Pharmacovigilance Plan Review

From:	Patricia Rohan, MD
To:	Elizabeth Valenti, MPH, REHS, Chair
Through:	Christopher Jankosky, MD, MPH, Branch Chief Michael Nguyen, MD, Acting DE Director
Subject:	BLA 125478
Applicant:	Merck Sharp & Dohme Corp.
Product:	Standardized Allergenic Extract, Short Ragweed *(Ambrosia artemisiifolia)* MK-3641 RAGWITEK
Proposed Indication:	As immunotherapy for diagnosed ragweed pollen induced allergic rhinitis, with or without conjunctivitis, in adults 18 years of age or older.
Submission Date:	11-MAR-2013
PVP Submission Date:	11-MAR-2013
Action Due Date:	11-MAR-2014

1. **Introduction**
   a. Product description
   Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., in collaboration with ALK-Abelló A/S (ALK), has developed a sublingual pharmaceutical formulation of the allergen extract from short ragweed pollen, *Ambrosia artemisiifolia,* (SCH 039641, hereafter referred to as MK-3641) as an allergen immunotherapy (AIT) for the treatment of allergic rhinitis (AR)/ allergic rhinoconjunctivits (ARC). MK-3641 is a fast-dissolving, orally disintegrating sublingual tablet for oromucosal delivery of short ragweed allergen.

   The drug substance is a ---b(4)---------- ----------

   The pollen is an important seasonal aeroallergen (pollenating in late summer and early fall). One study has shown that 54% of the United States (US) population had one or more positive skin test responses to 10 common allergens, and 26% of these subjects were sensitized to ragweed. [Arbes 2005]

   b. Pertinent regulatory history
   Standardized Allergenic Extract, Short Ragweed *(Ambrosia artemisiifolia),* MK-3641, has not been previously licensed in any country

   c. Objectives/Scope of the review
   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.

2. **Materials reviewed**
   a. Routine items:
      i. Section 1.11.4 Multiple Module Information Amendment
      Pharmacovigilance Plan

      ii. Pertinent sections of the licensing application selected by the reviewer
      Section 1.9 Pediatric Administration Information
      Requests for partial waiver and deferral
      Section 1.14 Labeling
      Section 2.5 Clinical Overview

Section 2.7	Summary of Clinical Safety Including Synopses of Individual Studies
Section 5.2	Tabular Listing of All Clinical Studies
Section 5.3.5.1	RT-01 Clinical Study Report (CSR), Table 5.16 P05233 CSR, 16.1, page 1037 P05234 CSR, 16.1, page 1098; P05234 CSR, 12.2.8.1, page 1100 P05234 Appendices, 16.4.1.1, page 3346
Section 5.3.5.3	Integrated Analysis of Safety

b. Other items

STN 125478.0.5	Pediatric study plan, submitted 28-JUN-2013 (protocol concept document)

3. **Pharmacovigilance Plan Review**
   a. Clinical safety database

   b. Safety concerns including planned pharmacovigilance actions including the sponsor's proposed actions (timelines indicated if provided)

      i. Important identified safety issues

      <u>Serious systemic allergic reactions, including anaphylactic reactions</u>
      Planned Actions:
      Routine pharmacovigilance, including use of an event-specific follow-up questionnaire for this event of interest

      Appropriate US PI and PPI information

      <u>Local allergic reactions with potential to compromise airway</u>
      Planned Actions:
      Routine pharmacovigilance, including use of an event-specific follow-up questionnaire for this event of interest

      Appropriate US PI and PPI information

      <u>Acute worsening of asthma symptoms (exacerbations)</u>
      Planned Actions:
      Routine pharmacovigilance, including use of an event-specific follow-up questionnaire for this event of interest

      Appropriate US PI and PPI information

      ii. Important potential safety issues

      <u>Anaphylactic shock</u> (known class risk for subcutaneous immunotherapy [SCIT])

Planned Actions:

Routine pharmacovigilance, including use of an event-specific follow-up questionnaire for this event of interest

Appropriate US PI and PPI information

iii. Important missing information

Pregnancy, lactation

Planned Actions:

- Appropriate US label language
- Routine pharmacovigilance

Use in children (<18 years of age)

Pursuant to 21 CFR 314.55(c)(3)(ii), Merck requests a partial waiver to the pediatric requirement to study MK-3641 for the immunotherapy treatment of diagnosed ragweed pollen induced allergic rhinitis, with or without conjunctivitis, in children <5 years old due to the expected limited population, necessary studies to demonstrate the efficacy of MK-3641 are highly impractical.

Pursuant to 21 CFR 314.55(c)(3)(ii), Merck requests a partial deferral to the pediatric requirement to study MK-3641 for the immunotherapy treatment of diagnosed ragweed pollen induced allergic rhinitis, with or without conjunctivitis in children 5 to <17 years old.

Planned Actions:

- Appropriate US label language

- Routine pharmacovigilance

- Pediatric Study of MK-3641

Timeline:	Q1 2015	Protocol completion
	Q4 2015	1st subject randomized
	Q4 2016	Last data collected
	Q2 2017	Submission of final clinical study report (CSR)

The sponsor cites Radulovic et. al. (Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev. 2010 Dec 8;(12)) to support the choice of the adult MK-3641 dose as appropriate for use in children 5-17 years of age; however, a lead cohort of children 5 – 17 years of age will be evaluated prior to completing enrollment of the entire study population.

Dose:

One sublingual tablet administered daily (12 Amb a 1 U) beginning approximately 12 weeks prior to ragweed season (RS)

- OR –

Placebo given on the same schedule

Sample size: 350 individuals
Randomization: 1:1 to treatment or placebo.

Entry Criteria:

- Age (at screening): 5 to 17 years old
- Significant, physician diagnosed ragweed‑induced allergic rhinoconjunctivitis of ≥1 year in duration
- Received treatment during previous RS
- Positive skin prick‑test to Ambrosia artemisiifolia at screening
- Positive for specific IgE against Ambrosia artemisiifolia at screening
- FEV1 ≥70% of predicted value at screening
- Normal laboratory tests and vital signs
- Individuals with any of the following will be excluded from study entry:
  - Symptomatic seasonal or perennial allergic rhinitis and/or asthma (requiring regular medication) due to another allergen during/potentially overlapping RS
  - Immunosuppressive treatment <3 months (except steroids for allergic/asthma symptoms)
  - Previous immunotherapy with ragweed for >1 month, or current immunotherapy to another allergen
  - Severe asthma or asthma requiring high-dose inhaled corticosteroids
  - Severe atopic dermatitis
  - Anaphylaxis with cardiorespiratory symptoms due to an inhalant allergen or due to an unknown cause
  - Chronic urticaria and angioedema
  - Chronic sinusitis

Outcome measures (during peak ragweed season):

- Rhinoconjunctivitis daily symptom score (DSS)
- Daily medication score (DMS)
- Total combined symptom and medication score (TCS = DSS + DMS)

NOTE: Data from a cohort of 70 subjects will be evaluated for safety after 28 days of treatment by an electronic Data Monitoring Committee (eDMC), although this cohort will continue treatment on study. Once there is concurrence with the eDMC, full study enrollment will commence.

<u>Co-administration of Ragweed AIT with Grass AIT</u>
Planned Actions:
Appropriate US label language

Post-approval co-administration study of Ragweed AIT and Grass AIT (Timeline not provided)

c. Review of Postmarketing Study proposal or protocol synopsis
No Phase 4 studies are planned at this time.

4. **Review of other information from the managed review process**

a. To date, this reviewer is not aware of any concern regarding any additional potential safety signal identified by product, clinical or statistical reviewers.

b. Sections of the licensing application selected by the OBE/DE reviewer:

Clinical Overview (Section 2.5)
The clinical program for the development of MK-3641 includes five randomized, placebo-controlled clinical trials:

Table 1: Overview of clinical study designs

Study						Population				
Protocol	Phase	Safety	Efficacy	Dose-finding	Duration	Ragweed sensitivity	Rhinoconjunctivitis	With / without asthma	Without asthma	Age (years)
RT-01	1	X	---	---	28 days	X	X	--	X	18-50
P06081	2	X	--	--	28 days	X	X	X	---	≥ 50
P05233	2/3	X	X	X	52 weeks	X	X	X	---	18-50
P05234	2/3	X	X	X	52 weeks	X	X	X	---	18-50
P05751	3	X	--	--	28 days	X	X	X	---	≥ 18

From STN 125478, Section 2.5, page 37

Overview of treatment across studies
The safety database includes 1747 subjects 18 years and older with short ragweed allergy randomized to receive MK-3641 in the clinical program, approximately 20% of whom suffered from mild concomitant asthma. The population with asthma was limited to those with stable asthma, as judged by the clinical investigator, and excluded subjects with asthma that had resulted in emergency treatment, hospitalization, or treatment with systemic corticosteroids at any time within the 3 months prior to screening. Use of short-acting beta agonists was allowed but use of long-acting beta agonists was not.

Note that all studies initiated treatment prior to the ragweed season and are summarized in the table immediately below. Once daily dosage ranged from 1.5 to 50 Amb a 1-U (majority of subjects received 12 Amb a 1-U), and treatment duration ranged from 1 to 400 days.

Table 2: Overview of treatment regimens across studies								
Study	**Total Subjects**	**Total Active**	**Daily Dose (Amb a 1-U)**					
			1.5	**3**	**6**	**12**	**24**	**50**
RT-01	53	40	0	9	9	9	9	4
P06081	203	136	0	0	69	67	0	0
P05751	913	609	0	0	0	609	0	0
P05233	565	377	0	0	190	187	0	0
P05234	783	585	196	0	195	194	0	0
Total	2517	1747	196	9	463	1066	9	4
Duration of treatment by dose			**Daily Dose (Amb a 1-U)**					
			1.5	**3**	**6**	**12**	**24**	**50**
Treated for 1 month			190	8	429	918	7	2
Treated for 6 month			165	0	301	301	0	0
Treated for 1 year			152	0	271	269	0	0
From STN 125478.0, Section 2.5, Table 8								

Overview of safety data across studies

Safety data from five studies, one Phase 1 study (RT-01), and four Phase 2 and/or 3 studies (P06081, P05233, P05234 and P05751), were evaluated. The Phase 1 study safety data were included as it evaluated subjects with ragweed allergy rather than healthy control subjects, but the Phase 1 safety data were not included in the integrated safety analyses due to differences in design as compared to the Phase 2 and/or 3 studies.

For integrated safety analyses data through Day 28 were pooled from the four Phase 2 and/or 3 studies, but since only studies P05233 and P05234 collected longer-term safety data, all 52-week safety analyses are based upon these two studies. Additionally,

Several dosages were studies in Phase 2 and/or 3 studies, but the final Phase 3 study utilized only the 12 Amb a 1-U dose, as studies P05233 and P05234 had established that dose a relatively more effective but with similar adverse events to the 6 Amb a 1-U dose, in the sponsor's opinion. The 1.5 Amb a 1-U dose was considered a "no effect" dose.

Overall adverse events through day 28

Overall, 49.5% - 57.5% of subjects reported adverse events in the treatment groups vs. 37.6% in the pooled placebo group through Day 28 on study. The three most commonly reported AEs were Throat irritation, Oral pruritus, and Ear pruritus.

Table 3: Subjects with treatment emergent[1] adverse events through Day 28					
Category	Dose (Amb a 1-U)				
	1.5	6	12	All Doses	Placebo
	Number[3] (%)				
Total Subjects in Group	**N=196**	**N=454**	**N=1057**	**N=1707**	**N=757**
Any AEs	97 (49.5)	261 (57.5)	597 (56.5)	955 (55.9)	285 (37.6)
Treatment-Related[2] AE	70 (35.7)	230 (50.7)	482 (45.6)	782 (45.8)	155 (20.5)
Serious AE	0	1 (0.2)	2 (0.2)	3 (0.2)	4 (0.5)
Serious Treatment-Related[2] AE	0	0	0	0	1 (0.1)
AEs Leading to Discontinuation	4 (2.0)	24 (5.3)	55 (5.2)	83 (4.9)	7 (0.9)
Treatment-Related[2] AEs Leading to Discontinuation	3 (1.5)	19 (4.2)	46 (4.4)	68 (4.0)	6 (0.8)

1. New or worsening AEs reported on or after treatment start date through end of follow-up period
Treatment-related AEs: "Probable" or "Possible" relationship to treatment , i.e., excluding those assessed "Unlikely" related
3. Subjects are counted once within each category
From STN 125478.0, Section 2.5, Table 9; Section 5.3.5.1, Section 5.3.5.1, Study RT-01 CSR Table 5.16

Overall adverse events through week 52

Overall, 75.5% to 80.6% of subjects reported adverse events in the treatment groups vs. 68.4% in the pooled placebo group through Week 52 on study. The three most commonly reported AEs were Throat irritation, Oral pruritus, and Nasopharyngitis.

Table 4: Subjects with treatment emergent[1] adverse events through Week 52					
Category	Dose (Amb a 1-U)				
	1.5	6	12	All Doses	Placebo
	Number[3] (%)				
Total Subjects in Group	**N=196**	**N=385**	**N=381**	**N=962**	**N=386**
Any AEs	148 (75.5)	296 (76.9)	307 (80.6)	751 (78.1)	264 (68.4)
Treatment-Related[2] AE	79 (40.3)	213 (55.3)	233 (61.2)	525 (54.6)	98 (25.4)
Serious AE	4 (2.0)	5 (1.3)	3 (0.8)	12 (1.2)	4 (1.0)
Serious Treatment-Related[2] AE	0	0	0	0	0
AEs Leading to Discontinuation	10 (5.1)	31 (8.1)	35 (9.2)	76 (7.9)	9 (2.3)
Treatment-Related[2] AEs Leading to Discontinuation	4 (2.0)	26 (6.8)	31 (8.1)	61 (6.3)	6 (1.6)

1. New or worsening AEs reported on or after treatment start date through end of follow-up period
2. Treatment-related AEs: "Probable" or "Possible" relationship to treatment , i.e., excluding those assessed "Unlikely" related
3. Subjects are counted once within each category
From STN 125478.0, Section 2.5, Table 10; Section 5.3.5.1, Study RT-01 CSR Table 5.16

Adverse events leading to discontinuation

Discontinuations due to AEs through Day 28 – Phase 1 study

A total of four subjects in the Phase 1 study, RT-01, were withdrawn due to AEs: one subject in the 3 Amb a 1-U group (ear pruritus, chest discomfort, throat irritation, oral pruritus), two subjects in the 24 Amb a 1-U group (flushing, oedema mouth and swollen tongue; and dysphagia, chest discomfort and chest pain, respectively), and one subject in the 50 Amb a 1-U group (periorbital oedema). None of these events was considered serious or life-threatening, and none were treated with epinephrine.

Discontinuations due to AEs through Day 28 – Phase 2 and/or 3 studies

Ninety subjects discontinued from Phase 2 and/or 3 studies in the first 28 days due to AEs, with evidence of a dose response: placebo (n = 7; 0.9%), 1.5 Amb a 1-U (n = 4;

2.0%), 6 Amb a 1-U (n = 24; 5.3%) and 12 Amb a 1-U (n = 55; 5.2%). Most of these discontinuations were considered treatment-related (74 / 90 subjects) with the most common events (n > 3 subjects across all treatment groups) being Dysphagia, Lip swelling, Oedema mouth, Oral pruritus, Palatal oedema, Swollen tongue, Tongue oedema, Pharyngeal oedema, Throat irritation, Throat tightness, Chest discomfort, Lip oedema, and Nausea. A comparison of the rates of treatment-related adverse events leading to discontinuations is summarized by treatment group in the table below.

Table 5: Discontinuations due to treatment-related adverse events[1] Days 0- 28 (Phase 2 and/or 3[2])

	Number (%) of Subjects									
	1.5 Amb a 1-U n=196		6 Amb a 1-U n=454		12 Amb a 1-U n=1057		All Active n=1707		Placebo n=386	
Subjects Reporting Any Adverse Event	3	(1.5)	19	(4.2)	46	(4.4)	68	(4.0)	6	(0.8)
Cardiac Disorders	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Palpitations	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Ear And Labyrinth Disorders	0	---	0	---	2	(0.2)	2	(0.1)	0	---
Ear Pruritus	0	---	0	---	2	(0.2)	2	(0.1)	0	---
Eye Disorders	0	---	1	(0.2)	1	(0.1)	2	(0.1)	1	(0.1)
Eye Pruritus	0	---	0	---	1	(0.1)	1	(0.1)	1	(0.1)
Eye Swelling	0	---	1	(0.2)	0	---	1	(0.1)	0	---
Lacrimation Increased	0	---	0	---	0	---	0	---	1	(0.1)
Gastrointestinal Disorders	3	(1.5)	12	(2.6)	34	(3.2)	49	(2.9)	1	(0.1)
Abdominal Discomfort	1	(0.5)	0	---	0	---	1	(0.1)	0	---
Abdominal Pain	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Abdominal Pain Lower	0	---	1	(0.2)	0	---	1	(0.1)	0	---
Diarrhoea	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Dysphagia	0	---	2	(0.4)	5	(0.5)	7	(0.4)	0	---
Gastritis	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Gingival Oedema	0	---	1	(0.2)	0	---	1	(0.1)	0	---
Glossitis	0	---	1	(0.2)	0	---	1	(0.1)	0	---
Hypoaesthesia Oral	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Lip Oedema	0	---	2	(0.4)	1	(0.1)	3	(0.2)	0	---
Lip Swelling	0	---	1	(0.2)	4	(0.4)	5	(0.3)	0	---
Nausea	0	---	2	(0.4)	2	(0.2)	4	(0.2)	0	---
Oedema Mouth	2	(1.0)	4	(0.9)	16	(1.5)	22	(1.3)	0	---
Oral Mucosal Blistering	0	---	1	(0.2)	1	(0.1)	2	(0.1)	0	---
Oral Pruritus	0	---	1	(0.2)	4	(0.4)	5	(0.3)	0	---
Palatal Oedema	1	(0.5)	0	---	3	(0.3)	4	(0.2)	0	---
Paraesthesia Oral	0	---	0	---	2	(0.2)	2	(0.1)	1	(0.1)
Salivary gland enlargement	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Salivary hypersecretion	0	---	1	(0.2)	0	---	1	(0.1)	0	---
Swollen tongue	0	---	0	---	8	(0.8)	8	(0.5)	0	---
Tongue disorder	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Tongue oedema	0	---	3	(0.7)	4	(0.4)	7	(0.4)	0	---
Tongue pruritus	0	---	0	---	1	(0.1)	1	(0.1)	0	---
General disorders & administration site	0	---	5		4		9		0	---
Chest discomfort	0	---	2		2		4		0	---
Face oedema	0	---	1		0	---	1		0	---

Table 5: Discontinuations due to treatment-related adverse events[1] Days 0- 28 (Phase 2 and/or 3[2])

	Number (%) of Subjects									
	1.5 Amb a 1-U n=196		6 Amb a 1-U n=454		12 Amb a 1-U n=1057		All Active n=1707		Placebo n=386	
Fatigue	0	---	0	---	1		1		0	---
Feeling cold	0	---	0	---	1		1		0	---
Feeling hot	0	---	1		0	---	1		0	---
Non-cardiac chest pain	0	---	1		0	---	1		0	---
Immune system disorders	0	---	0	---	1		1		1	
Anaphylactic reaction	0	---	0	---	1		1		1	
Infections and infestations	0	---	0	---	0	---	0	---	1	
Rhinitis	0	---	0	---	0	---	0	---	1	
Injury, poisoning & procedural complications										
Burn oesophageal										
Nervous system disorders										
Disturbance in attention										
Dizziness										
Headache										
Paraesthesia										
Respiratory, thoracic & mediastinal disorders	0	---	5	(1.1)	19	(1.8)	24	(1.4)	4	(0.5)
Asthma	0	---	0	---	1	(0.1)	1	(0.1)	1	(0.1)
Choking sensation	0	---	1	(0.2)	0	---	1	(0.1)	0	---
Cough	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Dry throat	0	---	0	---	0	---	0	---	1	(0.1)
Dyspnoea	0	---	0	---	1	(0.1)	1	(0.1)	1	(0.1)
Nasal congestion	0	---	0	---	1	(0.1)	1	(0.1)	1	(0.1)
Oropharyngeal discomfort	0	---	1	(0.2)	1	(0.1)	2	(0.1)	0	---
Oropharyngeal pain	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Oropharyngeal swelling	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Pharyngeal erythema	0	---	0	---	2	(0.2)	2	(0.1)	0	---
Pharyngeal oedema	0	---	1	(0.2)	3	(0.3)	4	(0.2)	1	(0.1)
Sneezing	0	---	0	---	1	(0.1)	1	(0.1)	1	(0.1)
Throat irritation	0	---	1	(0.2)	4	(0.4)	5	(0.3)	0	---
Throat tightness	0	---	1	(0.2)	4	(0.4)	5	(0.3)	0	---
Skin and subcutaneous tissue disorders	0	---	4	(0.9)	6	(0.6)	10	(0.6)	2	(0.3)
Angioedema	0	---	1	(0.2)	1	(0.1)	2	(0.1)	1	(0.1)
Erythema	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Pruritus	0	---	1	(0.2)	1	(0.1)	2	(0.1)	1	(0.1)
Pruritus generalized	0	---	1	(0.2)	2	(0.2)	3	(0.2)	0	---
Rash erythematous	0	---	0	---	0	---	0	---	1	(0.1)
Swelling face	0	---	1	(0.2)	0	---	1	(0.1)	0	---
Urticaria	0	---	0	---	2	(0.2)	2	(0.1)	0	---
Vascular disorders	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Flushing	0	---	0	---	1	(0.1)	1	(0.1)	0	---

1. Treatment related AEs: "Probable" or "Possible" relationship to treatment , i.e., excluding those assessed "Unlikely" related
2. Studies P-5233, P05234, P06081, P05751
From STN 125478.0, Section 2.7.4, Table 32; Section 5.3.5.1, Study RT-01 CSR Table 5.16

Study discontinuations due to AEs through Week 52

Safety monitoring through Week 52 was conducted for 2 studies, P05233 and P05234, both were Phase 2 and/or 3 studies, were included in the 28-Day evaluation of AEs resulting in study discontinuation, above.

As in the 28-day safety data, most study discontinuations due to an AE reported through Week 52 were considered treatment-related (67 of 85) and evidence for a dose response with respect to rate of such discontinuations was seen: placebo (n = 6; 1.6%), 1.5 Amb a 1-U (n = 4; 2.0%), 6 Amb a 1-U (n = 26 (6.8%) and 12 Amb a 1-U (n = 31; 8.1%)

Treatment-related AEs that led to study discontinuation through Week 52 were largely similar to those occurring through Day 28 including events. The most commonly reported events, i.e., those occurring in more than three subjects across all treatment groups at 52 weeks included: Dysphagia, Lip oedema, Lip swelling, Oedema mouth, Oral pruritus, Palatal oedema, Paresthesia oral, Swollen tongue, Tongue oedema, Chest discomfort, Pharyngeal oedema, Nausea, Pharyngeal erythema, and Throat irritation.

Deaths

No deaths occurred during any study.

Serious adverse events (SAEs)

One Phase 1 study subject who received 24 Amb a 1-U was hospitalized with an intestinal obstruction, and was discharged after two days and reported as recovered.

Rates of SAEs in Phase 2 and/or 3 studies ranged from 0% to 0.5% in the treatment groups with a placebo rate of 1.1% at Day 28 and 0.8% to 2.0% in the treatment groups with a placebo rate of 1.3% at Week 52. The combined data through Day 28 and through Week 52 are summarized in the table below.

Table 6: Summary of all serious adverse events – Phase 2 and/or 3 clinical studies[1]

MedDRA System Organ Class Preferred Term	Dose (Amb a 1-U)									
	1.5 N=196		6 N=454		12 N=1057		All Active N=1707		Placebo N=757	
	Number of subjects (%)									
Subjects reporting any serious adverse event	5	(2.6)	6	(1.3)	9	(0.9)	20	(1.2)	8	(1.1)
Blood and lymphatic system disorders	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Haemorrhagic anaemia	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Congenital, familial and genetic disorders	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Hydrocele	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Gastrointestinal disorders	1	(0.5)	0	---	0	---	1	(0.1)	1	(0.1)
Gastrointestinal haemorrhage	0	---	0	---	0	---	0	---	1	(0.1)
Pancreatitis acute	1	(0.5)	0	---	0	---	1	(0.1)	0	---
General disorders & administration site conditions	0	---	2	(0.4)	0	---	2	(0.1)	0	---
Hernia obstructive	0	---	1	(0.2)	0	---	1	(0.1)	0	---

Table 6: Summary of all serious adverse events – Phase 2 and/or 3 clinical studies[1]

MedDRA System Organ Class Preferred Term	Dose (Amb a 1-U)									
	1.5 N=196		6 N=454		12 N=1057		All Active N=1707		Placebo N=757	
	Number of subjects (%)									
Pelvic mass	0	---	1	(0.2)	0	---	1	(0.1)	0	---
Hepatobiliary disorders	1	(0.5)	0	---	1	(0.1)	2	(0.1)	1	(0.1)
Cholecystitis acute	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Cholelithiasis	1	(0.5)	0	---	0	---	1	(0.1)	1	(0.1)
Immune system disorders	0		0		1	(0.1)	1	(0.1)	1	(0.1)
Anaphylactic reaction	0	---	0	---	0	---	0	---	1	(0.1)
Hypersensitivity	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Infections and infestations	0	---	2	(0.4)	2	(0.2)	4	(0.2)	3	(0.4)
Appendicitis	---	---	0	---	1	(0.1)	1	(0.1)	1	(0.1)
Arthritis bacterial	---	---	0	---	0	---	0	---	1	(0.1)
Bronchitis	---	---	1	(0.2)	0	---	1	(0.1)	0	---
Lobar pneumonia	---	---	0	---	1	(0.1)	1	(0.1)	0	---
Pneumonia chlamydial	---	---	0	---	0	---	0	---	1	(0.1)
Postoperative abscess	---	---	1	(0.2)	0	---	1	(0.1)	0	---
Injury, poisoning and procedural complications	1	(0.5)	0		2	(0.2)	3	(0.2)	2	(0.3)
Ankle fracture	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Ligament rupture	1	(0.5)	0	---	0		1	(0.1)	0	---
Fibula fracture	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Post procedural complication	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Soft tissue injury	0	---	0	---	0	---	0	---	1	(0.1)
Stab wound	0	---	0	---	0	---	0	---	1	(0.1)
Tibia fracture	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Metabolism and nutrition disorders	0	---	---	---	1	(0.1)	1	(0.1)	0	---
Diabetes mellitus inadequate control	0	---	---	---	1	(0.1)	1	(0.1)	---	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.5)	1	(0.2)	0	---	2	(0.1)	0	---
Breast cancer	1	(0.5)	1	(0.2)	---		2	(0.1)	---	---
Pregnancy, puerperium and perinatal conditions	1	(0.5)	1	(0.2)	0	---	2	(0.1)	0	---
Abortion spontaneous	1	(0.5)	1	(0.2)	---		2	(0.1)	---	---
Renal and urinary disorders	0	---	0	---	1	(0.1)	1	(0.1)	0	---
Tubulointerstitial nephritis	---	---	---	---	1	(0.1)	1	(0.1)	---	
Reproductive system and breast disorders	0	---	1	(0.2)	1	(0.1)	2	(0.1)	0	---
Dysfunctional uterine bleeding	---	---	1	(0.2)	0		1	(0.1)	---	---
Ovarian cyst	---	---	1	(0.2)	1	(0.1)	2	(0.1)	---	---
Pelvic pain	---	---	1	(0.2)	0	---	1	(0.1)	---	---
Uterine enlargement	---	---	1	(0.2)	0	---	1	(0.1)	---	---
Uterine prolapse	---	---	1	(0.2)	0	---	1	(0.1)	---	---

Table 6: Summary of all serious adverse events – Phase 2 and/or 3 clinical studies[1]										
MedDRA System Organ Class Preferred Term	Dose (Amb a 1-U)									
	1.5 N=196		6 N=454		12 N=1057		All Active N=1707		Placebo N=757	
	Number of subjects (%)									
Respiratory, thoracic and mediastinal disorders	0	---	1	(0.2)	1	(0.1)	2	(0.1)	0	---
Hypoxia	---	---	0	---	1	(0.1)	1	(0.1)	---	---
Tonsillar hypertrophy	---	---	1	(0.2)	0	---	1	(0.1)	---	---
Skin and subcutaneous tissue disorders	0	---	0	---	0		---	---	1	(0.1)
Henoch-schonlein purpura	---		---		0	---	0	---	1	(0.1)
Surgical and medical procedures	1	(0.5)	0	---	0		---	(0.1)	0	---
Abortion induced	1	(0.5)	---		0	---	1	(0.1)	0	---
Vascular disorders	0	---	0	---	0	---	---	---	1	(0.1)
Thrombophlebitis superficial	---		---		0	---	0	---	1	(0.1)

1: Protocols P052333, P05234, P06081, P05751, 28-day and 52- week data combined

From STN 125478, Section 2.7.4, Table 23

Serious adverse events resulting in emergency room visit and/or hospitalization

Table 7: Adverse events resulting in emergency room visit and/or hospitalization				
Study	Treatment	Event	Treatment	Comments
RT-01	24 Amb a 1-U	Intestinal obstruction	Hospitalized x 2 days	Recovered
P05751	Placebo	Anaphylaxis	ER, not hospitalized	History of latex allergy
P05234	12 Amb a 1-U	Hypersensitivity	Hospitalized	Recovered, event followed ingestion of propolis (bee product made of goldenrod, willow, poppy seed, “colze”, hazelnut, lime pollen)
P05233	12 Amb a 1-U	Lobar pneumonia	Hospitalized	Event prior to randomization

From STN 125478, Section 2.7.4, pages 67-69; Section 5.3.5.1 P0523 CSR 16.1 page 1037& P0524 CSR 16.1, page 1098

Life-threatening adverse events

Life-threatening AEs were reported for 2 subjects through Day 28: hemorrhagic anemia in a 12 Amb a 1-U recipient following a leg fracture and an anaphylactic reaction in a placebo recipient on Day 1 which is reviewed further, below. Additional life-threatening AEs through Week 52 in two 1.5 Amb a 1-U recipients: one who had a spontaneous abortion and one who developed breast cancer.

Prespecified safety outcomes

The sponsor prospectively monitored for possible allergic reactions, including systemic and/or anaphylactic reactions, and for use of epinephrine, asthma-related events and local application site reactions.

Systemic allergic reactions - defined
Potential systemic allergic reaction were identified in the following ways: adverse events coded with as anaphylactic reactions (Preferred Term [PT]) /anaphylaxis (Lower Level Term [LT]); Hypersensitivity (PT); systemic allergic reactions (LLT); a review of subjects experiencing symptoms affecting 2 organ symptoms as defined by Food Allergy and Anaphylaxis Network (FAAN) Report anaphylaxis criteria; and review of all epinephrine administrations.

Anaphylaxis - defined
Anaphylaxis is a systemic allergic reaction with sudden onset after contact with an allergy-causing substance.

The US National Institute of Allergy and Infectious Diseases and FAAN conclude that these 3 criteria are likely to capture more than 95% of cases of anaphylaxis when ≥ 1 of the following criteria are met:

1. Acute onset (minutes to several hours) with involvement of skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (e.g., dyspnea, wheeze, bronchospasm, stridor, reduced pulmonary expiratory flow (PEF), hypoxemia)
   b. Reduced Blood Pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced pulmonary expiratory flow (PEF), hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Anaphylactic shock - defined
Anaphylactic shock (MedDRA preferred term 'Anaphylactic shock') was identified as the most severe form of anaphylaxis, and additionally required signs, e.g.,

hypotension (systolic blood pressure <90 mmHg or >30% decrease from baseline blood pressure), or symptoms, e.g., syncope, incontinence, and/or hypotonia which would suggest shock and decreased cerebral perfusion.

Systemic allergic reactions including anaphylactic reactions - Phase 1 Study RT-01:
In the Phase 1 study, 3 of the 9 subjects treated with ≥ 24 Amb a 1-U experienced symptoms suggestive of a systemic reaction, however none of these events were considered anaphylactic shock or anaphylaxis, and epinephrine was not required for treatment of any of the events.

Anaphylactic reactions - Phase 2 and/or Phase 3 studies
In Phase 2 and/or 3 studies, three events were determined to be anaphylactic reactions by the investigator as described in the table below - two in the 12 Amb a 1-U treatment group, and one in the placebo group. All three events required epinephrine treatment. Only the event occurring in the placebo recipient was considered serious and life-threatening.

Table 8: Anaphylactic reactions – Phase 2 and/or 3 studies

Study	Subject	Demographic	Dose (Amb a 1-U)	Preferred Term (reported symptoms)	SAE?	Study Day		Action
						Onset	End	
P05751	100741	45 yr. F (W)	Placebo	Anaphylactic reaction (urticaria, cough, dyspnea, pharyngeal pruritus, thoracic pain)	Y	1	2	RX / DC
P05751	101216	34 yr. M (W)	12	Anaphylactic reaction (throat swelling, shortness of breath, nausea, light-headedness)	N	6	6	RX / DC
P05234	000819	50 yr. M (W)	12	Anaphylactic reaction (syncope, vomiting) Note; Almond-allergic, ingested almonds shortly prior to event	N	41	41	RX

From STN 125478, Section 2.7.4, page 72; Section 5.3.5.1: P05234 Clinical Study Report, 12.2.8.1, page 1100 and P05234 Appendices, 16.4.1.1, page 3346.

Other systemic allergic reactions - Phase 2 and/or Phase 3 studies
Seven subjects were identified as having a possible systemic allergic reaction defined as ≥ 2 potential allergic AEs affecting ≥ 2 organ symptoms, or the same organ with symptoms distant from one another. These events are summarized in the table below, and include five subjects from the 12 Amb a 1-U group, one subject from the 6 Amb a 1-U group and one placebo recipient. None of the events were assessed as serious, none required treatment with epinephrine, and none were rapidly progressing, as would be expected with anaphylaxis, and therefore did not fulfill the FAAN criteria of anaphylaxis.

Table 9: Possible systemic allergic reaction[1] – database search – Phase 2 and/or 3 studies								
Study	**Subject**	**Demographic**	**Dose (Amb a 1-U)**	**Preferred Term**	**SAE?**	**Study Day[2]**		**Action[3]**
						Onset	**End**	
P05233	016174	31 yr. M (W)	12	Abdominal pain	N	7	13(1)	DC
				Diarrhoea	N	7	13(1)	DC
				Lip swelling	N	7	7	None
	021121	31 yr. F (/W)	12	Dyspnoea	N	24	24	RX
				Swollen tongue	N	24	24	DC
	016241	20 yr. F (W)	12	Dyspnoea	N	162	171	RX
				Wheezing	N	162	171	RX
	016362	37 yr. M (W)	Placebo	Dyspnoea	N	120	120	None
				Vomiting	N	120	120	None
	16160	39 yr. F (W)	12	Flushing	N	1	1	DC
				Palatal oedema	N	1	3(2)	DC
P05234	000181	31 yr. M (W)	6	Syncope	N	121	121	None
				Urticaria	N	121	121	RX
				Urticaria	N	121	121	RX
	000613	19 yr. F (M)	12	Palatal oedema	N	2	2	None
				Urticaria	N	2	3	None

1: Systemic Events defined as a combination of AEs that begin on the same day using NIAID/FAAN criteria. (Sampson 2006) Note: No such Systemic Events found for study P05233 and P05234
2: Days since start of treatment, (n) for days following end of study treatment.
3: Action: DC= treatment and study discontinuation, RX=additional medications
From STN 125478, Section 2.7.4, Table 24

Hypersensitivity / allergic reactions (not including systemic reactions)

Hypersensitivity / allergic-type adverse events, including oral pruritus, ear pruritus, throat irritation, oedema mouth, eye pruritus, nasal passage irritation and skin pruritus were monitored in all Phase 2 and/or Phase 3 studies. The majority of subjects reported hypersensitivity / allergic events considered to be related to their underlying allergic rhinitis/conjunctivitis. No events fulfilled FAAN criteria for anaphylaxis, nor were they considered by investigators to be evidence of anaphylaxis.

The following table summarizes non-systemic hypersensitivity / allergic reactions. Note that the first listing, subject #00123 from Study 05234 was reported to have a "systemic allergic reaction" and also reported as having had ≥ 2 potential allergic AEs affecting ≥ 2 organ symptoms or the same organ with symptoms distant from one another, as described above, as the definition of a systemic allergic reaction. It is not clear why this event is not reported by the sponsor as a systemic allergic reaction above.

Table 10: Hypersensitivity / allergic reactions[1] not including systemic reactions						
Subject	**Dose (Am a 1-U)**	**Age**	**Onset Day**	**Symptoms**	**Severity**	**Epinephrine self-administered**
123	12	41	237	Systemic allergic reaction to bee pollen: generalized urticaria, pruritus all over her body, facial angioedema, throat constriction	Severe	no
21331	6	32	358	increased allergy symptoms	Mod	no
16101	12	25	251	ear itching, itching and swelling right side of lip, tongue and cheek	Mod	no
742	1.5	47	338	allergy symptoms	Mod	no
450	6	34	98	allergy exacerbation	Severe	no
249	6	35	355	allergy symptoms	Mod	no
100400	12	45	4	allergy symptoms	Severe	no
100706	Placebo	23	3	allergic reaction on hands	Severe	no
101295	12	45	21	allergy symptoms	Mod	no
100696	12	69	4	worsening of allergy symptoms	Severe	no
2825	6	67	15	increased allergy symptoms	mild	no
1. Investigator assessed From STN 125478, Section 2.5, Table 12						

Use of epinephrine

All subjects were provided with self-injectable epinephrine and instructed in its use. A total of 8 subjects (7 who received the investigational product) received epinephrine on study, including 3 who received treatment by medical personnel and 5 who self-administered epinephrine.

Table 11: Subjects who received epinephrine						
Subject	**Dose (Am a 1-U)**	**Age**	**Onset Day**	**Symptoms**	**Severity**	**Epinephrine self-administered**
101216	12	34	6	swelling in the throat, shortness of breath, nausea, and light- headedness	severe	yes
100741	Placebo	45	1	urticaria, cough, dyspnea, pharyngeal pruritus, thoracic pain (history: latex allergy)	life threatening	no
16246	12	45	95	allergic reaction to peanut	severe	yes
819	12	50	41	anaphylactic reaction to almond	severe	yes
16026	6	21	22	pharyngeal edema	severe	no
2839	12	71	2	abdominal pain, vomiting, diarrhea (likely viral gastroenteritis)	mod	yes
100249	12	22	5	dysphagia, mouth edema, throat tightness	mod	no
100295	12	41	14	throat tightness	Severe	yes
From STN 125478, Section 2.5, Table 13						

Asthma-related events

An asthma-related event was defined as any eDiary report of wheezing, cough, chest tightness / discomfort or any AE reported as asthma, dyspnea, wheezing, cough, or chest tightness / discomfort. There were no severe or life-threatening or serious events related to asthma in either the 28-day or 52-week groups. Since diary data on asthma-related events were only collected for the 52-week studies (P05233 and P05234), only those data are included in the sponsor's analysis, as summarized in the two tables below.

Table 12: Asthma-related symptoms – all subjects (52 week studies[1])

		Dose (Amb a 1-U)						Placebo	
		1.5		6		12			
		N=196		N=385		N=381		N=386	
		n (%)		n (%)		n (%)		n (%)	
eDiary or Adverse Events		162	(82.7)	287	(74.5)	283	(74.3)	299	(77.5)
	Asthma	2	(1.0)	8	(2.1)	5	(1.3)	6	(1.6)
	Chest Tightness/Discomfort	97	(49.5)	171	(44.4)	190	(49.9)	200	(51.8)
	Cough	158	(80.6)	269	(69.9)	265	(69.6)	276	(71.5)
	Dyspnoea	2	(1.0)	2	(0.5)	10	(2.6)	6	(1.6)
	Wheezing	101	(51.5)	169	(43.9)	185	(48.6)	203	(52.6)
eDiary		161	(82.1)	284	(73.8)	274	(71.9)	298	(77.2)
	Chest Tightness/Discomfort	96	(49.0)	169	(43.9)	185	(48.6)	200	(51.8)
	Cough	157	(80.1)	268	(69.6)	262	(68.8)	275	(71.2)
	Wheezing	101	(51.5)	169	(43.9)	185	(48.6)	203	(52.6)
Adverse Events		17	(8.7)	41	(10.6)	44	(11.5)	27	(7.0)
	Asthma	2	(1.0)	8	(2.1)	5	(1.3)	6	(1.6)
	Chest Tightness/Discomfort	4	(2.0)	8	(2.1)	9	(2.4)	1	(0.3)
	Cough	11	(5.6)	24	(6.2)	28	(7.3)	11	(2.8)
	Dyspnoea	2	(1.0)	2	(0.5)	10	(2.6)	6	(1.6)
	Wheezing	2	(1.0)	3	(0.8)	1	(0.3)	5	(1.3)

1: 52 week studies include P0523 and P0524
From STN 125478, Section 2.7.4, Table 26

Table 13: Asthma-related symptoms – asthmatic subpopulation (52 week studies[1])

		Dose (Amb a 1-U)						Placebo	
		1.5		6		12			
		N=34		N=68		N=79		N=75	
		n (%)		n (%)		n (%)		n (%)	
eDiary or Adverse Events		33	(97.1)	63	(92.6)	76	(96.2)	72	(96.0)
	Asthma	1	(2.9)	5	(7.4)	4	(5.1)	6	(8.0)
	Chest Tightness/Discomfort	28	(82.4)	55	(80.9)	66	(83.5)	62	(82.7)
	Cough	32	(94.1)	60	(88.2)	70	(88.6)	67	(89.3)
	Dyspnoea	1	(2.9)	2	(2.9)	5	(6.3)	2	(2.7)
	Wheezing	25	(73.5)	55	(80.9)	68	(86.1)	62	(82.7)
eDiary		33	(97.1)	62	(91.2)	75	(94.9)	72	(96.0)
	Chest Tightness/Discomfort	28	(82.4)	54	(79.4)	65	(82.3)	62	(82.7)
	Cough	32	(94.1)	60	(88.2)	70	(88.6)	67	(89.3)
	Wheezing	25	(73.5)	55	(80.9)	68	(86.1)	62	(82.7)
Adverse Events		4	(11.8)	13	(19.1)	15	(19.0)	12	(16.0)
	Asthma	1	(2.9)	5	(7.4)	4	(5.1)	6	(8.0)
	Chest Tightness/Discomfort	1	(2.9)	2	(2.9)	3	(3.8)	0	---
	Cough	1	(2.9)	5	(7.4)	8	(10.1)	2	(2.7)
	Dyspnoea	1	(2.9)	2	(2.9)	5	(6.3)	2	(2.7)
	Wheezing	0	---	0	---	0	---	3	(4.0)

1: 52 week studies include P0523 and P0524
From STN 125478, Section 2.7.4, Table 26

The small safety database sample size, and even smaller size of the asthma subset serves to limit the ability to detect between group differences, particularly since asthma status, even within the study entry criteria limitations, was not controlled for at enrollment, e.g., by stratification.

The use of eDiary data is further limited by the relatively high background reporting rates observed in the placebo groups of the overall and asthma subset populations.

Comparisons among treatment groups in the overall study population and in the asthma subgroup did not reveal an increase in overall asthma-related events in MK-3641 treated subjects by dose or as compared to placebo. No dose-response was apparent in the rate of asthma-related events in the overall study population when events were analyzed, regardless of reporting source (whether by eDiary or by routine study adverse event reporting). However, an escalating dose-response effect was observed in the asthma subpopulation for adverse events chest tightness/discomfort, cough, dyspnea (Table 13).

Local application site reactions

Pre-specified analysis of the local application site reactions (listed below) was performed. Further, the number of days to onset and the number of days of occurrence of these AEs were also pre-specified and assessed. Across all active treatment groups, the three most commonly reported local application site AEs were Throat irritation, Ear pruritus, and Oral pruritus.

Dysphagia	Lip swelling	Stomatitis
Ear pruritus	Oral discomfort	Swelling face
Edema mouth	Oral pruritus	Swollen tongue
Glossodynia	Oropharyngeal swelling	Tongue edema
Hypoaesthesia oral	Palatal edema	Throat irritation
Larynx irritation	Paraesthesia oral	Throat tightness
Lip edema	Pharyngeal edema	

Local application site reactions - Phase 1 study

Twenty-eight of forty (70%) Amb a 1-U recipients reported local application site reactions versus only 2 (15.4%) placebo recipients in the Phase 1 study, the most common local application site AEs being Oral pruritus (62.5% Amb a 1-U recipients, 0% placebo recipients), Ear pruritus (30% Amb a 1-U recipients, 7.7% placebo recipients), Oedema mouth (15% Amb a 1-U recipients, 0% placebo recipients) and Throat irritation (10% Amb a 1-U recipients, 0% placebo recipients). The Phase 1 study did not reveal a dose response with respect to the overall rate of local applications site reactions or to any individual type of reaction.

Local application site reactions through Day 28 - Phase 2 and/or 3 studies

Six hundred and fifty-four (38.3%) Amb a 1-U recipients reported local application site reactions versus 88 (11.6%) placebo recipients in Phase 2 and/or 3 studies, the most

common local application site AEs being Throat irritation (17.5% Amb a 1-U recipients, 3.8% placebo recipients), Ear pruritus (11.1% Amb a 1-U recipients, 1.1% placebo recipients) and Oral pruritus (12.5% Amb a 1-U recipients, 2.0% placebo recipients). The onset of local application site reactions occurred in the MK-3641 group within a median of 1 to 14 days after treatment initiation.

Local application site reactions in Phase 2 and/or 3 studies through Week 52
For the two studies, P05233 and P05234, that evaluated safety through Week 52, a total of 3453 (47.1%) Amb a 1-U recipients reported local application site reactions versus 52 (13.5%) placebo recipients, the most common local application site AEs being Throat irritation (17.5% Amb a 1-U recipients, 3.8% placebo recipients), Ear pruritus (11% Amb a 1-U recipients, 1.1% placebo recipients), and Oral pruritus (12.5% Amb a 1-U recipients, 2% placebo recipients). As with the 28 Day data, the onset of the majority of local application site reactions occurred within a median of 1 to 14 days after treatment initiation.

Severe local application site reactions - Phase 2 and/or 3 studies (28-Day / 52-Week)
20 of the 2464 subjects had one or more local application site reaction classified as severe. This included 19 Amb a 1-U recipients and 1 placebo recipient, 13 of whom were discontinued from the study including 2 Amb a 1-U recipients who were treated with epinephrine for their symptoms.

Limitations of the safety database

- The majority of subjects were Caucasian (82%).
- Individuals with asthma classified as severe or uncontrolled, and asthmatics using high doses of inhaled corticosteroids (ICS) or controlled with long-acting beta agonists (LABA) were excluded from the studies. (The sponsor reports this is in keeping with current immunotherapy practice guidelines.)
- Individuals with a history of anaphylaxis, chronic urticaria or angioedema were excluded from the studies.
- Subjects who were pregnant, not using adequate contraception or breast-feeding were excluded from participation in the studies.
- Long-term safety, i.e., ≥ 1 year duration of treatment, has not been studied.
- Safety in children has not been studied, but a pediatric study is planned to begin after licensure in adults.

1. Postlicensure Safety Review

a. Regarding STN 125478.0.5 information on the planned post-licensure study in children 5-17 years of age, the sponsor should further clarify the wording of exclusion criteria in the pending protocol, Item 4. b: “Immunosuppressive treatment <3 months (except steroids for allergic/asthma symptoms)”.
   i. Does the sponsor intend this criterion to read “Any immunosuppressive treatment within 3 months prior to study entry”? How does the sponsor intend to define “steroids for allergic/asthma symptoms”, and is there a limitation on dose or duration of steroid treatment?

   ii. Does this include all immunosuppressives?

   iii. It would be useful for entry criteria to address the specific immunosuppressives or classes of immunosuppressives that might be used in this population, as well as other immunosuppressives that might be used for other reasons in a given individual.

   iv. Is any dose, route or duration of steroids allowed to treat allergic/asthma symptoms?

      1. Item 4. d: The term “high-dose inhaled corticosteroids” should be clarified as to dose or dose-equivalents.

      2. Are oral or parenteral corticosteroids allowed or is their usage restricted by dose, route, or time since last used?

b. Postlicensure safety data are not available as the product has not been marketed.

2. Integrated Risk Assessment

a. Description of important safety issues identified by the reviewer from any source that do not trigger a PMR or REMS

   The clinical development plan has shown that this oral allergen product has the potential to cause allergic reactions. Although significant increases in serious or life-threatening allergic-type adverse events were not reported in the clinical studies, it should be kept in mind that these studies enrolled relatively healthy subjects 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 anaphylaxis and/or angioedema

Also, the pooled Phase 2 and/or 3 study subjects' median age was 40 years, and individuals ≥ 50 years of age were excluded from long-term studies, i.e., studies conducted for more than 28 days.

The sponsor has proposed labeling, including a patient package insert, to address these issues.

b. Description of any signal(s) identified by the reviewer from any source that trigger a PMR or REMS:

None

c. 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.

3. **Recommendations**
Based upon the submitted information and current clinical knowledge, at this time OBE/DE agrees that routine pharmacovigilance as proposed by the sponsor is appropriate should this product be licensed

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