 3 subjects (2 of whom with food hypersensitivity) had anaphylactic reactions and 2 subjects had hypersensitivity reactions, all assessed as unrelated to study drug by the Investigator.

During the trial, there were 2 subjects who developed local swelling of severe intensity; 1 subject had an event assessed as drug-related by the Investigator, and the other subject's AE was assessed as not drug-related and related to environmental dust exposure. Both subjects self-administered epinephrine.

Of the 7 subjects who received epinephrine, 5 were included in the previous 2 ECI categories. Two additional subjects not already mentioned also received epinephrine. One administration was in a subject randomized to MK-8237 who developed throat and chest discomfort 30 minutes after administering the study drug. The subject self-administered epinephrine; his symptoms resolved before clinical examination. He continued in the trial and tolerated MK-8237 following these events. The other subject was a placebo-treated subject who self-administered epinephrine due to pharyngeal edema of moderate intensity that occurred as a result of a food allergic reaction.

Subjects with asthma generally tolerated treatment with MK-8237. Adverse events of all categories (ie, overall incidence of AEs, drug-related AEs, and discontinuations due to AE) were more frequently reported in subjects with asthma than in subjects without asthma in both the MK-8237 and placebo groups. Treatment differences in subjects with and without asthma were similar for all categories of AEs including local application site reactions. Although only a small number of subjects with asthma used inhaled corticosteroids (ICS), the AE profile appeared similar in subjects who did and did not use ICS.

CONCLUSIONS:	In adult and adolescent subjects ≥12 years of age with house-dust-mite allergic rhinitis/rhinoconjunctivitis (with or without asthma) treated with placebo or MK-8237 sublingual tablet up to a 12-month period: 1. MK-8237, compared with placebo, is effective in the treatment of HDM-induced allergic rhinitis/rhinoconjunctivitis based on the significant reduction in the average total combined rhinitis score (TCRS) during the last 8 weeks of treatment. 2. MK-8237, compared with placebo, significantly reduces the average rhinitis daily symptom score (DSS) during the last 8 weeks of treatment. 3. MK-8237, compared with placebo, is associated with numerical trends for improvement as measured by the average rhinitis daily medication score (DMS), average total combined rhinoconjunctivitis score (TCS), and average allergic rhinitis/rhinoconjunctivitis symptoms as assessed by Visual Analogue Scale (VAS) during the last 8 weeks of treatment. 4. MK-8237 is generally well tolerated with an AE profile characterized by frequent but transient local allergic events that are typically assessed as mild or moderate in intensity. Severe allergic reactions were rare. No new or unexpected safety findings were reported.
REPORT DATE:	01-DEC-2015