



Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

Pharmacovigilance Plan Review Memorandum

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Office of Vaccines Research and Review (OVRR)

Subject: BLA 125592/0

Applicant: Merck Sharp & Dohme Corp.

Product: House Dust Mites (*Dermatophagoides farinae* and
Dermatophagoides pteronyssinus) Allergen Extract
Sublingual Tablet
12 SQ-HDM
(MK-8237)
Proposed Trade Name: ODACTRA™

Proposed Indication: As immunotherapy for the treatment of house dust mite
(HDM)-induced allergic rhinitis, with or without
conjunctivitis, confirmed by positive skin test or in vitro
testing for *Dermatophagoides farinae* or *Dermatophagoides*
pteronyssinus IgE antibodies. The product is approved for
use in adults 18 through 65 years of age.

Submission Date: 09-FEB-2016

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1. Introduction

a. Objectives/Scope of the review

This memorandum is in response to a request from the Office of Vaccines Research and Review (OVRR) to the Office of Biostatistics and Epidemiology (OBE) to review the Pharmacovigilance Plan submitted by Merck Sharp & Dohme Corp. for the original BLA 125592/0 seeking initial licensure for the product MK-8237 (House Dust Mites Allergen Extract) developed as immunotherapy for the treatment of house dust mite (HDM)-induced allergic rhinitis (AR). The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance or further studies should the product be licensed.

a. Product description

Dust mites, 8-legged arthropods, thrive in carpeting, fabric-covered furniture and mattresses where humans shed skin – a key food source for the mites (Arlan 2001). House dust mite (HDM) antigen is a common worldwide allergen present in most geographical regions, with *D. farinae* and *D. pteronyssinus* (the most common HDM species in North America and Europe), responsible for more than 90% of HDM allergies worldwide (Thomas 2010). An estimated 84% of US homes have at least detectable levels of dust mite allergen (Portnoy 2013) and in areas where most houses have higher than 2 mcg of mite allergen per gram of dust, sensitization has consistently been found in a large proportion of children with asthma (National Academy of Sciences 2000).

HDM is the most important trigger of perennial allergic rhinitis (AR). The hypersensitivity is IgE-mediated and year round exposure to these environmental aeroallergens results in a greater disease burden due to the chronic nature of symptoms as compared to a seasonal aeroallergen.

Merck Sharp & Dohme Corp. (Sponsor), a subsidiary of Merck & Co., Inc., in collaboration with ALK-Abelló A/S (ALK), has developed a freeze-dried, sublingual pharmaceutical formulation of HDM allergen extract derived from mite (b) (4). This product, MK-8237, contains a 1:1 mixture of *Dermatophagoides farinae* [*D. farinae*/*Der f*/*Der far*] and *Dermatophagoides pteronyssinus* [*D. pteronyssinus*/*Der p*/*Der pte*] and is intended to treat HDM allergic rhinitis (AR) and allergic rhinitis with conjunctivitis (ARC).

One tablet contains 12 Development Units (DU) based upon an in-house reference, corresponding to approximately (b) (4) *D. farinae* and (b) (4) *D. pteronyssinus* (total potency of (b) (4)). The sponsor proposes the term SQ-HDM (SQ referencing potency standardization method) to replace DU for the licensed product.

Proposed Dose

MK-8237, 12 DU, is administered daily without dose escalation and current immunotherapy guidelines recommend continued treatment for at least 3 years for all allergen immunotherapy before discontinuing treatment to allow for the development of sustained clinical remission of allergic disease (Canonica 2014, Bousquet 2009).

b. Pertinent regulatory history

i. US

The product has not been licensed in the US.

- 07-APR-2012 Original IND submitted for HDM-associated AR
- 08-SEP-2015 Pre-BLA Meeting for HDM-associated AR
- 10-FEB-2015 Pre-IND Meeting: prevention of asthma in young children
- 09-FEB-2016 BLA submission

FDA Advisory Committee: No advisory committee is planned for this product.

ii. Europe

MK-8237, developed by ALK, was approved 31-August-2015, in 11 European countries (Austria, Czech Republic, Denmark, Finland, France, Germany, Italy, Norway, Poland, Slovakia and Sweden) as ACARIZAX™ (ACCARIZAX™ in Italy). The product is indicated for adults 18-65 years of age diagnosed by a clinical history and positive test for HDM sensitization with ≥1 of the following:

- Persistent moderate to severe HDM allergic rhinitis despite use of symptom relieving medication
- HDM allergic asthma not well controlled by inhaled corticosteroids and associated with mild to severe HDM allergic rhinitis and where patients' asthma status has been carefully evaluated. (Note: evaluation should include ensuring subject has a FEV1 ≥70% of predicted at initiation of treatment, has had no severe asthma exacerbations within the last 3 months, and has no ongoing respiratory tract infection.)

iii. Japan

ALK's MK-8237 was developed in collaboration with Torii Pharmaceutical Co., Ltd. (Torii) and licensed in Japan 28-SEP-2015 under the trade name of MITICURE™ for treatment of allergic rhinitis caused by house dust mites in those 12 – 64 years of age.

iv. Russia

MK-8237 (b) (4) .

v. Australia and New Zealand

MK-8237 (b) (4) .

2. Materials reviewed

a. Routine items

Module 1.11.4 Multiple Module Information Amendment - Pharmacovigilance Plan

b. Pertinent Module sections of the original licensing application selected by the reviewer

Cover Letter

Module 1.11.4 Pharmacovigilance Plan

Module 1.2 Regulatory History

Module 1.9.4 Pediatric Study Plan; Request for Partial Waiver and Partial Deferral

Module 1.14 Labeling

Module 2.5 Clinical Overview

Module 2.7.4 Summary of Clinical Safety

Module 2.7.6 Synopses of Individual Studies

Module 5.2 Tabular Listing of All Clinical Studies

Module 5.3.5.3.3 Integrated Analysis of Safety (ISS)

c. Other items reviewed

- 125592/0.1 Request for Proprietary Name Review
- 125592/0.8 Safety Update Report (International Postmarketing Experience)
Reporting period: 15-Apr-2015 to 9-Apr-2016
- 125592/0.9 Revised ISS tables restricted to 12 DU dose recipients, patients 18-65 years of age and >65 years of age, reported separately
Submitted in response to FDA Information Request of May 25, 2016
- 125592/0.48 Safety data for subjects in Phase 2 and Phase 3 studies who were crossed over to treatment other than that to which they were originally assigned at randomization, submitted in response to FDA Information Request of December 14, 2016.
[See Addendum to this review]

3. Pharmacovigilance Plan Review**a. Clinical safety database (see review below)****b. Safety concerns including planned pharmacovigilance and sponsor's proposals****i. Important identified safety issues**

- Serious systemic allergic reactions, including anaphylactic reactions
- Local allergic reactions with potential to compromise airway
- Acute worsening of asthma symptoms (exacerbations)

Manufacturer's Planned Actions for all identified safety issues:

Routine pharmacovigilance, use of an event-specific follow-up questionnaire
Appropriate US PI and Medication Guide information

ii. Important potential safety issues

- Anaphylactic shock
- Eosinophilic esophagitis (EoE)

Planned Actions for all potential safety issues:

Routine pharmacovigilance, use of an event-specific follow-up questionnaire
Appropriate US PI and Medication Guide information

iii. Important missing information

- Pregnancy, lactation
- Use in children (<18 years of age)
- Use in elderly (> 65 years of age)
- Use in severe, unstable or uncontrolled asthma
- Co-administration with other sublingual immunotherapy (SLIT) products

Manufacturer's Planned actions for all important missing information:

House Dust Mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract
(MK-8237) Proposed Trade Name: ODACTRAM

Routine pharmacovigilance

Appropriate US label language

Study in children and adolescents ages 5-17 years (see Section 4.b., below)

c. Review of Postmarketing Study proposal or protocol synopsis

Protocol Title: Post-Market Claims and EMR Based Study of Serious Allergic

Reactions and Eosinophilic Esophagitis in Marketed Use of MK-8237 in the United States

Two Phase 4 studies are planned under this PMC at this time: a claims-based study (from a large US health insurance database) and electronic medical record studies (from a large US integrated health system) will aim to assess general safety and specifically assess the risks of:

- Systemic allergic reactions, including anaphylactic reactions / anaphylactic shock
- Serious allergic reactions including local reaction w/ potential to compromise airway
- Eosinophilic esophagitis (EoE)
- Acute worsening of asthma symptoms

These studies will be incorporated into the database already being used for GRASTEK ((Timothy Grass Pollen Allergen Extract) Tablet for Sublingual Use, approved April 11, 2014) and RAGWITEK ((Short Ragweed Pollen Allergen Extract) Tablet for Sublingual Use, approved April 17, 2014). Based upon experience with US uptake of these two products, the sponsor estimates uptake for the DM product at (b) (4) patients over 3 years.

The study protocol, including any synopsis, will be submitted and milestones for this study will be determined after discussion between the sponsor and FDA.

4. Review of other information from the managed review process

a. Non-IND trials

Five clinical trials (P011/MT-01, P012/MT-02, P013/MT-03, P014/MT-04, and P015/MT-06) were conducted with MK-8237 by Merck's Partner, ALK-Abelló A/S. These foreign clinical trials were not conducted under US IND and studied MD-8237 use in asthmatics. The safety data are submitted to the BLA as supportive.

Summary of serious adverse events from clinical studies conducted in Japan

Full study reports are not available to Merck, only summary information on SAEs. No deaths were reported in any of the 3 Torii studies: TO-201 (Phase 1 study of 48 males with asthma); TO-203-AR (Phase 3 study of 946 allergic rhinitis subjects) and TO-203-AA (Phase 3 study of 824 subjects with allergic asthma).

No SAEs were reported in the Torii Phase 1 study and fifty-one SAEs were reported in forty-three subjects in the two Torii Phase 3 studies:

SAEs in fifteen subjects receiving MK-8237 (12 DU)

- Incisional hernia
- Sudden hearing loss
- Gastroenteritis
- Ovarian neoplasm

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- Breast cancer
- Alanine and aspartate aminotransferases increased, hepatic function abnormal
- Gastric cancer
- Asthma (onset: Day 163)
- Alanine aminotransferase increased, liver disorder
- Breast cancer
- Cervical dysplasia
- Anal fissure
- Back pain
- Abortion
- Arthroscopy

SAEs in twelve subjects receiving MK-8237 (6 DU)

- Tonsillitis
- Hemorrhoid operation
- Tooth hypoplasia
- Ulnar fracture
- Appendicitis
- Humerus fracture
- Blood pressure decreased
- Intervertebral disc protrusion
- Cervical dysplasia
- Pneumonia bacterial
- Abortion
- Enterocolitis

SAEs in sixteen subjects receiving placebo

- Contusion, haematoma evacuation
- Anaphylactic reaction (Day 74)
- Gastric cancer
- Premature labor, low birth weight baby, Apgar score low
- Pain
- Asthma (Day 37)
- Diverticulitis
- Gastroenteritis
- Influenza
- Osteonecrosis
- Enterocolitis
- Alanine and aspartate aminotransferases increased, autoimmune hepatitis*
- Pelvic infection
- Sudden hearing loss
- Imminent abortion
- Uterine leiomyoma

*SAEs reported as drug-related by the sponsor

House Dust Mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract (MK-8237) Proposed Trade Name: ODACTRAM

b. Pediatric Development Plan

Partial Waiver

A Partial Waiver is requested for the age range below 5 years of age as:

- The drug product does not represent a meaningful therapeutic benefit over existing therapies for children under the age of 5 years.
- Necessary studies are impossible or highly impracticable because the number of children younger than 5 years of age with allergic rhinitis who have been diagnostically confirmed with sensitivity to house dust mite is too small.
- Additionally, immunotherapy for AR/ARC is not likely to be used in a substantial ($\geq 50,000$ patients in the US) number of very young children.

Partial Deferral

A Partial Deferral to the pediatric requirement in children 5 to < 17 years of age is requested. The sponsor plans to conduct the following studies in support of use in this age group with a database of approximately 1000 subjects, 5-17 years of age, using 12 DU MK-8237 for at least 28 days):

Completed pediatric study:

Phase 1 Safety Study in 12-17 year olds (see Section 4.c.i., below)

Planned pediatric study #1:

Phase 3, double-blind, parallel-group, placebo-controlled trial to evaluate safety, tolerability, and efficacy of MK-8237 in pediatric subjects (5 - 17 years of age) with HDM-induced AR with or without asthma

Sample size: N ~ 580

Entry criteria

1. ≥ 5 and ≤ 17 years of age
2. ≥ 6 month history of HDM-induced allergic rhinitis/rhinoconjunctivitis (with or without asthma) requiring anti-allergy treatment during the prior year.
3. Positive skin prick test (average wheal diameter of two tests must be ≥ 5 mm larger than saline control) to *D. pteronyssinus* and/or *D. farinae* at screening.
4. Specific *D. pteronyssinus* and/or *D. farinae* IgE of \geq Class 2 [0.7 kU/L] at screening
5. FEV1 $\geq 80\%$ of predicted at Screening, Run-in, and Randomization Visits (following ≥ 6 hour wash-out of short acting beta2 agonist or ≥ 12 hour wash-out of long-acting beta-2 agonist)
6. Meeting symptom threshold during Run-in period
7. No immunosuppressive treatment within 3 months prior to screening
8. No unstable or severe asthma or prior life-threatening asthma attack or an occurrence of any clinical deterioration of asthma that resulted in emergency treatment, hospitalization, or treatment with systemic corticosteroids at any time within 3 months prior to screening visit
9. No asthma requiring high-dose inhaled corticosteroids (ICS) within 6 months prior to screening
10. No history of anaphylaxis with cardiorespiratory symptoms due to prior immunotherapy, unknown cause, or inhalant allergy
11. No history of chronic urticaria and/or angioedema within 2 years prior to screening and run-in
12. No immunotherapy with HDM allergen for >1 month and within 5 years prior to screening
13. No prior exposure to MK-8237
14. No ongoing treatment with any specific immunotherapy

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15. No history of allergy, hypersensitivity or intolerance to investigational medicinal products (except for *D. pteronyssinus* and/or *D. farinae*), rescue medications, self-injectable epinephrine
16. Not nursing, pregnant or expecting to conceive during the study

Run-in Period

- Daily symptoms recorded in an e-diary for up to 6 weeks
- Symptoms scores will determine whether a subject meets an appropriate symptom threshold during a time when they are expected to have natural exposure to HDM and when allergy relieving medications have been temporarily interrupted following a washout.
- In temperate climates, this period is intended not to overlap with pollen seasons in order to minimize exposure to non-HDM allergens, which may also cause allergic rhinitis symptoms
- This pre-randomization period may last for up to ~ 1 year

Treatment

MK-8237 12 DU or placebo daily for up to ~ 52 weeks (equal randomization), with the majority of subjects anticipated to receive a total of 32-40 weeks of treatment

Safety Evaluations (including induction and efficacy assessment period)

- Safety will be monitored as in P001, the adult pivotal Phase 3 trial:
 - AE collection cards Days 1-28 for all adverse events and to prompt for AEs associated with sublingual immunotherapy; filled out daily by subjects or parents
 - eCRFs will capture AEs reported during office visits or telephone contacts
- Symptoms and use of study reliever (symptomatic rescue) medication will be recorded during the last 12 weeks of treatment in daily electronic diary (e-diary)
- The last 8 weeks of the Treatment phase will be used as the efficacy assessment period, as this period is anticipated to occur when there is limited interference by other aeroallergens (e.g., pollens), HDM exposure is predominant, and subjects are affected most by HDM-induced AR symptoms.

Study Timeline

Protocol submission	4Q 2017
Start Screening	4Q 2018
Start Randomization	4Q 2019

Efficacy Assessments

Cohort 1 HDM peak season	2020-2021
Cohort 2* HDM peak season	2021-2022
Last patient visit	1Q 2021*
Submission of CSR	3Q 2021*
Supplemental BLA	3Q 2022 (if a 2 nd season is required)

*Extension of the study to a second season may be required depending on ability to randomize a sufficient number of subjects and deliver adequate induction prior to the efficacy peak HDM seasons.

Planned pediatric study #2:

Phase 3 double-blind, parallel-group, placebo-controlled trial to further evaluate the safety and tolerability of MK-8237 in pediatric subjects (5 to 17 years of age) with HDM-induced AR/ARC with or without asthma

- Approximately ~270 pediatric subjects will be treated over a longer duration of 28 - 52 weeks

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- AE collection cards will be filled out daily by subjects or parents, Days 1-28, to collect AEs as well as to prompt for AEs associated with sublingual immunotherapy
- Descriptive study, no hypothesis testing, endpoints or thresholds to trigger additional action

Study Timeline

Protocol submission	4Q 2017
Start Screening**	1Q 2020
Start Randomization	4Q 2020
Last patient visit	1Q 2022
Submission of CSR	3Q 2022
sBLA submission	3Q 2022

** Screening of Efficacy and Safety trials will be separated to avoid competition for recruitment between them.

c. Clinical safety data

i. Clinical Overview

The US clinical program for the development of MK-8237 for treatment of HDM-induced allergic rhinitis, with or without conjunctivitis, encompasses eight randomized, double-blind, placebo-controlled studies: three phase 1 studies, two phase 2 studies and three phase 3 studies.

Please note: DE defers to OVRP for full clinical review of premarket clinical safety database.

Study								Population				
Protocol	Phase	Location	Number enrolled	Safety	Efficacy	Dose-finding	Duration	Allergic rhinitis	Rhinoconjunctivitis	Asthma	Environmental Exposure Chamber	Age (years)
P011 / MT-01 ^{1,4}	1	Europe	71	X			28 days	+/-	+/-	X		18-65
P013 / MT-03 ^{1,4}	1	Europe	72	X		X	28 days	+/-	NS	X		5-14
P008 ⁵	1	N. America	195	X			28 days	X	X	+/-		12-17
P012 / MT-02 ^{1,4}	2	Europe	604	X	X	X	12 months	X	NS	X		≥14
P003 ^{3,5}	2	Europe	124	X	X	X	6 months	X	X	+/-	X	≥18
P014 / MT-04 ^{1,4}	3	Europe	834	X	X		14 months	X	NS	X		≥18
P015 / MT-06 ^{2,4}	3	Europe	992	X	X		12 months	X	NS	+/-		18-65
P001 ⁵	3	N. America	1482	X	X		≤12 months	X	X	+/-		≥12

1. Supportive safety data from non-IND studies (treatment of allergic asthma ± allergic rhinitis) included in this BLA.
 2. Supportive safety data from non-IND Phase 3 study (allergic rhinitis ± allergic asthma) included in this BLA
 3. Environmental chamber challenge; 4. ALK sponsored trial; 5. Merck sponsored trial
 NS: Not specified
 From STN 125592, Module 2.5, Table 2.5:1 and Module 2.7.4, Table 2.7.4:1

Events of clinical interest (ECIs) actively monitored during trials:

- Anaphylactic reactions, anaphylaxis and/or systemic allergic reactions

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- The assessment of anaphylaxis was guided by the recommendations in the Food Allergy & Anaphylaxis Network (FAAN) Report which proposed clinical criteria that would increase diagnostic precision in anaphylaxis (Sampson 2005; Sampson 2006).
- Events treated with epinephrine
- Severe local swelling or edema of the mouth and/or throat
- AST or ALT laboratory value greater than or equal to 3X the upper limit of normal and an elevated total bilirubin laboratory value greater than or equal to 2X the upper limit of normal.
- Overdose: above prescribed dose without associated clinical or laboratory abnormalities

Overview of treatment including dose ranging across studies

A total of 2734 subjects with a history of HDM allergy (allergic rhinitis/allergic rhinoconjunctivitis [AR/C] and/or asthma) received at least one dose of MK-8237 (0.5-32 DU) in randomized trials, with treatment durations ranging from a single dose to daily doses for up to approximately 18 months.

Study MT-01 evaluated MK-8237 doses from 0.5 – 32 DU. The 32 DU dose group was discontinued after one subject developed vomiting 15 minutes following tablet administration. After completion of study MT-01, the 16 DU dose was not further investigated due to the persistent nature of local adverse events which included swelling, moderate throat tightness and severe mouth oedema. There were no severe local swellings at doses lower than 16 DU, thus the 6 DU and 12 DU doses were selected for study in Phase 2 and 3 trials.

Overview of safety data across studies

The safety analysis population included all randomized subjects based upon treatment group assignment. Phase 2 and Phase 3 safety data were pooled to better characterize the safety profile of MK-8237 and includes subjects treated with 6 DU, 12 DU, and placebo doses. Studies MT-02 and MT-04 enrolled asthmatics who also had HDM allergic Rhinoconjunctivitis; studies P003, MT-06 and P001 enrolled individuals with HDM allergic rhinoconjunctivitis, many also had asthma.

Extent of exposure to the study drug

Phase 1 studies MT-01 and MT-03 were designed to study MK-8237 doses from 0.5 to 32 DU daily; however, the 32 DU dose group was discontinued after a single subject developed vomiting 15 minutes after tablet administration. The 16 DU dose was associated with persistent local adverse events including swellings (not further described), one occurrence of moderate throat tightness and two occurrences of severe mouth oedema, and the two subsequent Phase I trials, MT-03 and P008 evaluated doses up to 12 DU.

Phase 2 and Phase 3 subjects received 6 DU, 12 DU or placebo daily as summarized in the following table.

Table 2: Extent of Exposure – Phase 2 and Phase 3 studies¹		
	MK-8237 (12 DU)	MK-8237 (6 DU)
Subjects¹ in population	1383	808
Duration of exposure ² (days)		
Mean	281.4	345.4

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		MK-8237 (12 DU)	MK-8237 (6 DU)
Subjects¹ in population		1383	808
SD		125.8	111.64
Median		300.5	363
Range		0 to 550	0 to 550

1. All randomized subjects except MT-02 where only those randomized to MK-8237 (6 DU) and placebo are included
 2. Each subject counted once in each applicable dose category column and duration of exposure row.
 3. Duration of exposure was calculated assuming one day of dosing = 1 day of exposure.
 From STN 125592.0, Module 5.3.5.3.3, Table 1

Demographic data

Subjects were predominantly young, White adults, as illustrated in the following table summarizing the Phase 2 and Phase 3 populations.

		MK-8237 12 DU		MK-8237 6 DU		Placebo	
		n	(%)	n	(%)	n	(%)
Subjects in population		1,383	(100)	808	(100)	1,540	(100)
Gender	Male	629	(45.5)	392	(48.5)	728	(47.3)
	Female	754	(54.5)	416	(51.5)	812	(52.7)
Age (Years)	12 to <18	95	(6.9)	9	(1.1)	106	(6.9)
	18 to <50	1,105	(79.9)	719	(89.0)	1,247	(81.0)
	50 to <65	169	(12.2)	72	(8.9)	164	(10.6)
	≥65	14	(1.0)	8	(1.0)	23	(1.5)
	Mean	33.8		32.4		33.6	
	SD	12.7		11.5		12.7	
	Median	32.0		30.0		32.0	
	Range	12 to 77		15 to 75		12 to 85	
Race	American Indian or Alaska Native	6	(0.4)	0	(0.0)	4	(0.3)
	Asian	56	(4.0)	7	(0.9)	55	(3.6)
	Black or African American	82	(5.9)	2	(0.2)	78	(5.1)
	Multi-Racial	39	(2.8)	1	(0.1)	46	(3.0)
	Other	2	(0.1)	7	(0.9)	6	(0.4)
	White	1,195	(86.4)	791	(97.9)	1,347	(87.5)
	Unknown/Missing	3	(0.2)	0	(0.0)	4	(0.3)
	Hispanic or Latino	71	(5.1)	1	(0.1)	68	(4.4)
	Not Hispanic or Latino	1,301	(94.1)	807	(99.9)	1,451	(94.2)
	Unknown/Missing	11	(0.8)	0	(0.0)	21	(1.4)
Allergic characteristics	With asthma	686	(49.6)	594	(73.5)	2,100	(56.4)
	Sensitized to HDM only	394	(28.5)	224	(27.7)	415	(26.9)
	Sensitized to HDM and others	987	(71.4)	581	(71.9)	1,117	(72.5)

1. All randomized subjects except MT-02 where only those randomized to MK-8237 (6 DU) and placebo are included
 From STN 125592.0, Module 5.3.5.3.3 Table 10 and Table

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Subject disposition

The proportion of subjects completing the studies was highest in the placebo groups (83.0% overall in Phase 2 and Phase 3 studies), and lowest in the MK-8237 (12 DU) treatment group (78.5% overall in Phase 2 and Phase 3 studies).

In the Phase 1 clinical trials, 9 subjects (1 in MT-01 and 8 in P008) discontinued due to AEs, all considered drug related by the manufacturer, and all classified as non-serious. In Phase 2 and Phase 3 clinical trials, a total of 180 subjects (4.8%) discontinued due to AEs. The percentage of discontinuations due to AEs was greater in the 12 DU group (n=113; 8.2%) than in the 6 DU group (n=26; 3.2%), and least in the placebo group (n=40; 2.6%) as seen in the table below.

	MK-8237 (12 DU)		MK-8237 (6 DU)		Placebo	
	N = 1383		N = 808		N = 1540	
	n	%	n	%	n	%
Completed	1086	78.5	676	83.7	1278	83.0
Discontinued	296	21.4	132	16.3	262	17.0
Adverse event	114	8.2	26	3.2	40	2.6
Lack of efficacy	2	0.1	3	0.4	4	0.3
Lost to follow-up	46	3.3	16	2.0	44	2.9
Non-Compliance with study drug	0	0.0	0	0.0	5	0.3
Other	31	2.2	34	4.2	35	2.3
Physician decision	2	0.1	0	0.0	3	0.2
Pregnancy	3	0.2	2	0.2	16	1.0
Progressive disease	1	0.1	0	0.0	0	0.0
Protocol violation	14	1.0	12	1.5	21	1.4
Technical problems	0	0.0	0	0.0	1	0.1
Withdrawal by subject	83	6.0	39	4.8	93	6.0
Status not recorded	1	0.1	0	0.0	0	0.0
Treatment interruption	138	9.9	89	11.0	80	5.2

1. All randomized subjects except MT-02 (MK-8237, 6 DU and placebo subjects only). Subject classified by last recorded disposition. From STN 125592.0, Module 2.5, Table 12, Module 5.3.5.3.3, Table 9

Safety data from Phase 2 and Phase 3 studies

A dose-response was seen in the rates of overall AEs (82.9%, 68.6% and 63.6%) and of drug-related AEs (68.8%, 44.1% and 27.5%), but not in the overall rates of SAEs (1.2%, 2.5% and 2.0%) in the 12 DU, 6 DU and placebo groups, respectively.

Category	12 DU		6 DU		Placebo	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total subjects	1382		808		1540	
Any adverse event	1146	(82.9)	554	(68.6)	979	(63.6)
Death	0	(0.0)	0	(0.0)	0	(0.0)
Serious adverse event ⁵	17	(1.2)	20	(2.5)	31	(2.0)
Discontinued due to an adverse event	113	(8.2)	26	(3.2)	41	(2.7)
Discontinued ² due to a serious adverse event	5	(0.4)	3	(0.4)	10	(0.6)
Drug-related ³ adverse event	951	(68.8)	356	(44.1)	423	(27.5)
Drug-related ³ serious adverse event	3	(0.2)	2	(0.2)	2	(0.1)
Drug-related ³ adverse event leading to discontinuation	113	(8.2)	26	(3.2)	41	(2.7)
Drug-related ³ serious adverse event leading to discontinuation ^{4,5}	1	(0.1)	0	(0.0)	2	(0.1)

1. All randomized subjects except study MT-02 where only MK-8237 (6 DU) & placebo recipients are included; 2. Study medication withdrawn; 3. Determined by the investigator to be related to the study drug; 4. Two subjects (12 DU group) had accidental overdoses, i.e., total daily dose of 24 DU, and subsequent development of mild adverse events (oral pruritus and throat irritation in one subject and oral pain in the other). In Merck-sponsored trials, reports of adverse events associated with an overdose were classified as serious for safety monitoring; reports of overdose without additional adverse events were classified as non-serious events of clinical interest (ECI). Adverse events reported for the two subjects identified as having had an accidental overdose are not listed in this table as serious as they did not meet International Conference on Harmonisation (ICH) criteria for seriousness. Adverse events for both subjects assessed as drug-related by the investigator.
From STN 125592.0, Module 2.5, Table 2.5: 13

In response to FDA/OVRR’s request, the sponsor additionally provided these data from adults in Phase 2 and Phase 3 studies who received MK-8273 12 DU dose, with those 18-65 years of age and those >65 years of age reported separately. There do not appear to be any notable differences between the results in Table 5b, below, as compared to Table 5a, above. The numbers of individuals in the >65 years of age group are quite small, making it difficult to draw any useful conclusions from those results.

Category	18-65 years of age				>65 years of age			
	12 DU		Placebo		12 DU		Placebo	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
Total subjects	1,277		1,282		11		20	
Any adverse event	1,047	(82.0)	811	(63.3)	10	(90.9)	16	(80.0)
Death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Serious adverse event ⁵	16	(1.3)	23	(1.8)	1	(9.1)	2	(10.0)
Discontinued due to an adverse event	104	(8.1)	38	(3.0)	0	(0.0)	1	(5.0)
Discontinued ² due to a serious adverse event	5	(0.4)	8	(0.6)	0	(0.0)	1	(5.0)
Drug-related ³ adverse event	857	(67.1)	351	(27.4)	7	(63.6)	7	(35.0)
Drug-related ³ serious adverse event	3	(0.2)	2	(0.2)	0	(0.0)	0	(0.0)
Drug-related ³ adverse event leading to discontinuation	82	(6.4)	11	(0.9)	0	(0.0)	0	(0.0)
Drug-related ³ serious adverse event leading to discontinuation ^{4,5}	1	(0.1)	2	(0.2)	0	(0.0)	0	(0.0)

1. Adult recipients receiving MK-8273 (12 DU dose) in Studies MT-04, P003, MT-06, P001
2. Study medication withdrawn
3. Determined by the investigator to be related to the study drug
4. Two subjects had an accidental overdose (each with total daily dose of 24 DU) and subsequent development of mild adverse events (oral pruritus and throat irritation in one subject, and oral pain in the other subject). In Merck-sponsored trials, reports of adverse events associated with an overdose were classified as serious for safety monitoring; reports of overdose without additional adverse events were classified as non-serious events of clinical interest (ECI). The adverse events reported for the two subjects identified as having had an accidental overdose are not listed in this table as serious as they did not meet International Conference on Harmonisation (ICH) criteria for seriousness. The adverse events for both subjects were assessed as drug-related by the investigator.
From STN 125592.0009, Table 1 (selected ISS data restricted to 12 DU dose adult recipients)

The most commonly reported AEs classified as drug-related by the manufacturer were events localized in or around the mouth, in the throat, or in the ear and showed a dose-response relationship to MK-8237 dose. The three most commonly reported specific AEs by MedDRA Preferred Term, each occurring in ≥15% of subjects in the 12 DU group, were ear pruritus, oral pruritus, and throat irritation. The median time from treatment initiation to onset in the 12 DU group was 1 day with median duration ranging between 30-42 minutes for these AEs.

Table 6a: Adverse events in Phase 2 and Phase 3 studies¹ by SOC and PT (incidence > 2% in any treatment group)						
	MK-8237 12 DU N = 1,383		MK-8237 6 DU N = 808		Placebo N = 1,540	
	n	%	n	%	n	%
Subjects reporting ≥ 1 adverse event	1,146	(82.9)	554	(68.6)	979	(63.6)
Ear and labyrinth disorders	427	(30.9)	43	(5.3)	102	(6.6)
Ear pruritus	413	(29.9)	33	(4.1)	95	(6.2)
Eye disorders	61	(4.4)	23	(2.8)	64	(4.2)
Eye pruritus	28	(2.0)	5	(0.6)	22	(1.4)
Gastrointestinal disorders	867	(62.7)	306	(37.9)	359	(23.3)
Abdominal pain upper	100	(7.2)	10	(1.2)	48	(3.1)
Diarrhoea	67	(4.8)	7	(0.9)	31	(2.0)
Dyspepsia	34	(2.5)	16	(2.0)	0	(0.0)
Glossodynia	133	(9.6)	13	(1.6)	28	(1.8)
Lip oedema	28	(2.0)	9	(1.1)	4	(0.3)
Lip swelling	161	(11.6)	14	(1.7)	20	(1.3)
Mouth swelling	83	(6.0)	10	(1.2)	12	(0.8)
Mouth ulceration	85	(6.1)	0	(0.0)	30	(1.9)
Nausea	134	(9.7)	4	(0.5)	62	(4.0)
Oedema mouth	59	(4.3)	61	(7.5)	1	(0.1)
Oral pruritus	594	(43.0)	136	(16.8)	131	(8.5)
Palatal swelling	82	(5.9)	0	(0.0)	11	(0.7)
Paraesthesia oral	106	(7.7)	42	(5.2)	24	(1.6)
Stomatitis	31	(2.2)	9	(1.1)	15	(1.0)
Swollen tongue	137	(9.9)	8	(1.0)	18	(1.2)
Tongue pruritus	67	(4.8)	33	(4.1)	14	(0.9)
Tongue ulceration	96	(6.9)	0	(0.0)	22	(1.4)
Vomiting	36	(2.6)	3	(0.4)	15	(1.0)
General disorders and administration site conditions	82	(5.9)	28	(3.5)	70	(4.5)
Infections and infestations	474	(34.3)	314	(38.9)	526	(34.2)
Bronchitis	43	(3.1)	31	(3.8)	46	(3.0)
Influenza	34	(2.5)	25	(3.1)	32	(2.1)
Nasopharyngitis	164	(11.9)	137	(17.0)	188	(12.2)
Pharyngitis	43	(3.1)	32	(4.0)	46	(3.0)
Respiratory tract infection	10	(0.7)	20	(2.5)	16	(1.0)
Sinusitis	42	(3.0)	19	(2.4)	42	(2.7)
Upper respiratory tract infection	93	(6.7)	36	(4.5)	116	(7.5)
Viral infection	22	(1.6)	18	(2.2)	15	(1.0)
Injury, poisoning and procedural complications	105	(7.6)	35	(4.3)	118	(7.7)
Accidental overdose	44	(3.2)	6	(0.7)	41	(2.7)

Table 6a: Adverse events in Phase 2 and Phase 3 studies¹ by SOC and PT (incidence > 2% in any treatment group)						
Musculoskeletal and connective tissue disorders	74	(5.4)	32	(4.0)	69	(4.5)
Nervous system disorders	164	(11.9)	52	(6.4)	128	(8.3)
Dysgeusia	76	(5.5)	1	(0.1)	29	(1.9)
Headache	50	(3.6)	29	(3.6)	77	(5.0)
Respiratory, thoracic and mediastinal disorders	718	(51.9)	211	(26.1)	394	(25.6)
Asthma	40	(2.9)	44	(5.4)	57	(3.7)
Cough	35	(2.5)	17	(2.1)	36	(2.3)
Dyspnoea	26	(1.9)	21	(2.6)	29	(1.9)
Oropharyngeal pain	39	(2.8)	21	(2.6)	29	(1.9)
Pharyngeal oedema	123	(8.9)	11	(1.4)	23	(1.5)
Rhinitis allergic	20	(1.4)	27	(3.3)	32	(2.1)
Throat irritation	603	(43.6)	91	(11.3)	192	(12.5)
Skin and subcutaneous tissue disorders	95	(6.9)	43	(5.3)	98	(6.4)
1. All randomized subjects except study MT-02 where only MK-8237 (6 DU) & placebo recipients are included. Every subject is counted a single time for each applicable row and column. A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding. For MT-02, only subjects randomized to MK-8237 6 DU and placebo were included. From STN 125592.0, Module 2.7.4, Table 16						

In response to FDA/OVRR’s request, the sponsor additionally provided these data from adults in Phase 2 and Phase 3 studies who received MK-8273 12 DU dose, with those 18-65 years of age and those >65 years of age reported separately. There do not appear to be any notable differences between the results in Table 6b, below, as compared to Table 6a, above, although the incidence of several events rise above the 2% cutoff in the adult-only group and are listed in Table 6b, e.g., various cardiac disorders, although the database is underpowered to detect significant differences between groups. As in Table 5b, the numbers of individuals in the >65 years of age group are quite small, making it difficult to draw any useful conclusions from those results.

Table 6b: Adverse events in in adults in Phase 2 and Phase 3 studies¹ - 12 DU dose (incidence > 2% in any treatment group any treatment group)								
	18-65 years of age				> 65 years of age			
	MK-8237 12 DU N = 1,277		Placebo N = 1,282		MK-8237 12 DU N = 11		Placebo N = 20	
	n	%	n	%	n	%	n	%
Subjects reporting ≥ 1 adverse event	1,047	(82.0)	811	(63.3)	10	(90.9)	16	(80.0)
Cardiac disorders	8	(0.6)	6	(0.5)	1	(9.1)	2	(10.0)
Coronary artery disease	1	(0.1)	0	(0.0)	1	(9.1)	0	(0.0)
Myocardial infarction	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.0)
Tachycardia	1	(0.1)	1	(0.1)	0	(0.0)	1	(5.0)
Ear and labyrinth disorders	376	(29.4)	90	(7.0)	3	(27.3)	1	(5.0)
Ear pruritus	364	(28.5)	83	(6.5)	2	(18.2)	1	(5.0)
Sudden hearing loss	0	(0.0)	0	(0.0)	1	(9.1)	0	(0.0)
Eye disorders	58	(4.5)	55	(4.3)	2	(18.2)	3	(15.0)
Cataract	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.0)
Eye irritation	5	(0.4)	1	(0.1)	1	(9.1)	0	(0.0)
Eye pruritus	26	(2.0)	19	(1.5)	1	(9.1)	2	(10.0)

House Dust Mites (Dermatophagoides farinae and Dermatophagoides pteronyssinus) Allergen Extract
(MK-8237) Proposed Trade Name: ODACTRAM

Table 6b: Adverse events in adults in Phase 2 and Phase 3 studies1 - 12 DU dose (incidence > 2% in any treatment group any treatment group)								
Gastrointestinal disorders	781	(61.2)	304	(23.7)	7	(63.6)	5	(25.0)
Abdominal pain upper	77	(6.0)	33	(2.6)	1	(9.1)	0	(0.0)
Diarrhoea	59	(4.6)	29	(2.3)	1	(9.1)	0	(0.0)
Dyspepsia	34	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrooesophageal reflux disease	20	(1.6)	3	(0.2)	0	(0.0)	1	(5.0)
Glossodynia	109	(8.5)	23	(1.8)	1	(9.1)	1	(5.0)
Lip oedema	27	(2.1)	4	(0.3)	0	(0.0)	0	(0.0)
Lip pain	1	(0.1)	0	(0.0)	1	(0.0)	0	(0.0)
Lip swelling	140	(11.0)	19	(1.5)	3	(27.3)	0	(0.0)
Mouth swelling	74	(5.8)	10	(0.8)	0	(0.0)	0	(0.0)
Mouth ulceration	73	(5.7)	27	(2.1)	2	(18.2)	0	(0.0)
Nausea	117	(9.2)	51	(4.0)	1	(9.1)	0	(0.0)
Oedema mouth	58	(4.5)	1	(0.1)	1	(9.1)	0	(0.0)
Oral pain	23	(1.8)	6	(0.5)	0	(0.0)	1	(5.0)
Oral pruritus	522	(40.9)	109	(8.5)	3	(27.3)	3	(15.0)
Palatal swelling	71	(5.6)	9	(0.7)	1	(9.1)	1	(5.0)
Paraesthesia oral	101	(7.9)	23	(1.8)	0	(0.0)	0	(0.0)
Stomatitis	27	(2.1)	14	(1.1)	0	(0.0)	0	(0.0)
Swollen tongue	117	(9.2)	14	(1.1)	1	(9.1)	1	(5.0)
Tongue pruritus	64	(5.0)	14	(1.1)	0	(0.0)	0	(0.0)
Tongue ulceration	80	(6.3)	16	(1.2)	2	(18.2)	2	(10.0)
Vomiting	31	(2.4)	13	(1.0)	0	(0.0)	0	(0.0)
General disorders & administration site conditions	78	(6.1)	58	(4.5)	0	(0.0)	3	(15.0)
Asthenia	3	(0.2)	1	(0.1)	0	(0.0)	1	(5.0)
Chest discomfort	12	(0.9)	7	(0.5)	0	(0.0)	1	(5.0)
Fatigue	19	(1.5)	12	(0.9)	0	(0.0)	1	(5.0)
Immune system disorders	8	(0.6)	15	(1.2)	0	(0.0)	1	(5.0)
Allergy to animal	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.0)
Infections and infestations	446	(34.9)	432	(33.7)	6	(54.5)	7	(35.0)
Bronchitis	42	(3.3)	41	(3.2)	0	(0.0)	0	(0.0)
Conjunctivitis	3	(0.2)	4	(0.3)	1	(9.1)	0	(0.0)
Diverticulitis	2	(0.2)	1	(0.1)	1	(9.1)	0	(0.0)
Influenza	30	(2.3)	23	(1.8)	0	(0.0)	1	(5.1)
Lower respiratory tract infection	5	(0.4)	4	(0.3)	0	(0.0)	1	(5.1)
Nasopharyngitis	155	(12.1)	152	(11.9)	3	(27.3)	3	(15.0)
Pharyngitis	42	(3.3)	41	(3.2)	0	(0.0)	0	(0.0)
Rhinitis	14	(1.1)	8	(0.6)	1	(9.1)	0	(0.0)
Sinusitis	39	(3.1)	38	(3.0)	0	(0.0)	0	(0.0)
Upper respiratory tract infection	88	(6.9)	94	(7.3)	2	(18.2)	3	(15.0)
Urinary tract infection	8	(0.6)	15	(1.2)	1	(9.1)	0	(0.0)
Vaginal infection	3	(0.2)	2	(0.2)	1	(9.1)	0	(0.0)
Viral upper respiratory tract infection	11	(0.9)	20	(1.6)	0	(0.0)	1	(5.0)
Injury, poisoning and procedural complications	98	(7.7)	102	(8.0)	1	(9.1)	1	(5.0)
Accidental overdose	40	(3.1)	36	(2.8)	1	(9.1)	1	(5.0)
Procedural pain	4	(0.3)	4	(0.3)	0	(0.0)	1	(5.0)
Metabolism and nutrition disorders	13	(1.0)	10	(0.8)	0	(0.0)	1	(5.0)
Dyslipidaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.0)
Musculoskeletal and connective tissue disorders	70	(5.5)	57	(4.4)	1	(9.1)	1	(5.0)

Table 6b: Adverse events in in adults in Phase 2 and Phase 3 studies1 - 12 DU dose (incidence > 2% in any treatment group any treatment group)								
Arthralgia	8	(0.6)	8	(0.6)	1	(9.1)	0	(0.0)
Musculoskeletal pain	6	(0.5)	4	(0.3)	1	(9.1)	0	(0.0)
Osteoarthritis	2	(0.2)	2	(0.2)	0	(0.0)	1	(5.0)
Nervous system disorders	155	(12.1)	109	(8.5)	2	(18.2)	0	(0.0)
Dysgeusia	69	(5.4)	25	(2.0)	2	(18.2)	0	(0.0)
Headache	48	(3.8)	67	(5.2)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	640	(50.1)	317	(24.7)	4	(36.4)	7	(35.0)
Asthma	40	(3.1)	44	(3.4)	0	(0.0)	1	(5.0)
Cough	32	(2.5)	31	(2.4)	1	(9.1)	2	(10.0)
Dyspnoea	26	(2.0)	25	(2.0)	0	(0.0)	0	(0.0)
Oropharyngeal pain	37	(2.9)	23	(1.8)	0	(0.0)	1	(5.0)
Pharyngeal erythema	17	(1.3)	5	(0.4)	1	(9.1)	0	(0.0)
Pharyngeal inflammation	1	(0.1)	1	(0.1)	0	(0.0)	1	(5.0)
Pharyngeal oedema	105	(8.2)	15	(1.2)	1	(9.1)	0	(0.0)
Respiratory tract congestion	1	(0.1)	2	(0.2)	0	(0.0)	1	(5.0)
Rhinitis allergic	20	(1.6)	29	(2.3)	0	(0.0)	0	(0.0)
Rhinorrhoea	9	(0.7)	10	(0.8)	0	(0.0)	1	(5.0)
Throat irritation	529	(41.4)	153	(11.9)	4	(36.4)	3	(15.0)
Skin and subcutaneous tissue disorders	88	(6.9)	79	(6.2)	0	(0.0)	4	(20.0)
Hyperhidrosis	2	(0.2)	0	(0.0)	0	(0.0)	1	(5.0)
Pruritus	15	(1.2)	12	(0.9)	0	(0.0)	1	(5.0)
Urticaria	24	(1.9)	15	(1.2)	0	(0.0)	2	(10.0)

1. Adult recipients receiving MK-8273 (12 DU dose) in Studies MT-04, P003, MT-06, P001 (the only Phase II-III trials that tested the MK-8237 12 DU dose)
 Every subject is counted a single time for each applicable row and column.
 A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
 From STN 125592.0009, Table 2 (selected ISS data restricted to 12 DU dose adult recipients)

Deaths

No cases of deaths or anaphylactic shock were reported within the clinical development program.

Serious adverse events

These included events described as one or more of the following:

- | | |
|---|--|
| Death | Life-threatening |
| Persistent or significant disability/incapacity | Resulted in or prolonged inpatient hospitalization |
| Congenital anomaly/birth defect | Cancer* |
| Associated with an overdose** | Any important medical event |

*In Merck-sponsored trials, reports of cancer were classified as serious, whether or not other serious criteria were met.

**In Merck-sponsored trials, reports of adverse events associated with an overdose were classified as serious and reports of overdose without additional adverse events were classified as non-serious events of clinical interest (ECI)

NOTE: These above types of adverse events were not necessarily classified as serious in and of themselves, in ALK-sponsored trials, but were included in the safety data bases for each ALK-sponsored study. (see Table 1, including footnotes for trials listed by sponsor)

Serious adverse events in Phase 1 studies

A single serious adverse event was reported in Phase 1 studies. A child in study MT03 experienced an asthmatic crisis with hospitalization prior to receiving any study treatment. This subject fully recovered and continued on study as planned.

Serious adverse events in Phase 2 and Phase 3 studies

Serious adverse events were reported in 68 subjects: 37 on MK-8237 (17 on 12 DU and 20 on 6 DU) and 31 on placebo in the five Phase 2 and 3 studies.

Table 7: Summary of all serious adverse events – Phase 2 and/or 3 clinical studies¹						
MedDRA System Organ Class	Dose (MK-8237)					
	12 DU N=1,383		6 DU N=808		Placebo N=1,540	
	n	%	n	%	n	%
Subjects reporting any serious adverse event	15	(1.1)	20	(2.5)	31	(2.0)
Blood and lymphatic system disorders	0	(0.0)	1	(0.1)	0	(0.0)
Cardiac disorders	1	(0.1)	1	(0.1)	1	(0.1)
Ear and labyrinth disorders	2	(0.1)	0	(0.0)	1	(0.1)
Eye disorders	0	(0.0)	1	(0.1)	1	(0.1)
Gastrointestinal disorders	0	(0.0)	2	(0.2)	5	(0.3)
Hepatobiliary disorders	0	(0.0)	1	(0.1)	2	(0.1)
Immune system disorders	0	(0.0)	0	(0.0)	2	(0.1)
Injury, poisoning and procedural complications	2	(0.1)	2	(0.2)	6	(0.4)
Musculoskeletal and connective tissue disorders	1	(0.1)	1	(0.1)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0)	0	(0.0)	4	(0.3)
Nervous system disorders	0	(0.0)	2	(0.2)	2	(0.1)
Pregnancy, puerperium and perinatal conditions	1	(0.1)	0	(0.0)	0	(0.0)
Psychiatric disorders	0	(0.0)	1	(0.1)	3	(0.2)
Renal and urinary disorders	3	(0.2)	1	(0.1)	2	(0.1)
Respiratory, thoracic and mediastinal disorders	3	(0.2)	1	(0.1)	2	(0.1)
Vascular disorders	2	(0.1)	0	(0.0)	0	(0.0)

1. All randomized subjects except MT-02 where only those randomized to MK-8237 (6 DU) & placebo arms are included. Every subject is counted a single time for each applicable row and column.
 MedDRA: Medical Dictionary for drug-related adverse events SOC: System Organ Class PT: Preferred Term
 No treatment group reported >2 subjects for any MedDRA PT, thus none are listed in this table.
 From STN 125592.0, Section 5.3.5.3.3, Table 35

Serious adverse events not meeting the ICH definition of seriousness

Merck trial protocol guidance for reporting of overdoses required that any adverse events temporally associated with the overdose itself were to be reported as serious, whether or not they met the ICH definition of serious. Three such adverse events (in 2 subjects treated with MK8237 12 DU) were reported as summarized in the following table. Note that these adverse events are not included in evaluations or tabulations of the safety database serious adverse events.

Table 8: Protocol-defined serious adverse events not meeting ICH criteria Phase 2 and/or Phase 3 studies¹						
MedDRA System Organ Class Preferred Term	Dose (MK-8237)					
	12 DU N=1,383		6 DU N=808		Placebo N=1,540	
	n	%	n	%	n	%
Subjects with ≥ 1 event	2	(0.1)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	2	(0.1)	0	(0.0)	0	(0.0)
Oral pain	1	(0.1)	0	(0.0)	0	(0.0)
Oral pruritus	1	(0.1)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	1	(0.1)	0	(0.0)	0	(0.0)
Throat irritation	1	(0.1)	0	(0.0)	0	(0.0)

1. All randomized subjects except MT-02 where only those randomized to MK-8237 (6 DU) and placebo are included. Every subject is counted a single time for each applicable row and column. From STN 125592, Module 5.3.6.3.3, Table 39

Adverse events upgraded to serious after database lock

The classification of two adverse events was upgraded to serious after database lock, one each in the MT-04 and MT-06 trials; these events were not included in the pooled database or in the serious adverse event tables and listings. In the MT-04 trial, the serious adverse event reported post-database lock was placenta praevia hemorrhage in a placebo recipient; in the MT-06 trial, the serious adverse event reported post-database lock was idiopathic thrombocytopenic purpura in a subject in the MK-8237 6 DU treatment group.

Life-threatening adverse events

No SAEs in the clinical development program were considered life-threatening

Serious adverse events considered related to study drug

5 subjects experienced SAEs deemed by the manufacturer as related to study drug in the clinical development program - all occurring in the MT-04 trial. In the 12 DU group, one subject experienced moderate worsening of asthma; in the 6 DU group, 1 subject experienced mild arthralgia and 1 subject experienced moderate laryngeal oedema; and in the placebo group, 1 subject experienced hepatocellular injury and 1 subject experienced erosive oesophagitis.

Discontinuations

The most common types of adverse events leading to discontinuation included local application site, skin, gastrointestinal and respiratory systems, which appeared highest in the MK-8237 (12 DU) arm as compared to placebo, with rates in the MK-8237 (6 DU) arm generally falling in between the other two groups.

Table 9: Discontinuations due to adverse events - Phase 2 and Phase 3¹ (all SOCs, PT with n > 2 any treatment group)						
	MK-8237: 12 DU		MK-8237: 6 DU		Placebo	
	n	%	n	%	n	%
Subjects in population	1383	(100)	808	(100)	1540	(100)
With ≥1 adverse event leading to discontinuation	113	(8.2)	26	(3.2)	41	(2.7)
Cardiac Disorders	1	(0.1)	2	(0.2)	1	(0.1)
Ear And Labyrinth Disorders	15	(1.1)	0	(0.0)	1	(0.1)
Ear Pruritus	15	(1.1)	0	(0.0)	0	(0.0)
Endocrine disorders	0	(0.0)	0	(0.0)	1	(0.1)
Eye Disorders	2	(0.1)	1	(0.1)	1	(0.1)
Gastrointestinal Disorders	73	(5.3)	14	(1.4)	5	(0.3)
Abdominal pain upper	5	(0.4)	2	(0.2)	1	(0.1)
Diarrhoea	4	(0.3)	0	(0.0)	1	(0.1)
Dyspepsia	4	(0.3)	1	(0.1)	0	(0.0)
Dysphagia	4	(0.3)	1	(0.1)	0	(0.0)
Glossodynia	7	(0.5)	0	(0.0)	0	(0.0)
Lip swelling	9	(0.7)	1	(0.1)	0	(0.0)
Mouth swelling	15	(1.1)	0	(0.0)	0	(0.0)
Mouth ulceration	7	(0.5)	0	(0.0)	1	(0.0)
Nausea	13	(0.9)	0	(0.0)	0	(0.0)
Oedema mouth	7	(0.5)	3	(0.4)	0	(0.0)
Oral pain	3	(0.2)	0	(0.0)	0	(0.0)
Oral pruritus	17	(1.2)	4	(0.5)	0	(0.0)
Palatal swelling	7	(0.5)	0	(0.0)	0	(0.0)
Paraesthesia oral	3	(0.2)	0	(0.0)	0	(0.0)
Swollen tongue	14	(1.1)	1	(0.1)	0	(0.0)
Tongue oedema	6	(0.4)	0	(0.0)	0	(0.0)
General disorders & administration site conditions	3	(0.2)	3	(0.4)	1	(0.1)
Hepatobiliary disorders	0	(0.0)	1	(0.1)	0	(0.0)
Immune system disorders	1	(0.1)	0	(0.0)	0	(0.0)
Infections and infestations	7	(0.5)	3	(0.4)	5	(0.3)
Injury, poisoning & procedural complications	0	(0.0)	0	(0.0)	1	(0.1)
Musculoskeletal and connective tissue disorders	1	(0.1)	0	(0.0)	1	(0.1)
Neoplasms benign, malignant and unspecified (incl cysts & polyps)	0	(0.1)	0	(0.0)	1	(0.1)
Nervous system disorders	5	(0.4)	1	(0.1)	4	(0.3)
Pregnancy, puerperium and perinatal conditions	1	(0.1)	0	(0.0)	0	(0.0)
Psychiatric disorders	1	(0.1)	1	(0.1)	4	(0.3)
Renal and urinary disorders	1	(0.1)	0	(0.0)	0	(0.0)
Reproductive system and breast disorders	0	(0.0)	1	(0.1)	0	(0.0)
Respiratory, thoracic & mediastinal disorders	46	(3.3)	8	(1.0)	12	(0.8)
Asthma	7	(0.5)	3	(0.4)	5	(0.3)
Dyspnoea	6	(0.4)	2	(0.2)	5	(0.3)
Pharyngeal oedema	6	(0.4)	0	(0.0)	0	(0.0)
Throat irritation	23	(1.7)	2	(0.2)	0	(0.0)
Skin and subcutaneous tissue disorders	13	(0.9)	1	(0.1)	8	(0.5)
Pruritus	3	(0.2)	0	(0.0)	0	(0.0)
Rash	3	(0.2)	0	(0.0)	1	(0.1)
Urticaria	6	(0.4)	0	(0.0)	4	(0.3)
Vascular disorders	0	(0.0)	0	(0.0)	1	(0.1)

1. All randomized subjects except MT-02 where only those randomized to MK-8237 (6 DU) and placebo are included
 SOC: Medical Dictionary for drug-related adverse events (MedDRA) System Organ Class; PT: MedDRA Preferred Term
 From STN 125592.0 Module 5.3.5.3.3 Table 27

Treatment interruptions

Treatment interruptions were highest in the MK-8237 (12 DU) treatment arm, and similar in the MK-8237 (6 DU) and placebo arms. Of note, discontinuations from the study after treatment interruptions due to AEs were notably higher in the 12 DU group (14.5% of all interruptions) as compared to the 6 DU group (3.4% of all interruptions) and placebo group (3.8% of all interruptions).

	MK-8237 (12 DU)		MK-8237 (6 DU)		Placebo	
	N = 138		N = 89		N = 80	
	n	%	n	%	n	%
Completed despite interruption	109	(79.0)	75	(84.3)	67	(83.8)
Discontinued after interruption	29	(21.0)	14	(15.7)	13	(16.3)
Due to adverse event	20	(14.5)	3	(3.4)	3	(3.8)
Due to being lost to follow-up	1	(0.7)	0	(0.0)	0	(0.0)
Due to other reason	3	(2.2)	5	(5.6)	2	(2.5)
Due to protocol violation	0	(0.0)	5	(5.6)	2	(2.5)
Due to withdrawal by subject	5	(3.6)	1	(1.1)	6	(7.5)

1. All randomized subjects except MT-02 where only those randomized to MK-8237 (6 DU) & placebo are included. Subject classified by last recorded disposition
 Percentages based upon subjects randomized and the subset whose treatment was interrupted in a treatment group
 From STN 125592.0, Module 2.5, Table 12, Module 5.3.5.3.3, Table 9

The manufacturer notes that the rate of adverse events leading to treatment interruption and related to local application site reactions, i.e., within the Gastrointestinal Disorders System Organ Class and/or involving the mouth, throat or ear, tended to be higher in the 12 DU group with some dose-response trends as shown in the following table.

This reviewer agrees that there is evidence of a dose-response effect for events classified under the System Organ Class of Gastrointestinal Disorders for the Preferred Terms: Glossodynia, Lip swelling, Mouth Swelling, Mouth ulceration, Nausea, Oral pruritus, Stomatitis, Swollen tongue, Tongue ulceration, Toothache and Vomiting, and under the System Organ Class of Respiratory, Thoracic & Mediastinal Disorders for the Preferred Terms: Cough, Oropharyngeal pain, Pharyngeal oedema and Throat irritation.

	MK-8237: 12 DU		MK-8237: 6 DU		Placebo	
	n	%	n	%	n	%
Subjects in population	1383		808		1540	
With one or more AE leading to treatment interruption	138	(10.0)	89	(11.0)	307	(8.2)
Blood and lymphatic disorders	0	(0.0)	0	(0.0)	2	(0.1)
Cardiac disorders	0	(0.0)	1	(0.1)	1	(0.1)
Ear and labyrinth disorders	6	(0.4)	0	(0.0)	1	(0.1)
Ear pruritus	6	(0.4)	0	(0.0)	1	(0.1)
Eye Disorders	1	(0.1)	2	(0.2)	2	(0.1)
Gastrointestinal Disorders	50	(3.6)	20	(2.5)	16	(1.0)
Diarrhoea	3	(0.2)	2	(0.2)	2	(0.1)
Glossodynia	3	(0.2)	1	(0.1)	1	(0.1)
Lip swelling	5	(0.4)	0	(0.0)	0	(0.0)
Mouth swelling	7	(0.5)	0	(0.0)	0	(0.0)

Table 11: Adverse events leading to treatment interruptions - Phase 2 and Phase 3 studies¹						
All events by SOC and for any PT with n > 2 in any of the treatment groups						
Mouth ulceration	3	(0.2)	0	(0.0)	2	(0.1)
Nausea	2	(0.1)	0	(0.0)	3	(0.2)
Oral pruritus	9	(0.7)	3	(0.4)	1	(0.1)
Stomatitis	3	(0.2)	1	(0.1)	1	(0.1)
Swollen tongue	4	(0.4)	1	(0.1)	0	(0.0)
Tongue ulceration	3	(0.2)	0	(0.0)	3	(0.2)
Toothache	4	(0.4)	1	(0.1)	0	(0.0)
Vomiting	3	(0.2)	1	(0.1)	1	(0.1)
General disorders & administration site conditions	3	(0.2)	2	(0.2)	1	(0.1)
Immune system disorders	0	(0.0)	1	(0.1)	0	(0.0)
Infections and infestations	68	(4.9)	60	(7.4)	48	(3.1)
Acute tonsillitis	6	(0.4)	4	(0.5)	1	(0.1)
Bronchitis	4	(0.3)	5	(0.6)	6	(0.4)
Gastroenteritis	2	(0.1)	1	(0.1)	4	(0.3)
Influenza	5	(0.4)	5	(0.6)	2	(0.1)
Nasopharyngitis	16	(1.2)	15	(1.9)	15	(1.0)
Pharyngitis	13	(0.9)	8	(1.0)	6	(0.4)
Respiratory tract infection	3	(0.2)	4	(0.5)	1	(0.1)
Upper respiratory tract infection	8	(0.6)	7	(0.9)	8	(0.5)
Viral infection	2	(0.1)	4	(0.3)	3	(0.2)
Injury, poisoning & procedural complications	8	(0.6)	0	(0.0)	2	(0.1)
Investigations	1	(0.1)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	1	(0.1)	0	(0.0)	1	(0.1)
Musculoskeletal and connective tissue disorders	2	(0.1)	0	(0.0)	1	(0.1)
Neoplasms benign, malignant and unspecified (incl cysts & polyps)	2	(0.1)	0	(0.0)	1	(0.1)
Nervous system disorders	4	(0.4)	0	(0.0)	4	(0.4)
Reproductive system and breast disorders	0	(0.0)	1	(0.1)	0	(0.0)
Respiratory, thoracic & mediastinal disorders	26	(1.9)	16	(2.0)	10	(0.6)
Asthma	6	(0.4)	7	(0.9)	3	(0.2)
Cough	3	(0.2)	0	(0.0)	0	(0.0)
Oropharyngeal pain	4	(0.4)	2	(0.2)	1	(0.1)
Pharyngeal oedema	4	(0.4)	0	(0.0)	1	(0.1)
Throat irritation	6	(0.4)	2	(0.2)	1	(0.1)
Skin and subcutaneous tissue disorders	7	(0.5)	2	(0.2)	4	(0.4)
Urticaria	3	(0.2)	0	(0.0)	3	(0.2)
Surgical and medical procedures	2	(0.1)	0	(0.0)	2	(0.1)
Vascular disorders	0	(0.0)	0	(0.0)	1	(0.1)

1. All randomized subjects except MT-02 where only those randomized to MK-8237 (6 DU) and placebo arms are included. SOC: Medical Dictionary for drug-related adverse events (MedDRA) System Organ Class; PT: MedDRA Preferred Term From STN 125592.0 Module 5.3.5.3.3 Table 46

Events of clinical interest (ECIs)

ECIs were evaluated in all of the trials in the clinical development program. Merck-sponsored studies prospectively monitored for ECIs, while data from ALK- sponsored studies were evaluated for ECIs *post hoc*.

The ECIs included the following:

- Drug-induced liver injury (DILI)
AST or ALT laboratory value greater than or equal to 3X the upper limit of normal and an elevated total bilirubin laboratory value greater than or equal to 2X the upper limit of normal.

NOTE: DILI was not identified as an ECI in the Phase I-III trials sponsored by ALK (MT-01, MT-03, MT-02, MT-04, and MT-06).

- **Overdose**
Use above prescribed dose without additional associated adverse events, including any clinical and laboratory abnormalities. Overdose events were classified as serious for the purposes of monitoring and follow-up, but unless another event associated with the overdose was itself classified as serious, the overdose itself was not reported or analyzed as an SAE in the clinical study report.
- **Anaphylactic reactions, anaphylaxis and/or systemic allergic reactions***
*Determined by investigators and guided by the recommendations in the Food Allergy & Anaphylaxis Network (FAAN) Report which proposed clinical criteria that would increase diagnostic precision in anaphylaxis (Sampson 2005; Sampson 2006).
- **Events treated with epinephrine**
- **Severe local swelling or edema of the mouth and/or throat**

Table 12: Summary of events of clinical interest (ECI)^{1,2}						
	MK-8237 12 DU N = 1383		MK-8237 6 DU N = 808		Placebo N = 1540	
	n	%	n	%	n	%
Subjects with ≥1 event of clinical interest	56	(4.0)	6	(0.7)	47	(3.1)
Drug-induced liver injury (DILI) ³	0	(0.0)	0	(0.0)	0	(0.0)
Overdose ⁴	45	(3.3)	6	(0.7)	43	(2.8)
Systemic allergic reactions (anaphylactic / hypersensitivity reactions) ⁵	4	(0.3)	0	(0.0)	3	(0.2)
Adverse events treated with epinephrine	5	(0.4)	0	(0.0)	3	(0.2)
Severe local swelling or oedema of the mouth and/or throat	5	(0.4)	0	(0.0)	0	(0.0)

1. All randomized subjects except MT-02 where only those randomized to MK-8237 (6 DU) and placebo are included.
 2. These ECIs were prospectively defined and monitored only in Merck sponsored trials (P001, P003, P008); but were evaluated retrospectively in the ALK sponsored studies.
 3. AST or ALT laboratory value ≥ 3X the upper limit of normal and total bilirubin laboratory value ≥ 2X the upper limit of normal and, at the same time, an alkaline phosphatase laboratory value < 2X the upper limit of normal (protocol-specified or unscheduled laboratory testing).
 4. Use above prescribed dose without additional associated adverse events.
 5. Systemic allergic reactions as determined by investigators
 Every subject counted once for each applicable row and column
 From STN 125592, Module 5.3.5.3.3, Table 57; Module 2.7.4, page 169-170 and Table 51.

Drug-induced liver injury (DILI)

Drug Induced Liver Injury (DILI) was identified as an ECI for the Phase 1-3 trials conducted by Merck (P008, P003 and P001). The DILI definition was based on criteria defined in regulatory guidance documents; the purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The criteria for DILI are as follows:

AST or ALT laboratory value ≥ 3X the upper limit of normal and a total bilirubin laboratory value ≥ 2X the upper limit of normal and, at the same time, an alkaline phosphatase laboratory value ≤ 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

House Dust Mites (Dermatophagoides farinae and Dermatophagoides pteronyssinus) Allergen Extract (MK-8237) Proposed Trade Name: ODACTRAM

No subject met these DILI criteria in any of the 3 Merck trials (P008, P003, P001).

While DILI was not identified as an ECI in the Phase I-III trials sponsored by ALK (MT-01, MT-03, MT-02, MT-04, and MT-06), overall, few liver-related adverse events were reported in the MK-8237 clinical development program. The manufacturer reports they found no evidence of any association between MK-8237 and hepatic injury (manufacturer’s analyses not provided).

Overdose

Two subjects, both in the 12 DU group, had accidental overdoses (total daily dose of 24 DU) and subsequent development of mild adverse events (oral pruritus and throat irritation in one subject and oral pain in the other subject). In the Merck-sponsored trials, reports of adverse events associated with an overdose were classified as serious for safety monitoring; reports of overdose without additional adverse events were classified as non-serious events of clinical interest (ECI). The adverse events reported for the two subjects identified as having had an accidental overdose did not meet International Conference on Harmonisation (ICH) criteria for seriousness and are not included in evaluations of serious adverse events. The adverse events for both subjects were assessed as drug-related by the investigator.

Systemic allergic reactions

Phase 1 systemic allergic reactions

No systemic allergic reactions were reported in Phase 1 trials.

Phase 2 systemic allergic reactions

Seven subjects experienced a systemic allergic reaction in Phase 2 and Phase 3 studies: four in the 12 DU treatment group and 3 in the placebo group, summarized in the following table. Only a single reaction, in the 12 DU treatment group, was considered related to treatment by the investigator.

Table 13: Systemic Allergic Reactions ¹ in Phase 2 and Phase 3 Trials ²								
Study	Demographics	Onset (Day)	Last recorded study drug (day)	Adverse Event	Serious	Action Taken	Outcome	Suspected trigger
Active treatment: MK-8237 12 DU								
001	16 y W M	18	16	Anaphylactic reaction	N	N/A	Resolved	Food
001	47 y W F	245	309	Hypersensitivity	N	None	Unknown	Dust
001	34 y W F	1	1	Hypersensitivity	N	Discontinued	Resolved	MK-8237
014	48 y W F	392	456	Drug hypersensitivity	N	Non	Resolved	Amoxicillin
Placebo								
001	23 y W M	147	207	Drug hypersensitivity	N	None	Resolved	Bactrim
001	38 y W F	7	4	Anaphylactic reaction	N	None	Resolved	Unidentified
001	29 y AA F	26	25	Anaphylactic reaction	Y	None	Resolved	Food
1. As Determined by Investigator 2. All randomized subjects except MT-02 where only those randomized to MK-8237 (6 DU) and placebo are included From 125592.0, Module 2.5, Table 15								

Systemic allergic reactions - modified Sampson criteria – Phase 2 and 3 studies

Phase 2 and Phase 3 clinical trial data were also evaluated using the modified Sampson criteria, which requires subjects to have at least 2 adverse events affecting at least 2 organ systems.

Only two subjects met the modified Sampson criteria for a systemic allergic reaction:

A subject in the 12 DU group experienced urticaria and oropharyngeal swelling on Day 1, and chest tightness and dyspnea, on 3 separate occasions, Days 2, 3 and 6. All events were classified as mild in severity and resolved without treatment. The subject discontinued on Day 57 due to mouth ulceration (sublingual ulcer reported by patient). None of these events, in any combination, were classified as anaphylaxis by the sponsor.

A subject in the placebo group experienced generalized pruritus and dyspnea on Day 28 resolved within 1 day; lip, ear and oral pruritus together with dyspnea on Days 29, 47-51, 59, 64-66, 69, 70 and 74-76; mild wheezing on Days 61-63; facial pruritus and dyspnea on Days 216-248. All events resolved without treatment and the subject completed the study. None of these events, in any combination, were classified as anaphylaxis by the sponsor.

Use of epinephrine

Adverse events treated with epinephrine in Phase 2 and Phase 3 studies are summarized in the following table. Notably, North American study subjects were provided self-injectable epinephrine and instructed that it be used for significant systemic allergic reactions, which were attributed to the study drug. Self-injectable epinephrine was not provided to subjects enrolled in studies conducted outside the US.

Table 14: Overview of adverse events treated with epinephrine – Phase 2 and Phase 3 studies^{1,2}

	MK-8237 12 DU N = 1383		MK-8237 6 DU N = 808		Placebo N = 1540	
	n	%	n	%	n	%
One or more adverse events (PT) treated with epinephrine	5	(0.4)	0	(0.0)	3	(0.2)
Oedema mouth	1	(0.1)	0	(0.0)	0	(0.0)
Chest discomfort	1	(0.1)	0	(0.0)	0	(0.0)
Anaphylactic reaction	0	(0.0)	0	(0.0)	2	(0.1)
Food allergy	0	(0.0)	0	(0.0)	1	(0.1)
Hypersensitivity	1	(0.1)	0	(0.0)	0	(0.0)
Dyspnoea	1	(0.1)	0	(0.0)	0	(0.0)
Laryngeal oedema	1	(0.1)	0	(0.0)	0	(0.0)
Oropharyngeal discomfort	1	(0.1)	0	(0.0)	0	(0.0)
Pharyngeal oedema	1	(0.1)	0	(0.0)	0	(0.0)
Throat tightness	1	(0.1)	0	(0.0)	0	(0.0)

1. All randomized subjects except MT-02 where only those randomized to MK-8237 (6 DU) and placebo are included
 2. A given subject may have >1 associated PT (MedDRA Preferred Term)
 From STN 125592.0, Module 5.3.5.3.3, Table 59

Adverse events treated with epinephrine were attributed to study drug in three subjects (12 DU group); dust allergy in one subject (12 DU group), food allergy in two subjects (placebo group), and undetermined in one subject (placebo group).

Table 15: Subjects with treated with epinephrine in Phase 2 and Phase 3^{1,2}					
Subject ID	AE Onset (day)	Adverse Event	Serious?	Treatment ²	Discontinued?
Active treatment: MK-8237 12 DU					
120368	128	Chest discomfort	No	Epinephrine (self-administered)	No
		Oropharyngeal discomfort	No		
120147	7	Body temperature increased ³	No	Epinephrine (self-administered) Diphenhydramine hydrochloride Prednisone	Yes
		Dyspnoea ³	No		
		Gastroenteritis ³	No		
		Glossodynia ³	No		
		Oedema mouth ³	No		
		Throat tightness ³	No		
220835	12	Pharyngeal oedema ⁴	No	Epinephrine (self-administered) Diphenhydramine hydrochloride Fexofenadine hydrochloride	No
		Throat irritation ⁴	No		
220529	1	Hypersensitivity ³	No	Epinephrine, Pseudoephedrine Desloratadine	Yes
1705	1	Laryngeal oedema ³	No	Epinephrine Desloratadine Methylprednisolone	No
Placebo					
120354	234	Food allergy ⁵	Yes	Epinephrine (self-administered)	No
120098	7	Anaphylactic reaction ⁶	No	Epinephrine Fexofenadine hydrochloride Diphenhydramine hydrochloride Famotidine Prednisone Montelukast sodium	No
		Tremor ⁶	No		
220571	26	Anaphylactic reaction ⁵	Yes	Epinephrine (self-administered)	No

1. All randomized subjects except MT-02 where only those randomized to MK-8237 (6 DU) and placebo are included.
 2. North American study sites provided epinephrine for self-administration; if self-administered, it is indicated under treatment
 3. Attributed to MK-8237; 4. Attributed to dust allergy; 5. Attributed to food allergy; 6. Attributed to unknown cause
 From 125592.0, Module 2.5, Table 17

Local allergic reactions

Local reactions tended to occur early in the course of treatment with median onset in the MK-8237 group between 1 and 7 days after treatment initiation, and were typically transient (median duration 13.5 to 60 minutes after the first dose). The most common local reactions (occurring in > 15% of subjects) were compared in the 12 DU treatment group and the placebo group in the table below.

Table 16: Timing of the most commonly¹ reported local reactions - Phase 2 and Phase 3² studies^{1,2}						
	MK-8237 12 DU (N=1383)			Placebo (N=1540)		
	Median			Median		
	Onset [†] (n)	Duration - Day 1 [‡] (n)	Recurrence [§] (n)	Onset [†] (n)	Duration - Day 1 [‡] (n)	Recurrence [§] (n)
Ear pruritus	1 day (413)	30 minutes (289)	10 days (411)	4 days (95)	60 minutes (30)	3 days (93)
Oral pruritus	1 day (594)	30 minutes (414)	12 days (588)	2 days (131)	60 minutes (62)	3 days (128)
Throat irritation	1 day (603)	42 minutes (460)	12 days (596)	2 days (192)	45 minutes (94)	3 days (189)

1. >15% of subjects
 2. All randomized subjects except MT-02 where only those randomized to MK-8237 (6 DU) and placebo are included
[†] Onset reflects the time (in days) that an adverse event was first experienced after treatment initiation.
[‡] Duration reflects the length of time (in minutes) that an adverse event lasted after the first dose administered on Day 1.
[§] Recurrence reflects occurrence of adverse event measured over the course of consecutive days.
 From STN 125592.0, Module 2.5, Table 14

No reported local allergic swelling resulted in respiratory distress or airway compromise were reported in the Phase 1 studies, but two subjects experienced three events of severe mouth edema in the 16 DU group, a dose higher than the dose subsequently chosen to be evaluated for licensure.

A dose-response was noted with respect to local application site reactions in the Phase 2 and Phase 3 studies as illustrated in the table immediately below.

A single report of local allergic swelling was classified as a serious adverse event in a subject in the 6 DU treatment group with a history of asthma and allergic rhinitis, who experienced laryngeal oedema on Day 176. Direct laryngoscopy revealed edema of the left arytenoid, and no edema of the epiglottis or oropharynx. Study drug was interrupted for eight days and after treatment and resolution of symptoms, study drug was re-initiated and the subject completed the trial.

Table 17: Pre-specified local reactions - Phase 2 and Phase 3 studies¹						
MedDRA Preferred Term	Dose (MK-8237)					
	12 DU N=1383		6 DU N=808		Placebo N=1540	
	n	%	n	%	n	%
With any local application site reaction	871	(63.0)	277	(34.3)	293	(19.0)
Ear pruritus	413	(29.9)	33	(4.1)	95	(6.2)
Laryngeal oedema	1	(0.1)	1	(0.1)	0	(0.0)
Lip oedema	28	(2.0)	9	(1.1)	4	(0.3)
Lip swelling	161	(11.6)	14	(1.7)	20	(1.3)
Mouth swelling	83	(6.0)	10	(1.2)	12	(0.8)
Oedema mouth	59	(4.3)	61	(7.5)	1	(0.1)
Oral pruritus	594	(43.0)	136	(16.8)	131	(8.5)
Oropharyngeal swelling	3	(0.2)	3	(0.4)	1	(0.1)
Palatal oedema	10	(0.7)	2	(0.2)	0	(0.0)
Palatal swelling	82	(5.9)	0	(0.0)	11	(0.7)
Pharyngeal oedema	123	(8.9)	11	(1.4)	23	(1.5)
Throat tightness	7	(0.5)	1	(0.1)	3	(0.2)
Swollen tongue	137	(9.9)	8	(1.0)	18	(1.2)
Tongue oedema	23	(1.7)	4	(0.5)	1	(0.1)
Throat irritation	603	(43.6)	91	(11.3)	192	(12.5)
Tongue pruritus	67	(4.8)	33	(4.1)	14	(0.9)

1. All randomized subjects except MT-02 where only subjects randomized to MK-8237(6 DU) & placebo are included. Every subject is counted a single time for each applicable row and column.
From STN 125592.0, Module 5.3.5.3.3, Table 40

In the combined Phase 2 and Phase 3 trials, the majority of subjects treated with MK-8237 experienced local adverse events of mild or moderate in intensity. A dose-response can be seen for local reactions overall, as summarized in the table immediately above, and by each level of intensity of those local reactions classified as moderate or severe as summarized in the table below. The two most frequently reported local reactions classified as severe were throat irritation occurring in 5 subjects (all in the 12 DU group) and oral pruritus occurring in 6 subjects (5 in the 12 DU group and 1 in 6 DU group).

Table 18: Local reactions classified as moderate or severe – Phase 2 & Phase 3²

System Organ Class Preferred Term		Intensity	MK-8237 12 DU		MK-8237 6 DU		Placebo	
			N = 1383		N = 808		N = 1540	
			n	%	n	%	n	%
With ≥ 1 local reaction		Moderate	150	(10.8)	34	(4.2)	18	(1.2)
		Severe	15	(1.1)	2	(0.2)	0	(0.0)
Ear and labyrinth disorders		Moderate	50	(3.6)	3	(0.4)	9	(0.6)
		Severe	2	(0.1)	0	(0.0)	0	(0.0)
Ear pruritus	Moderate	50	(3.6)	3	(0.4)	9	(0.6)	
	Severe	2	(0.1)	0	(0.0)	0	(0.0)	
Gastrointestinal disorders		Moderate	126	(9.1)	26	(3.2)	8	(0.5)
		Severe	9	(0.7)	2	(0.2)	0	(0.0)
Lip edema	Moderate	7	(0.5)	1	(0.1)	1	(0.1)	
	Severe	1	(0.1)	0	(0.0)	0	(0.0)	
Lip swelling	Moderate	26	(1.9)	1	(0.1)	2	(0.1)	
	Severe	0	(0.0)	1	(0.1)	0	(0.1)	
Mouth swelling	Moderate	25	(1.8)	0	(0.0)	0	(0.0)	
	Severe	0	(0.0)	0	(0.0)	0	(0.0)	
Oedema mouth	Moderate	14	(1.9)	7	(0.9)	0	(0.0)	
	Severe	2	(0.1)	0	(0.0)	0	(0.0)	
Oral pruritus	Moderate	70	(5.1)	14	(1.7)	5	(0.3)	
	Severe	5	(0.4)	1	(0.1)	0	(0.0)	
Palatal oedema	Moderate	0	(0.0)	0	(0.0)	0	(0.0)	
	Severe	0	(0.0)	0	(0.0)	0	(0.0)	
Palatal swelling	Moderate	18	(1.3)	0	(0.0)	0	(0.0)	
	Severe	0	(0.0)	0	(0.0)	0	(0.0)	
Swollen tongue	Moderate	23	(1.7)	4	(0.5)	2	(0.1)	
	Severe	0	(0.0)	0	(0.0)	0	(0.0)	
Tongue oedema	Moderate	8	(0.6)	2	(0.2)	0	(0.0)	
	Severe	1	(0.1)	0	(0.0)	0	(0.0)	
Tongue pruritus	Moderate	8	(0.6)	1	(0.1)	1	(0.1)	
	Severe	1	(0.1)	0	(0.0)	0	(0.0)	
Respiratory, mediastinal & thoracic disorders		Moderate	83	(6.0)	11	(1.4)	7	(1.1)
		Severe	7	(0.5)	0	(0.0)	0	(0.0)
Laryngeal oedema	Moderate	0	(0.0)	1	(0.1)	0	(0.0)	
	Severe	0	(0.0)	0	(0.0)	0	(0.0)	
Oropharyngeal swelling	Moderate	0	(0.0)	0	(0.0)	0	(0.0)	
	Severe	0	(0.0)	0	(0.0)	0	(0.0)	
Pharyngeal oedema	Moderate	26	(1.9)	3	(0.4)	2	(0.1)	
	Severe	1	(0.1)	0	(0.0)	0	(0.0)	
Throat irritation	Moderate	73	(5.3)	8	(1.0)	6	(0.4)	
	Severe	5	(0.4)	0	(0.0)	0	(0.0)	
Throat tightness	Moderate	0	(0.0)	0	(0.0)	0	(0.0)	
	Severe	1	(0.1)	0	(0.0)	0	(0.0)	

1. All randomized subjects except MT-02 where only those randomized to MK-8237 (6 DU) & placebo are included. Each subject counted once for a specific adverse event, classified according to highest intensity grade indicated. From STN 125592.0, Section 5.3.5.3.3, Table 41

Five adverse events with the potential for airway obstruction were reported and all occurred in the 12 DU treatment arm. Four of these five subjects were discontinued from the study as summarized in the following table.

Table 19 Local swelling with potential for airway obstruction - Phase 2 and Phase 3 trials¹							
Study/Subject ID	Demographics	Onset (Day)	Last recorded study drug (Day)	Adverse Event	Serious	Action Taken	Outcome
Active treatment: MK-8237 12 DU							
001 / 120147	19 y W F	7	7	Throat tightness	N	Discontinued	Resolved
001 / 220835	42 y B F	12	263	Pharyngeal oedema	N	None	Resolved
014 / 1483	55 y W F	2	6	Oedema mouth	N	Discontinued	Resolved
014 / 1639	21 y W M	38	71	Tongue oedema	N	Discontinued	Resolved
015 / 1395	34 y W F	15	25	Oedema mouth	N	Discontinued	Resolved
Placebo: No reports of local swelling with potential for airway obstruction							
1. All randomized subjects except MT-02 where only those randomized to MK-8237 (6 DU) and placebo are included. From 125592.0, Module 2.5, Table 16							

Other events of interest

Asthma

Subjects with a history of asthma were eligible for the trials, provided their asthma was stable: no exacerbations within three months of initiating study drug, a forced expiratory volume in 1 second (FEV1) $\geq 70\%$ of predicted (MT-06 and P003) and $\geq 80\%$ (P001), and did not require maintenance with high-dose inhaled corticosteroids.

Phase 1 trials (MT-01 and MT-03) were conducted in subjects with asthma, a population that is potentially at increased risk for adverse events. The Phase 2 asthma trial, MT-02, evaluated 1, 3 and 6 DU doses of MK-8237, in subjects with asthma. Doses higher than 6 DU were not assessed due to a potential safety concern with the trial design which used steroid tapering while subjects were on MK-8237 treatment.

The subsequent Phase 3 trial, MT-04, is the only study in the Phase 2 and Phase 3 safety database to evaluate the proposed dose of 12 DU (as well as 6 DU) exclusively in an asthmatic population. The study prescribed inhaled corticosteroids for 7-12 months with reduction and withdrawal over a 6 month period.

Study entry requirements for the Phase 3 trial included HDM-induced asthma treated according to GINA Guidelines and FEV1 $\geq 70\%$ of the predicted value. Individuals were excluded if they had a history of persistent allergic asthma or rhinitis caused by an allergen other than HDM to which they were regularly exposed and sensitized or a history of intermittent allergic asthma or allergic rhinitis with the seasonal allergen causing symptoms in the period of the year corresponding to the ICS reduction period (period 3; October to April); previous treatment with immunotherapy with HDM allergen for more than 1 month within the last 5 years; a history of chronic sinusitis (>3 months) or hospitalisations for more than 12 hours due to an asthma exacerbation within the last 3 months prior to screening visit.

The population was overwhelmingly White (99%), with a median age of 31 years (17.0 – 83.0).

Although MT-04 describes equal randomization (1:1:1) following screening, there were 2 more subjects enrolled in the placebo group and 7 more enrolled in the 12 DU group vs. the 6 DU group.

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During period 3, sixty-five of the eighty-one “other” reasons for discontinuation (80%) were due to asthma exacerbations; the remaining reasons included to travel, use of prohibited medication, or planning of pregnancy.

	12 DU (N = 282)		6 DU (N = 275)		Placebo (N = 277)	
Entered period 3 (ICS taper)	248	88%	237	86%	257	93%
Completed entire trial ²	227	80%	229	83%	237	86%
Discontinuations (entire trial)	77	27%	72	26%	68	25%
Due to AE	25	9%	12	4%	8	3%
Due to lack of efficacy	1	<1%	1	<1%	2	<1%
Lost to follow-up	3	1%	6	2%	5	2%
Noncompliant with protocol	7	2%	6	2%	8	3%
Pregnancy	1	<1%	1	<1%	6	2%
Withdrawal of consent	15	5%	16	6%	13	5%
Other ³	25	9%	30	11%	26	9%
Asthma exacerbation ²	19	7%	22	8%	24	9%

1. MT-04 is the only Phase 3 study with the population limited to asthmatics, specifically those with HDM-induced asthma
 2. Completers defined as either attending final study visit or experiencing asthma exacerbation fulfilling primary study endpoint. During period 3A (ICS reduction), asthma exacerbation did not require discontinuation; subjects could continue in trial up to 3 exacerbations. During period 3B (ICS withdrawal) the protocol required subjects be discontinued following an exacerbation
 3. During period 3, 65 of 81 “other” reasons for discontinuation (80%) were due to asthma exacerbations; the remaining reasons included to travel, use of prohibited medication, or planning of pregnancy.
 From STN 125592.0, Module 2.7.6, page 70.

No deaths, local allergic reactions compromising the airways, anaphylactic reactions (including anaphylactic shock) or AEs requiring treatment with epinephrine were reported in MT-04.

	12 DU N = 282		6 DU N = 275		Placebo N = 277	
Any adverse event	223	79%	204	74%	175	63%
Serious adverse event	7	2.5%	10	3.6%	11	4.0%
Discontinuation due to a treatment related AE	17	6%	9	3%	4	1%

From STN 125592.0, Module 2.7.6, page 78.

Potential asthma-related adverse events from Phase 2 and Phase 3 studies were compared by treatment assignment. No safety issue was identified as summarized in the following table.

	MK-8237 12 DU N = 1383		MK-8237 6 DU N = 808		Placebo N = 1540	
	n	%	n	%	N	%
Subjects ≥1 asthma-related adverse event	110	(8.0)	82	(10.1)	126	(8.2)
General disorders and administration site conditions	14	(1.0)	2	(0.2)	9	(0.6)
Chest discomfort	14	(1.0)	2	(0.2)	9	(0.6)
Respiratory, thoracic and mediastinal disorders	99	(7.2)	80	(9.9)	119	(7.7)
Asthma	40	(2.9)	44	(5.4)	57	(3.7)
Cough	35	(2.5)	17	(2.1)	36	(2.3)
Dyspnoea	26	(1.9)	21	(2.6)	29	(1.9)
Wheezing	2	(0.1)	4	(0.5)	10	(0.6)

1. All randomized subjects except MT-02 (MK-8237, 6 DU and placebo arms only). Each subject counted once for each applicable row and column.
 From STN 1025592.0, Module 5.3.5.3.3, Table 52

Eosinophilic oesophagitis (EoE)

At the Pre-BLA meeting of 08-SEP-2015, based upon concerns regarding the potential for orally administered allergenic products to induce or exacerbate EoE, the higher prevalence of EoE in atopic patients as compared to the general population, and the identification by the OVRP clinical reviewer of 2 cases of EoE in the MK-8237 clinical database (2338 subjects), FDA requested that the sponsor conduct a *post hoc* evaluation of cases of EoE, potential cases of EoE and cases for which EoE had been ruled out.

Two cases of EoE were reported in Phase 2 and/or Phase 3 studies: one in an MT-06 subject receiving 6 DU and a second in a P001 subject treated with 12 DU. Both subjects also reported GERD and were treated with swallowed budesonide/fluticasone and with lansoprazole / omeprazole. The subjects continued on study and subsequently completed the trials. One subject was reported as not recovered from either EoE or GERD at the time of trial completion. The other subject was reported as having recovered both from GERD and EoE.

A search for additional potential cases of EoE in subjects without a reported adverse event of EoE was conducted. This involved review of cases with the following PTs:

abdominal pain upper

dyspepsia

dysphagia

eosinophilic oesophagitis

erosive oesophagitis

gastric disorder

gastritis

gastrooesophageal reflux disease

nausea

odynophagia

oesophageal discomfort

oesophageal irritation

oesophageal pain

oesophageal spasm

oesophagitis

From the review of data from this subset of subjects with the above PTs, potential cases were considered to be those cases in which subjects had documented endoscopic procedures or biopsies suggestive of EoE and/or subjects who were administered swallowed corticosteroids. Using this search strategy, 1 potential case was identified in a placebo-treated subject. The subject had a history of GERD and biopsy confirmed EoE. The subject was treated with lansoprazole and symptoms resolved.

Gastrointestinal disorders - overview

A dose-response was seen with respect to the incidence of adverse events of the upper gastrointestinal tract, including overall gastrointestinal tract adverse events, abdominal pain upper, dyspepsia, gastroesophageal reflux disease, nausea, and oesophageal pain, although relatively higher incidences of upper abdominal pain and of nausea were reported in the placebo group.

Table 23: Adverse events involving upper gastrointestinal tract – Phase 2 and Phase 3 studies¹

	MK-8237 12 DU N = 1383		MK-8237 6 DU N = 808		Placebo N = 1540	
	n	%	n	%	N	%
Subjects with ≥ 1 upper gastrointestinal tract adverse event	238	(17.2)	47	(5.8)	93	(6.0)
Abdominal pain upper	100	(7.2)	10	(1.2)	48	(3.1)
Dyspepsia	34	(2.5)	16	(2.0)	0	(0.0)
Dysphagia	18	(1.3)	5	(0.6)	2	(0.1)
Eosinophilic oesophagitis	1	(0.1)	1	(0.1)	0	(0.0)
Erosive oesophagitis	0	(0.0)	0	(0.0)	1	(0.1)
Gastric disorder	0	(0.0)	1	(0.1)	0	(0.0)
Gastritis	4	(0.3)	4	(0.5)	1	(0.1)
Gastroesophageal reflux disease	23	(1.7)	10	(1.2)	7	(0.5)
Nausea	134	(9.7)	4	(0.5)	62	(4.0)
Odynophagia	1	(0.1)	1	(0.1)	0	(0.0)
Oesophageal discomfort	0	(0.0)	1	(0.1)	0	(0.0)
Oesophageal irritation	1	(0.1)	0	(0.0)	0	(0.0)
Oesophageal pain	4	(0.3)	1	(0.1)	0	(0.0)
Oesophageal spasm	1	(0.1)	0	(0.0)	0	(0.0)
Oesophagitis	1	(0.1)	1	(0.1)	0	(0.0)

1. All randomized subjects except MT-02 where only those randomized to MK-8237, 6 DU and placebo are included. Every subject is counted a single time for each applicable row and column.
From: STN 125592.0, Module 5.3.5.3.3, Table 60

Use during pregnancy and lactation – all studies

The safety of MK-8237 in pregnant and/or lactating females has not been formally studied and subjects who became pregnant during the course of a clinical trial were to be discontinued from further use of study drug and followed up for outcome of the pregnancy. There were a total of 30 pregnancies reported by 30 randomized subjects. All pregnancies occurred in the Phase 2 and 3 trials. Six complications were reported: 4 spontaneous abortions (1 in the MK-8237, 12 DU group; and 3 in the placebo group), 1 induced abortion (MK-8237, 12 DU group), and 1 placenta praevia haemorrhage (placebo group). All complications were reported as recovered or resolved.

Limitations of the safety database

- Phase 2 and Phase 3 study subjects were overwhelmingly classified as White (87.5%).
- Asthmatics enrolled in Phase 2 and Phase 3 studies were limited to those with mild to moderate, well-controlled disease. Exclusions included:
 - An asthma exacerbation within 3 months of study treatment initiation.
 - Classification of asthma as severe or uncontrolled
 - Use of high-dose inhaled corticosteroids or long-acting beta agonists (LABA)
 - Individuals with a history of anaphylaxis, chronic urticaria or angioedema were excluded.
 - Individuals with a forced expiratory volume in 1 second (FEV_1) < 70% predicted were excluded from studies MT-06 and P003; those with FEV_1 < 80% were excluded from study P001.
- Study designs did not formally take asthma status and severity into account, e.g., by stratification at enrollment.
- In the overall safety database (see Table 3, above), the imbalance in the proportion of subjects with asthma (49.6% in 12 DU group, 73.5% in 6 DU group and 56.4% in the placebo group) limits the ability to interpret between group differences.
- Subjects who were pregnant, not using adequate contraception or breast-feeding were excluded from participation in the studies.
- Long-term safety has not been studied (mean and median exposure in combined Phase 2 and Phase 3 studies were both less than 1 year).
- Safety in children has not been adequately studied, but a pediatric study is planned to begin after US licensure in adults.

5. Postlicensure Safety Review**a. Post-market Safety Update Report (PSUR)**

A PSUR covering the period 15 April-2015 to 09-April-2016, submitted as amendment #8, was received by FDA on 08-JUNE-2016.

During the reporting period, the HDM SLIT-tablet was approved in Belgium (Special License), and Australia (via Authorised Prescriber Program and Special Access Scheme). In September 2015, the HDM SLIT-tablet, licensed by ALK to Torii Pharmaceutical Co., Ltd. under the trade name of MITICURE™, was approved for use in Japan (10,000 JAU [equivalent to 6 SQ-HDM] and 3,300 [2 SQ-HDM]). MITICURE is indicated in adults and adolescents (≥12 years) as hyposensitization therapy (allergy immunotherapy) for the treatment of allergic rhinitis caused by house dust mites.

As of 09-April-2016, the product had been launched in Germany, Denmark, Austria and Japan.

HDM SLIT-tablet postmarketing information is available from market introduction, 23-September-2015, to 09-Apr-2016, and is based upon spontaneous and non-interventional postmarketing reports for MK-8237 managed in the Merck Adverse Reporting and Review System (MARRS) database. The MARRS database was queried on 26-April-2016 for reports received from healthcare providers (HCP) from 23-Sep-2015 to 09-Apr-2016.

A total of 149 spontaneous and non-interventional HCP confirmed postmarketing reports (12 serious) of 407 events (30 serious) were identified. There were no reports with a fatal outcome. Reports were received from Germany (n=111), Japan (n=33), Denmark (n=4), and Austria (n=1).

Among the 407 total events, the preferred terms (PTs) of the five most frequently reported AEs were: mouth swelling (n=29), oral pruritus (n=25), throat irritation (n=23), lip swelling (n=20), paraesthesia oral (n=18), and dyspnoea (n=18).

Among the 30 serious events, there were 2 events each of lip swelling, mouth swelling, and swollen tongue. Each of the remaining 24 events was reported once. Those PTs were as follows: abdominal pain upper, anaphylactic reaction, angioedema, chronic sinusitis, dysphagia, dyspnoea, epiglottic oedema, erythema, eyelid oedema, facial bones fracture, hyperplasia, hypertensive crisis, laryngeal oedema, nasal septum deviation, palatal swelling, paraesthesia, paraesthesia oral, respiratory distress, sinusitis, swelling face, throat irritation, tongue oedema, tonsillar hypertrophy, and vomiting.

Important identified and potential risks

Serious reports possibly associated with the important identified and potential risks within the pharmacovigilance plan for MK-8237:

- Systemic Allergic Reactions Including Anaphylactic Reactions
Queried PTs: anaphylactic reaction, angioedema, hypersensitivity, and drug hypersensitivity

Serious reports retrieved: anaphylactic reaction (n=1) and angioedema (n=1).
- Local allergic reactions with potential to compromise airway
Queried PTs: dysphonia, oedema mouth, laryngeal oedema, oropharyngeal swelling, palatal oedema, pharyngeal oedema, throat tightness, tongue oedema, upper airway obstruction, stridor, and choking sensation

Serious reports retrieved: tongue oedema (n=1), laryngeal oedema (n=1), throat tightness and dysphonia (n=1).
- Acute worsening of Asthma
Queried PTs: asthma, asthmatic crisis, and status asthmaticus

Serious reports retrieved: None
- Anaphylactic Shock

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Queried PTs: anaphylactic shock, circulatory collapse, shock, and shock syndrome

Serious reports retrieved: None

- Eosinophilic Esophagitis
Queried PTs: eosinophilic esophagitis

Serious reports retrieved: None

Epinephrine utilization

The narratives for the 149 reports were reviewed for use of epinephrine, No use was reported.

Sponsor's evaluation of SUR data:

No new safety signals have been identified based on postmarketing use for the period queried. The safety data presented during the period of this SUR remain consistent with the safety data presented in the original marketing application and do not change the overall risk/benefit conclusions provided in the original marketing application.

b. Post-approval studies outside the US

A post-approval pediatric investigational plan (PIP) to include two pediatric studies, one for treatment of allergic rhinitis and one for the prevention of asthma, both enrolling children 5 years to less than 18 years of age in Europe, is scheduled for completion by December 2028.

A post-approval phase 3 study of pediatric patients 5-11 years of age is planned to enroll approximately 400 subjects in Japan. No schedule is provided.

6. Integrated Risk Assessment

- a. Description of important safety issues identified by the FDA reviewer from any source that does not trigger a PMR or REMS
 - i. Safety assessments should be based on actual treatment received, regardless of treatment assigned rather than an "as randomized" or intent-to-treat population. Specifically, Studies P014 and P015 used the Full Analysis Set for safety analyses, and for Study P012, it was decided, after unblinding, to analyze subjects as randomized. However, the pre-specified statistical plan for Study P012 called for safety analyses to be performed based on the actual treatment received.
 - ii. The clinical development plan has shown that this oral allergen product has the potential to cause allergic reactions largely manifested by local oropharyngeal and upper gastrointestinal adverse events, similar to other licensed SLIT products, GRASTEK and RAGWITEK. Significant increases in serious or life-threatening allergic-type adverse events were not reported in the clinical studies, but the studies were relatively small, enrolled healthy younger adults (median age 31 years) who are likely to have had low background rates of chronic cardiovascular or respiratory conditions, and excluded individuals with the following conditions or history who may be treated with the product once it is licensed:

- severe, persistent asthma
- use of high-dose inhaled corticosteroids
- use of long-acting beta agonists
- history of severe allergic reactions, anaphylaxis and/or angioedema

The sponsor proposes to mitigate risks in asthmatics and those with pertinent histories through routine pharmacovigilance, safety surveillance for signal detection, selected event-specific follow-up questionnaires, labeling and a patient medication guide.

- b. Signals identified by the reviewer from any source that trigger a PMR or REMS: None
- c. This reviewer has no additional comments on the submitted Postmarketing Commitment protocol synopsis: Post-Market Claims and EMR Based Study of Serious Allergic Reactions and Eosinophilic Esophagitis in Marketed Use of MK-8237 in the United States.
- d. Final determination of the safety profile of the product used in the studies submitted to this BLA is pending final clinical, statistical and/or product reviews.

7. Recommendation

Based upon the submitted information and current clinical knowledge, at this time OBE/DE requests that the sponsor:

- c. Explain why safety data analysis did not following the pre-specified data analysis plan for P012.
- d. Provide the following information for any subjects in any Phase 2 or 3 study who crossed over to a treatment arm to which they were not assigned:
 - i. Study name
 - ii. Randomized treatment assignment
 - iii. Actual treatment(s) received by study day
 - iv. A description of adverse events experienced by subject, including onset by study day, whether the AE was classified as serious, and the AE outcome.
- a. Routine pharmacovigilance will include:
 - i. Event-specific questionnaires to be used to follow-up reports of:

Important identified safety issues:

- Serious systemic allergic reactions, including anaphylactic reactions
- Local allergic reactions with potential to compromise airway
- Acute worsening of asthma symptoms (exacerbations)

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Important potential safety issues

- Anaphylactic shock
 - Eosinophilic esophagitis (EoE)
- ii. Periodic safety review on all spontaneous postmarketing adverse event reports including those related to important missing information:
- Pregnancy and lactation
 - Use in children (<18 years of age)
 - Use in elderly (> 65 years of age)
 - Use in severe, unstable or uncontrolled asthma
 - Co-administration with other SLIT products
- b. Two postmarket phase 4 studies will be conducted under a single title: “Post-Market Claims and EMR Based Study of Serious Allergic Reactions and Eosinophilic Esophagitis in Marketed Use of MK-8237 in the United States.” One study is based upon health claims from a large US health insurance database and the other study is based on electronic medical records from a large US integrated health system. Together the studies will aim to assess general safety and specifically assess the risks of:
- Systemic allergic reactions, including anaphylactic reactions / anaphylactic shock
 - Serious allergic reactions including local reaction w/ potential to compromise airway
 - Eosinophilic esophagitis (EoE)
 - Acute worsening of asthma symptoms

The studies will be incorporated into the database already being used for GRASTEK and RAGWITEK postmarketing studies. Based upon experience with US uptake of these two products, the sponsor estimates uptake for the DM product at (b) (4) patients over 3 years. Study protocols will be submitted in another submission.

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House Dust Mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract (MK-8237) Proposed Trade Name: ODACTRAM

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Addendum to OBE/DE Review

In response to OBE/DE concerns as described Items 7. a. Integrated Risk Assessment and 8. Recommendations, above, communicated in the FDA Information Request of December 14, 2016, the sponsor has submitted their response, STN 125592.0.48.

- For Study P012, the Statistical Analysis Plan described a procedure for including subjects in the safety analysis based on treatment group allocation dependent on whether the erroneous dose was placebo or a dose lower than/equal to versus higher than the dose to which the subject was randomized. Of the four subjects reported as having received treatment other than that to which they were randomized, all subjects received MK-8237, including one whose randomization number actually corresponded to the same treatment group as the wrong treatment taken, and therefore was actually treated as randomized.

Only one subject received a higher dose:

This subject was randomized to the 1 DU treatment group but actually received 6 DU from between Study Days 290 and 415, although the exact start and end dates of the erroneous treatment are not known. This subject experienced 2 adverse events – both prior to the dispensing of the incorrect dose: asthma (duration 7 days) and upper respiratory tract infection (duration 19 days). Both were characterized by the sponsor as “mild.”

- Subjects in Phase 2 and Phase 3 trials (except P012, discussed above) receiving treatment other than as assigned.

Study	Subject ID Planned Treatment	Erroneous Treatment			Adverse Event			
		Received	Start - End (Relday)	Duration (Days)	Term	Onset (Relday)	Seriou s	Outcome
P001	014600006 MK-8237 12 DU	Placebo	30 - 39	10	Ear pruritus	1	N	Recovered/Resolved
					Glossodynia	1	N	Recovered/Resolved
					Lip swelling	1	N	Recovered/Resolved
					Oral pruritus	1	N	Recovered/Resolved
					Throat irritation	1	N	Recovered/Resolved
					Ear pruritus	7	N	Recovered/Resolved
					Throat irritation	7	N	Recovered/Resolved
					005500008 MK-8237 12 DU	Placebo	216 - 228	13
	Throat irritation	1	N	Recovered/Resolved				
	Ear pruritus	1	N	Recovered/Resolved with Sequelae				
	Oral pruritus	1	N	Recovered/Resolved with Sequelae				
	Nausea	6	N	Recovered/Resolved				
	Palatal swelling	8	N	Recovered/Resolved with Sequelae				
	Pharyngeal oedema	8	N	Recovered/Resolved				
	Pharyngeal oedema	11	N	Recovered/Resolved				
	Throat irritation	17	N	Recovered/Resolved				
	Ear pruritus	25	N	Recovered/Resolved				
	Throat irritation	26	N	Recovered/Resolved with Sequelae				
	Ear pruritus	29	N	Recovered/Resolved				
Lip swelling	51	N	Recovered/Resolved					

House Dust Mites (Dermatophagoides farinae and Dermatophagoides pteronyssinus) Allergen Extract
(MK-8237) Proposed Trade Name: ODACTRAM

Table A: Adverse events in subjects who received a treatment to which they were not assigned ¹								
	002400027 Placebo	MK-8237 12 DU	245 – 266	22	Throat irritation	1	N	Recovered/Resolved
					Oral pruritus	2	N	Recovered/Resolved
					Oral pruritus	3	N	Recovered/Resolved
					Nasopharyngitis	294	N	Recovered/Resolved
	010100010 Placebo	MK-8237 12 DU	1– 30	30	Sinus congestion	25	N	Recovered/Resolved
					Asthma	365	N	Recovering/Resolving
	011700016 Placebo	MK-8237 12 DU	190 – 224	35	Abdominal pain upper	1	N	Recovered/Resolved
					Mouth ulceration	13	N	Recovered/Resolved
					Rash	182	N	Recovered/Resolved
					Acute sinusitis	182	N	Recovered/Resolved
MT-02	50965 MK-8237 1 DU	MK-8237 6 DU	290 – 415	66§†	Asthma	53	N	Recovered
					Upper Respiratory Tract Infection	134	N	Recovered
	50968 MK-8237 3 DU	MK-8237 1 DU	266 – 287	12§	Upper Respiratory Tract Infection	349	N	Recovered
	51092 MK-8237 6 DU	MK-8237 3 DU	159 - 194	20§†	Sinusitis	-164#	N	Recovered
					Blepharoplasty	-37#	N	Recovered
					Sinusitis	41	N	Recovered
					Lower Respiratory Tract Infection	82	N	Recovered
					Lower Respiratory Tract Infection	196	N	Recovered
	Pharyngolaryngeal pain	248	N	Recovered				
	Lower Respiratory Tract Infection	289	N	Recovered				
MT-04	50261 MK-8237 12 DU	MK-8237 6 DU	197 - 281	84§	Dyspepsia	209	N	Recovered
MT-06	50600 Placebo	MK-8237 12 DU	93 - 113	21	No AEs reported	---	---	---
§ In the period of erroneous treatment this number of tablets was from the erroneous IMP box (based on tablet accountability) # Before first IMP; ¶ Start date reported as unknown – set to the first day of the month † Exact dates of erroneous treatment unknown; hence end date of treatment is next visit date. Subject took the number of erroneous treatments between visits. 1. No subjects in Study P003 received incorrect study treatment, i.e., other than that to which they were assigned.								

Conclusion:

1. The sponsor has provided adequate information in their response to address OBE/DE concerns.
2. The adverse events occurring in subjects who were crossed over to treatment other than that to which they were assigned include: 1. A variety of transient, non-specific, non-serious events expected to occur in a healthy population; and 2. Events consistent with those associated with administration of MK-8237 as well as other sub-lingual immunotherapy products, i.e., local allergic-type reactions.
3. No new safety signals were identified in review of the data submitted in STN 125592.0.48.
4. OBE/DE agrees that the sponsor proposed postmarket pharmacovigilance plan is acceptable should this product be licensed for use in adults 18-65 years of age.