1 TITLE PAGE

CLINICAL STUDY REPORT

Sponsor Name	Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc.
Compound Name	MK-8237
Protocol Title	Safety Study of MK-8237 Treatment in House-Dust-Mite Allergic Adolescents (Protocol 008)
CSR Identification	P008
Indication	Treatment of House Dust Mite-Induced Allergic Rhinitis/Rhinoconjunctivitis
Trial Design	Safety and tolerability, parallel assignment, double-blind, placebo-controlled, treatment.
Phase	1
Trial Initiation Date	08-OCT-2012
Trial Early Termination Date	Not Applicable
Trial Completion Date	17-MAY-2013
Previous CSR Identification	Not Applicable
Responsible Medical Officer	[redacted] PharmD
Investigator Name/Affiliation	Multicenter (19)
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**	
INDICATION:	Allergic Rhinitis/Rhinoconjunctivitis	
PROTOCOL TITLE:	Safety Study of MK-8237 Treatment in House-Dust-Mite Allergic Adolescents (Protocol 008)	
TRIAL IDENTIFIERS:	Protocol Number:	P008
	Clinical Phase:	1
	EudraCT Number:	Not applicable.
	ISRCT Number:	Not applicable.
TRIAL CENTERS:	This trial was conducted at 19 trial centers in the United States.	
DESIGN:	Randomized, placebo-controlled, parallel-group, multi-site, double-blind safety trial evaluating MK-8237 (12 DU; 6 DU) for the treatment of house dust mite (HDM) induced-allergic rhinitis/rhinoconjunctivitis in adolescent subjects	
	Planned duration of main phase: Planned duration of run-in phase: Planned duration of extension phase:	28 days Not applicable Not applicable
Objectives	<u>Primary:</u> To assess the safety and tolerability of two doses of MK-8237 sublingual tablet (12 DU; 6 DU) versus placebo, as evidenced by the proportion of subjects with adverse events (AEs) in adolescent subjects with HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma. <u>Secondary:</u> To assess the safety and tolerability of MK-8237, as evidenced by the proportion of subjects who discontinue due to an AE in adolescent subjects with HDM-induced allergic rhinitis/rhinoconjunctivitis with or without asthma. <u>Exploratory:</u> To evaluate the safety and tolerability of MK-8237 by: 1) Assessing the proportion of subjects reporting pre-specified local AEs expected to commonly occur with application of the tablet, namely, lip swelling/edema; mouth edema; palatal edema; swollen tongue/edema; oropharyngeal swelling/edema; pharyngeal edema; throat tightness; oral pruritus; throat irritation; tongue pruritus; and ear pruritus; and 2) Assessing the duration (in minutes) of pre-specified, local AEs (lip swelling/edema; mouth edema; palatal edema; swollen tongue/edema; oropharyngeal swelling/edema; pharyngeal edema; throat tightness; oral pruritus; throat irritation; tongue pruritus; ear pruritus) following the first dose of medication.	

Hypothesis	Hypothesis for Primary Objective: At least one dose of the MK-8237 sublingual tablet (12 DU; 6 DU) is safe and well-tolerated, based on an assessment of the proportion of subjects reporting AEs and the review of clinical and laboratory results, to permit further clinical investigation.
Treatments groups	A total of 195 subjects were randomized in a 1:1:1 ratio to receive sublingually 1 tablet per day of 12 DU MK-8237, 6 DU MK-8237, or placebo for 28 days.

Clinical Supplies Dispensed to Subjects

Product Name	Potency	Dosage Form	Bulk Lot ID
MK-8237	12 DU	Sublingual Tablet	GL00000479
MK-8237	6 DU	Sublingual Tablet	GL00000479
MK-8237	Placebo	Sublingual Tablet	GL00000479

Endpoints and definitions	Primary endpoint	Safety	Proportion of subjects with any AEs. With 65 subjects per treatment arm and assuming the incidence rates of AEs of 45% in the placebo arm, the rate difference of 29% can be detected with 90% power at an alpha level of 0.05 (2-sided test), and the corresponding half-width is about 16% for the 95% confidence interval (CI) around the between-treatment differences.
	Secondary endpoint	Safety	Proportion of subjects who discontinued due to an AE.
	Exploratory endpoints	Safety	1) Proportion of subjects with any pre-specified local AEs, and 2) Duration (in minutes) of pre-specified local AEs following the first dose of study medication.
Database lock	31-MAY-2013	Trial status	08-OCT-2012 (first subject first visit) to 17-MAY-2013 (last subject last visit)

RESULTS AND ANALYSIS:	**Efficacy:** No efficacy parameters were assessed for this study. **Safety:** All analyses for safety were performed according to the protocol.

Subject Baseline Characteristics/Disposition:

	MK-8237 12 DU n (%)	MK-8237 6 DU n (%)	Placebo n (%)	Total n (%)
SUBJECTS NOT RANDOMIZED:				161[a]
RANDOMIZED:	65	65	65	195
Gender				
Male (age range, 12-17 years)	40 (61.5)	38 (58.5)	44 (67.7)	122 (62.6)
Female (age range, 12-17 years)	25 (38.5)	27 (41.5)	21 (32.3)	73 (37.4)
Baseline asthma status				
Asthma subject	24 (36.9)	22 (33.8)	22 (33.8)	68 (34.9)
Non asthma subject:	41 (63.1)	43 (66.2)	43 (66.2)	127 (65.1)
ASaT POPULATION:	65	65	65	195
COMPLETED:	61 (93.8)	60 (92.3)	65 (100)	186 (95.4)
DISCONTINUED:	4 (6.2)	5 (7.7)	0 (0.0)	9 (4.6)
Clinical adverse experience	4 (6.2)	4 (6.2)	0 (0.0)	8 (4.1)
Consent withdrawal by parent/guardian	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)

Abbreviation: ASaT=All Subjects as Treated.

Each subject is counted once for Study Disposition based on the latest corresponding disposition record.

The denominator for percentage was based on number of subjects randomized.

a: Includes 157 subjects who screen failed, three consent withdrawals by Parent/Guardian, and one consent withdrawal by Subject.

Analysis description	**Analysis for Primary Endpoint** Analyses of the safety endpoints followed the tiered approach. The 95% CIs (Tier 2) were provided for between-group comparisons for proportion of subjects with any AEs and were based on the Miettinen and Nurminen method stratified by asthma status.
Analysis population and time point description	The All Subject as Treated (ASaT) population included all randomized subjects who received at least one dose of treatment. Subjects were analysed in the treatment group corresponding to the actual treatment received. Time frame: approximately 28-day treatment period.
Summary	The proportion of subjects with any AEs was numerically higher in the active treatment groups (12 DU and 6 DU) compared with that in the placebo group (Table 2-1).

Table 2-1
Analysis of Safety Endpoints
All-Subjects-as-Treated

Treatment	N	n	(%)	Difference in % vs. Placebo Estimate (95% CI)[†]
Proportion of Subjects With Any AEs (Primary Endpoint)				
MK-8237 12 DU	65	37	(56.9)	13.8 (-3.4, 30.3)
MK-8237 6 DU	65	35	(53.8)	10.8 (-6.4, 27.4)
Placebo	65	28	(43.1)	--
Proportion of Subjects Who Discontinued[‡] Due to an AE (Secondary Endpoint)				
MK-8237 12 DU	65	4	(6.2)	6.2 (0.4, 14.8)
MK-8237 6 DU	65	4	(6.2)	6.2 (0.4, 14.8)
Placebo	65	0	(0.0)	--
Proportion of Subjects With Any Pre-Specified Local AEs (Exploratory Endpoint)				
MK-8237 12 DU	65	26	(40.0)	23.1 (7.7, 37.7)
MK-8237 6 DU	65	22	(33.8)	16.9 (1.9, 31.5)
Placebo	65	11	(16.9)	--

[†] Based on Miettinen & Nurminen method stratified by Asthma Status; if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
[‡] Study medication withdrawn.
AE = adverse event; DU = development unit; CI = confidence interval.

Analysis description	**Analysis for Secondary Endpoint** Analyses of the safety endpoints followed the tiered approach. The 95% CIs (Tier 2) were provided for between-group comparisons for the proportion of subjects who discontinued due to an AE and were based on the Miettinen and Nurminen method stratified by asthma status.
Analysis population and time point description	The All Subject as Treated (ASaT) population included all randomized subjects who received at least one dose of treatment. Subjects were analysed in the treatment group corresponding to the actual treatment received. Time frame: approximately 28-day treatment period.
Summary	The proportion of subjects who discontinued due to an AE was similar in the 12 DU and 6 DU groups (Table 2-1); there were no discontinuations in the placebo group.

Analysis description	**Analysis for Exploratory Endpoints** Analyses of the safety endpoints followed the tiered approach. The p-values and 95% CIs (Tier 1) were provided for between-group comparisons of the proportion of subjects with pre-specified local application site AEs and were based on the Miettinen and Nurminen method stratified by asthma status. Analyses of the duration (in minutes) of pre-specified local application site AEs following the first dose of study medication were based on summary statistics (including mean, standard deviation, median, minimum and maximum).
Analysis population and time point description	The All Subject as Treated (ASaT) population included all randomized subjects who received at least one dose of treatment. Subjects were analysed in the treatment group corresponding to the actual treatment received. Time frame for the proportion of subjects with pre-specified local application site AEs: 28-day treatment period. Time frame for the duration (in minutes) of pre-specified local application site AEs following the first dose of study medication: over first day of treatment.
Summary	There was a statistically significantly higher proportion of subjects with any pre-specified local AEs in both the 12 DU (p=0.004) and 6 DU (p=0.027) groups compared with the placebo group (Table 2-1). Duration of pre-specified local AEs following the first dose of study medication ranged from a median of 1 to 43 minutes (Table 2-2).

Table 2-2
Summary of Duration (in minutes) of
Pre-Specified Local Application Site Reactions
After Dosing on Day 1
All-Subjects-as-Treated

	MK-8237 12 DU	MK-8237 6 DU	Placebo
Subjects in population	65	65	65
Lip swelling / edema			
Number of Subjects (n/N)	2/2	-	-
Median	42	-	-
Range	37.00 to 46.00	-	-
Mouth Edema			
Number of Subjects (n/N)	-	1/1	-
Median	-	8	-
Range	-	8.00 to 8.00	-
Swollen tongue / edema			
Number of Subjects (n/N)	2/2	-	-
Median	20	-	-
Range	20.00 to 20.00	-	-
Pharyngeal edema / throat tightness			
Number of Subjects (n/N)	3/3	2/2	1/1
Median	26	37	43
Range	15.00 to 30.00	33.00 to 41.00	43.00 to 43.00
Oral Pruritus			
Number of Subjects (n/N)	9/9	9/9	3/3
Median	20	9	5
Range	0.50 to 36.00	1.00 to 54.00	1.00 to 15.00
Throat Irritation			
Number of Subjects (n/N)	10/10	9/9	2/2
Median	10	8	24
Range	3.00 to 30.00	1.00 to 25.00	23.00 to 25.00
Tongue Pruritus			
Number of Subjects (n/N)	5/5	7/7	-
Median	10	10	-
Range	2.00 to 49.00	5.00 to 33.00	-
Ear Pruritus			
Number of Subjects (n/N)	1/1	4/4	-
Median	1	29	-
Range	0.50 to 0.50	8.00 to 35.00	-

N: number of subjects with specific AE occurring on Day 1 after dosing | n: number of AE records with non-missing duration.

Treatment with MK-8237 (12 DU and 6 DU) was generally well-tolerated (Table 2-3). During the study, there were no serious adverse events, deaths, anaphylactic and/or systemic reactions (including those requiring epinephrine as rescue medication), or severe local swelling or edema of the mouth and/or throat. Three subjects (1.5%; 12 DU MK-8237 group) experienced AEs of severe intensity (eye pruritus, throat irritation, infectious monomucleosis, and streptococcal pharyngitis), all other AEs were assessed as mild (48.2%

of subjects) or moderate (14.9% of subjects) in intensity. No safety signal was detected in subjects with asthma compared to those without asthma.

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

	MK-8237 12 DU		MK-8237 6 DU		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	65		65		65		195	
with one or more adverse events	37	(56.9)	35	(53.8)	28	(43.1)	100	(51.3)
with no adverse event	28	(43.1)	30	(46.2)	37	(56.9)	95	(48.7)
with drug-related[†] adverse events	34	(52.3)	29	(44.6)	16	(24.6)	79	(40.5)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	4	(6.2)	4	(6.2)	0	(0.0)	8	(4.1)
discontinued due to a drug-related adverse event	4	(6.2)	4	(6.2)	0	(0.0)	8	(4.1)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the drug.
[‡] Study medication withdrawn.

CONCLUSIONS:	In adolescent subjects with house dust mite-induced allergic rhinitis/rhinoconjunctivitis, with or without asthma: 1) MK-8237 sublingual tablet is generally well tolerated at both doses of 12 DU and 6 DU, with a higher proportion of subjects at both doses reporting AEs compared to placebo; 2) The proportion of subjects who discontinue due to an AE are similar (~6%) between the 12 DU and 6 DU doses of MK-8237; 3) The proportion of subjects reporting pre-specified local adverse experiences expected to commonly occur with application of the MK-8237 sublingual tablet are significantly higher with both doses (12 DU and 6 DU) compared with placebo. These events are generally mild or moderate in intensity; 4) The duration of pre-specified local AEs following the first dose of MK-8237 (12 DU and 6 DU) are self-limited, with median durations up to approximately 45 minutes; and 5) No serious AEs, systemic allergic reactions/anaphylaxis, AEs requiring use of epinephrine, severe local swelling or edema of the mouth and/or throat, or overdose are reported, and no differential AE profile between subjects with asthma and those without asthma are observed.