Pharmacovigilance Plan Review

From: Patricia Rohan, MD

To: Jon Daugherty, PhD, Chair

Through: Christopher Jankosky, MD, MPH, Branch Chief

Michael Nguyen, MD, Acting DE Director

Subject: BLA 125473

Applicant: Merck Sharp & Dohme Corp.

Product: Standardized Allergenic Extract, Timothy Grass (Phleum pratense)
MK-7243
GRASTEK
Marketed as GRAZAX outside the US

Proposed Indication: For treatment of diagnosed Timothy and related grass pollen induced allergic rhinitis, with or without conjunctivitis in adults and children 5 years of age and older

Submission Date: 25-JAN-2013

PVP Submission Date: 25-JAN-2013

Action Due Date: 25-JAN-2014

1. Introduction

a. Product description

The product, variously referred to as GRASTEK, GRAZAX or MK-7243, is a fast-dissolving (e.g., less than 10 seconds), sublingual tablet for oromucosal delivery.

The active substance is a natural grass pollen extract which is partially purified and standardized from Timothy grass. Timothy grass, a member of the Pooideae subfamily, demonstrates distinct cross-reactivity with other Pooideae members such as rye (*lolium*), meadow fescue (*festuca*), bluegrass/june (*poa*), orchard/cocksfoot (*dactylis*), sweet vernal (*anthoxanthum*), and redtop/bent/velvet (*agrostis*) and is partially cross-reactive with Johnson grass, all of which are major aeroallergens in North America (White 2003).

The tablet has a potency of 2800 BAU (Bioequivalent Allergy Unit).

b. Pertinent regulatory history

i. Prior licensure

A Marketing Authorization Application for GRAZAX® (MK-7243) was filed by the Mutual Recognition Procedure in the European Union (EU) and ALK-Abello A/S (referred to as ALK in this document) received its first approval in 2006 in Sweden. Subsequently, ALK has received marketing authorizations in 30 countries.

1. **Summary of indications and usage**
   GRAZAX is indicated in the EU for the disease-modifying treatment of grass pollen-induced rhinitis and conjunctivitis in adults and children (5 years or older) with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen.

2. **Major postmarketing safety finding**
   a. Sublingual administration of allergen in allergic individuals may result in local allergic events in the mouth and throat, as might be anticipated. These events include pruritus, paraesthesia and swelling.

   b. Asthmatic symptoms were common features of serious treatment-related AEs in postmarketing studies.

   c. Severe asthma and/or progressive/persistent local symptoms with continued treatment appears to identify individuals who should not receive sublingual immunotherapy.

i. CBER Complete Response letters: None

ii. Relevant prior Advisory Committee meetings: None

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 studies should the product be licensed.

2. Materials reviewed

a. Routine items:

i. Pharmacovigilance Plan:

STN 125473.0 **-** Section 1.11.4

ii. Pertinent sections of the licensing application selected by the reviewer

STN 125473.0:
1.11.4 Pharmacovigilance Plan
1.14 Labeling
2.5 Clinical Overview
2.7.4 Summary of Clinical Safety
2.7.6 Synopses of Individual Studies

STN 125473.0.5:
120 Day Safety Update Report
Including updates of spontaneously reported adverse events from Europe and updates on ongoing non-IND studies, including one for asthma prevention

STN 125473.0.12
Revised Section 2.7.4 to provide the correct numbers of exposed subjects from post-marketing observational studies

i. Postlicensure Safety Data

The product is not licensed in the U.S.; non-U.S. experience is reviewed below.

ii. Input from CBER Product, Clinical and Statistical reviewers

Final determination of the safety profile of the product used in the studies submitted to this BLA is pending final clinical, statistical and product reviews.

iii. Medical Literature

Respiratory allergy is estimated to affect up to half of the population in some countries, and up to 500 million people worldwide (Bousquet 2008). In North America, allergy to grass pollen is one of the most common inhalant allergies (Arbes 2005) and the third National Health and Nutrition Examination Survey study recently reported that the prevalence of atopic sensitization among the US population aged 6 to 59 years was 27% to perennial rye grass, a northern pasture grass with high cross-reactivity to *Phleum pratense* (Arbes 2005).

Available treatments include environmental control and avoidance, pharmacologic products (antihistamines, leukotriene-receptor antagonists, glucocorticosteroids) and subcutaneous allergen injections.

The rate of fatal reactions with subcutaneous immunotherapy has been estimated at 1 death per 2 million injections (Reid 1993); while retrospective chart review of 338 patients who presented for 10,497 injection visits at the

Mayo Clinic found the rate of anaphylactic shock reactions to be 0.12% of injections and 3.8% of patients (Rank 2008).

There have been two published reports of documented anaphylactic shock with use of sublingual immunotherapy products, but not Grastek (Antico 2006; Blazowski 2008).

b. Other items (if available)

i. Information under MOU (foreign regulatory or public health agencies): None

ii. Advisory Committee reviews: None

iii. International postmarketing experience with the same product

GRAZAX has an estimated 112,981 patient-years of postmarketing use in Europe from initial licensure in 2006 through 30 SEP 2012.

Exposure estimates – marketed product

Exposure methodology: GRASTEK (marketed as GRAZAX® outside the U.S.) is distributed in packages of 30 and 100 tablets (oral lyophilisates), respectively, and 364 tablets equals 1 treatment year (TY). It is important to note that the estimated patient-treatment years (PTYs) are not equivalent to the absolute number of patients treated. It should also be noted that the overall PTY estimates are likely to underestimate the true number of patients exposed to the product due to the fact that PTY estimates the number of patients who could have been treated for one year based on the tablets distributed.

Spontaneous reporting

Spontaneous data is based upon an estimated MK-7243 exposure of approximately 112,981 patient treatment years.

A total of 1,268 spontaneous postmarketing healthcare provider reports were submitted to ALK through 30 SEP 2012, of which 116 were classified as serious. Of these 116 cases, 27 were assessed as serious systemic allergic reactions.

The most frequently reported spontaneous AEs were oral pruritus, edema mouth, lip swelling, throat irritation, and swollen tongue; the most frequently reported serious spontaneous AE was dyspnea.

Fatalities – spontaneous reports

No reported treatment-related fatalities were reported in the post-marketing safety data as of 30 SEP 2012.

Anaphylactic shock– spontaneous reports

One spontaneous report of anaphylactic shock was reported, received after the cutoff date of 30 SEP 2012. See safety update section below.

Serious systemic allergic reactions– spontaneous reports
Twenty-seven reports of serious systemic allergic reactions were received through 30 SEP 2012, 11 of which overlap with the serious local allergic reaction reports.

Serious local allergic reactions– spontaneous reports
Thirty-five reports of serious local reactions have been received through SEP 2012; 11 of which overlap with the serious systemic allergic reaction reports.

Epinephrine use – spontaneous reports
Epinephrine was used on 10 occasions as treatment in 9 individuals (one 12 year old patient was treated on two separate occasions). The epinephrine was administered by intramuscular or subcutaneous route in 4 cases, by inhalational route in 4 cases, and by an unspecified route in 2 cases.

EU-registration postmarketing support studies
A total of 1749 adult subjects with or without asthma participated in 6 post-EU approval market-support studies, 1666 who received MK-7243 at 2800 BAU dose daily. These studies were performed as life cycle management studies and not as post-approval commitment studies, e.g., related to specific safety issues.

Table 1: Post EU-Registration Market Support Studies

Study	MK-7243[1] (N)	Placebo (N)	Age Range (Yrs.)
GT-10	460	---	17 - 66
GT-10 (extension study)	264	---	19 - 67
GT-15	628	---	18 - 73
GT-16	52	26	18 - 61
GT-17	261	---	18 - 63
GT-18 (Initiation during allergen season)	219	57	18 - 66
GT-19	46	---	21 - 65
Total Subjects by treatment	1666	83	17 - 73

1. Daily dose of 2800 BAU.
From STN 125473.0, Section 2.5, Table 12

The sponsor reports no new safety signals were identified, and the pattern of reported AEs was consistent with that observed in the clinical studies, with a predominance of local application site reactions. There was one serious anaphylactic reaction reported in these trials (Study GT-10), no reports of anaphylactic shock and one report of death (Study GT-15, extension phase) as summarized in Table 2.

Study	Treatment	Serious Adverse Events
GT-10	MK-7243	Asthma exacerbation
		Acute allergic reaction, acute asthma
		Hoarseness, laryngitis
		Knee arthralgia/surgery
		Work accident – cut to hand
		Anaphylactic reaction to multiple wasp stings
		Car accident – tinnitus
		Sigmoid diverticulitis
GT-10 Extension	MK-7243	Hysterectomy
		Gallbladder disorder
GT-15	MK-7243	Acute recurrent of ulcerative colitis
		Oral ulcerations, pain, cervical adenopathy, fever, staphylococcus and streptococci infection
		Asthma attack
GT-15 Extension	MK-7243	Death, cardiac arrest
GT-16		No SAEs reported
GT- 17		No SAEs reported
GT-18	MK-7243	Sinusitis
		Traffic accident
		Salmonellosis
		Rupture of meniscus
GT-19		No SAEs reported

1. 54 year old male on MK-7243 12-DEC-2007 to 30-JUN-2008 without AE. Resumed treatment 04-FEB-2009. Cardiac arrest [redacted]. History of precordial pains on effort that the sponsor reports is "likely" ischemic heart disease", i.e., angina pectoris, but this is not reported as medically confirmed. No history of asthma, hypertension, hypercholesterolemia or thrombosis.
From STN 125473.0, Sections 2.7.4.6.1 - 2.7.4.6.7 (including update from STN 125473.0.12)Sect

Postmarketing studies and other post approval programs

To date, 20 MK-7243 observational postmarketing studies have been completed; four are ongoing; and one was cancelled. Approximately 8,500 subjects have been exposed to at least 1 dose of MK-7243 in these post-marketing trials with the majority of these subjects being adults. No deaths or treatment-related anaphylactic shock have been reported.

Table 3: Completed Postmarketing Observational Studies			
Study	**Country**	**Individuals (N)**	**SAEs (N)**
SHX0801	Germany	1109	4
SHX0802	Germany	364	0
SHX0804	Germany	271	0
PMS-GT-AT-01	Austria	577	2
PMS-GT-NL-01	Netherlands	247	0
PMS-GT-SE-01	Sweden	269	4
PMS-GT-SE-02	Sweden	74	0
PMS-GT-FI-01	Finland	47	0
PMS-GT-01	Switzerland	247	0
PMS-GT-02[a]	Germany	1718	6
PMS-GT-03[a]	Austria	43	0
PMS-GT-04	Netherlands	245	2
PMS-GT-05	Spain	115	0
PMS-GT-06	Finland	156	2
PMS-GT-07	Netherlands	55	0
PMS-NI-GT-08	Germany	672	4
OBS-SIT-01	Germany	655	No clinical study report
IMMUNIS	Germany	61	No clinical study report
NI-GT-09	Austria	364	0
NI-GT-12	Spain	129	0
NI-GT-15	N/A	Cancelled	---
a. 797 subjects were ≤ 17 years of age From STN 125473.0, Section 2.7.4, Table 87 (including update from STN 125473.0.12)			

Twenty-four individuals were reported to have treatment-related allergic SAEs, eight at the time of the first tablet administration.

Five individuals were reported to have experienced treatment-related anaphylactic or hypersensitivity reactions; four of these individuals were treated with epinephrine. Nine serious local allergic reactions occurred, one subject received inhaled epinephrine, and no subject received injectable epinephrine.

Ongoing Postmarketing Studies

Four postmarketing observational studies are classified as ongoing, although NI-GT-14 (France) was recently completed but the study report is not yet available. According to the sponsor the reported rates of SAEs were similar to rates seen in previous postmarketing observational studies.

Table 4: Ongoing Postmarketing Observational Studies[a]			
Study	**Country**	**Individuals (N)**	**SAEs (N)**
NI-GT-10	Switzerland	44	2
NI-GT-13	Finland	500 (planned)	1
NI-GT-14[b]	France	494	3
NI-GT-16	Germany	300 (planned)	0

a. Data cut-off date 30-SEP-2012
b. NI-GT-14 has been completed but the clinical study report is not yet available
From STN 125473.0, Section 2.7.4, Table 88

STN 125473.0.5 Safety Update Report (01-OCT-2012 to 30-APR-2013)
The purpose of this submission is to provide an update with respect to serious adverse events occurring between 01-OCT-2012 (the original submission's data lock point) and 30-APR-2013.

This submission contains updates on serious adverse experiences (AEs) that occurred in observational, non-interventional studies and other post approval programs that were still active after the original marketing application cut-off date, 30-Sep-2012.

The post-marketing spontaneous reporting experience has also been updated, as MK-7243 has been approved by the European Medicines Agency (EMA) since 2006.

Note that no additional information from the clinical development program (i.e. clinical trials) is included since these trials were completed at the time of the original marketing submission.

<u>Spontaneous postmarketing reports – safety update</u>
Note: A given adverse event report may appear in more than one risk group, in the following tables.

Spontaneously reported serious adverse events (safety update report)
From 01-OCT-2012 through 30-APR-2013, a cumulative total of 139 spontaneous postmarketing reports of SAEs in MK-7243 recipients had been received by the sponsor. This number includes 15 reports that were not been included in an IND Annual Report, the original BLA, or included in a specific risk group in this Safety Update Report, e.g., Systemic Allergic Events, and which are summarized in the following table.

Age/Sex	Event	Treatment	Outcome
65 yr. M[1]	Anaphylactic shock, depressed level of consciousness, hypotension, heart rate increased, wheezing, urticaria, face edema, altered consciousness (no loss of consciousness)	Epinephrine (IM, IV), corticosteroids (IV), oxygen	Recovered
24 yr. M	Swelling and angioedema of face	None specified	Recovered
22 yr. M	Dizziness, nausea, vomiting	None specified	Recovered
12 yr. M	Swelling – sublingual, tongue and lip; itchy/irritated tongue, nausea, headache, feeling unwell, oral pain, dry throat. After MK-7243 was stopped and symptoms, he was re-started with oral antihistamine premedication. Only subsequent symptom was dry throat	None specified	Recovered
9 yr. M	Lip oedema, oral pruritus	Antihistamine (oral), corticosteroid (oral)	Recovered
17 yr. M	Exanthema generalized	Possibly antihistamines	Recovered
10 yr. M	Swollen tongue, compromised speech	Antihistamine	Recovered
15 yr. M	Abdominal discomfort, diarrhea, vomiting, headache, temper tantrum	Unknown	Recovered
11 yr. M	Swollen tongue, pruritus, erythema	Corticosteroids (IV), antihistamine (IV)	Recovered
5 yr. F	Erythema facial, laryngeal discomfort	Antihistamine (oral)	Recovered
39 yr. F	Vomiting, stomach pain, trembling, palpitations, headache	Unknown	Recovered
40 yr. M	Swollen tongue	Unknown	Recovered
Adult M	Angioedema	Unknown (hospitalized overnight)	Unknown
43 yr. F	Asthma exacerbation, 3 months later sinus congestion	Asthma – steroid (oral), antibiotic (oral) Sinus congestion – steroid (oral), antibiotic (oral)	Recovered
16 yr. M	Nummular exanthema with central epidermolysis	Topical corticosteroid	Unknown

1 Previously reported as late-breaking safety information, including CIOMS, in original BLA submission. It is summarized in narrative of this safety update.
From STN 125473.0.5, Safety Update, Appendix 1: CIOMS for Serious Spontaneous Post-Marketing Reports

Spontaneously reported serious systemic allergic adverse events (safety update report)
Ten reports of serious systemic allergic adverse events were reported spontaneously from 01-OCT-2012 to 30-APR-2013, which were coded with one more of the following PT terms: anaphylactic reaction, anaphylactic shock and/or hypersensitivity. These reports are summarized in the following table.

Table 6: Spontaneously Reported Serious Systemic Allergic Adverse Events[1]
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Age/Sex	Event	Treatment	Outcome
17 yr. F	Hypersensitivity, oedema lips, mouth, throat; difficulty speaking, dysphagia, throat pruritus, anxiety, rash over arms	Antihistamine (oral)	Recovered
18 yr. F	Anaphylaxis, swelling of tongue, lip; asthma, dyspnea, tachycardia, oral paraesthesia	Antihistamine (IV), corticosteroid (IV), volume substitute	Recovered
65 yr. M	Anaphylactic shock, depressed level of consciousness, hypotension, heart rate increased, wheezing, urticaria, face edema, altered consciousness (no loss of consciousness)	Epinephrine (IM, IV), corticosteroid (IV), oxygen	Recovered
40 yr. F	Anaphylactic reaction, hypotension (BP=80/60), heart rate increased (112 bpm), vital capacity decreased (82%), chest tightness, wheezing, oral pruritus	β-2 agonist (inhaled), antihistamine (oral)	Recovered
14 yr. M	Anaphylactic reaction, respiratory distress, dyspnoea, pruritus generalised, urticaria, dysphonia	Epinephrine (IV), Antihistamine (oral), corticosteroid (IV), β-2 agonist (inhaled)	Recovered
36 yr. F	Anaphylactic reaction, throat tightness, wheezing, lip swelling, agitation	Epinephrine (inhaled), antihistamine (IV), corticosteroid (IV),	Recovered
7 yr. M	Allergic/anaphylactic reaction, swelling of face, drowsiness, lip swelling, mouth oedema, redness around lips	Epinephrine (IM), antihistamine (unknown route), corticosteroid (oral)	Recovered
14 yr. F	Anaphylaxis, bronchial obstruction, throat swelling, dyspnea, chest pressure, oedema of mouth	Epinephrine (IM), antihistamine (oral), corticosteroid (oral), β-2 agonist (inhaled)	Recovered
17 yr. F	Anaphylactic reactions, dyspnea, angioedema, swelling of neck and lips, tremor	Epinephrine (SQ), antihistamine (IV), corticosteroid (IV),	Recovered
16-18 yr. M	Anaphylactic reaction, cardiovascular disorder (not further specified)	Antihistamine, corticosteroid, β-2 agonist (inhaled), possibly epinephrine	Unknown

1 Reports coded with any of the following preferred terms: Anaphylactic reaction, Anaphylactic shock, and Hypersensitivity
From STN 125473.0.5, Safety Update, Appendix 4: CIOMS for Serious Systemic Allergic Adverse Events from Spontaneous Post-Marketing Reports

Spontaneously reported serious asthmatic adverse events (safety update report)
Thirteen reports of serious asthmatic adverse events were reported spontaneously from 01-OCT-2012 to 30-APR-2013, based upon one or more of the following preferred terms: asthma, asthma exercise induced, bronchial hyperreactivity, bronchial obstruction, bronchospasm, cough, dysphonia, dyspnoea, forced expiratory volume decreased, hyperventilation, obstructive airways disorder, peak expiratory flow rate decreased, prolonged expiration, asthma late onset, asthmatic crisis, reactive airways dysfunction syndrome, status asthmaticus and wheezing.

- Seven of the 13 reports were also classified as serious systemic allergic reactions, with asthma symptoms such as dyspnea and wheezing.

- One of the 13 cases, the 1 case of anaphylactic shock (serious asthmatic reaction, as well as serious systemic allergic reaction), was considered life-threatening by the reporter. The other 12 cases identified were not reported as life-threatening or resulting in death.

- Eleven of the 13 patients recovered from the events, 1 report had an unknown outcome, and 1 outcome was reported as not recovered – for this latter report, no additional information is expected.

These reports are summarized in the following table.

Table 7: Spontaneously Reported Asthma – Serious Adverse Events[1]
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Age/Sex	Event	Treatment	Outcome
18 y F	Anaphylactic reaction, swollen tongue, lip swelling, asthma, dyspnoea, tachycardia, paraesthesia oral	Antihistamine, corticosteroid	Recovered
47 y F	Pneumonia, heart rate irregular, dyspnea	Corticosteroid, β-2 agonist	Not Recovered
65 y M	Anaphylactic shock, depressed level of consciousness, hypotension, heart rate increased, wheezing, urticaria, face edema, altered consciousness (no loss of consciousness)	Corticosteroid, epinephrine	Recovered
40 y F	Anaphylactic reaction, hypotension, heart rate increased, vital capacity decreased, chest discomfort	Antihistamine, β-2 agonist	Recovered
14 y M	Anaphylactic reaction, respiratory distress, dyspnoea, pruritus generalised, rash generalised, dysphonia, sensation of foreign body, urticaria, oral pruritus, throat irritation, drug ineffective	Antihistamine, corticosteroid, β-2 agonist, epinephrine	Recovered
11 y F	Dyspnoea, oedema mouth, oral pruritus	Antihistamine	Recovered
36 y F	Anaphylactic reaction, throat tightness, wheezing, lip swelling, agitation	Antihistamine, corticosteroid, epinephrine	Recovered
43 y F	Asthma (exacerbation), dyspnoea, cough	Corticosteroid, antibiotics	Recovered
36 y M	Asthma, hypersensitivity, cough, throat irritation, feeling abnormal, pneumonia (suspected)	Corticosteroid, β-2 agonist, anti-cholinergic, leukotriene receptor antagonist	Not specified
37 y M	Asthma, hypersensitivity	Not specified	Not recovered
3 y M	Asthma, oxygen saturation decreased, cough, off label use	Corticosteroid, β-2 agonist	Recovered
14 y F	Anaphylactic reaction, bronchial obstruction, pharyngeal oedema, dyspnoea, chest discomfort, oxygen saturation decreased, oedema mouth, anxiety, oral discomfort	Antihistamine, corticosteroid, β-2 agonist, epinephrine	Recovered
17 y F	Anaphylactic reaction, dyspnoea, angioedema, local swelling, lip swelling, tremor	Antihistamine, corticosteroid, epinephrine	Recovered

1 Reports coded with any of the following preferred terms: asthma, asthma exercise induced, bronchial hyperreactivity, bronchial obstruction, bronchospasm, cough, dysphonia, dyspnoea, forced expiratory volume decreased, hyperventilation, obstructive airways disorder, peak expiratory flow rate decreased, prolonged expiration, asthma late onset, asthmatic crisis, reactive airways dysfunction syndrome, status asthmaticus and wheezing.
From STN 125473.0.5, Safety Update, Appendix 5: CIOMS for Serious Asthma Adverse Events from Spontaneous Post-Marketing Reports

Spontaneously reported serious local reactions with throat symptoms (safety update report)
Six reports of serious local reactions with throat symptoms were reported spontaneously from 01-Oct-2012 to 30-Apr-2013, based upon the following preferred terms: choking sensation, dysphagia, dysphonia, laryngeal edema, larynx irritation, oropharyngeal swelling, pharyngeal edema, stridor, throat tightness and upper airway obstruction.

Four of the 6 reports were also classified a serious systemic allergic reaction, 2 of which were also classified as a serious asthmatic reaction.

- None of the 6 reports were reported as life-threatening or resulting in death.
- All 6 patients recovered from the reported events.

These reports are summarized in the following table.

Age/Sex	Event	Treatment	Outcome
17 y F	Hypersensitivity, oedema mouth, pharyngeal oedema, dysphagia, throat irritation	Antihistamine	Recovered
14 y M	Anaphylactic reaction, respiratory distress, dyspnoea, pruritus generalised, rash generalised, dysphonia, sensation of foreign body, urticaria, oral pruritus, throat irritation, drug ineffective	Antihistamine, corticosteroid, β-2 agonist, epinephrine	Recovered
5 y M	Oedema mouth, oral pruritus, lip swelling, dysphagia	Antihistamine	Recovered
36 y F	Anaphylactic reaction, throat tightness, wheezing, lip swelling, agitation	Antihistamine, corticosteroid, epinephrine	Recovered
14 y F	Anaphylactic reaction, bronchial obstruction, pharyngeal oedema, dyspnoea, chest discomfort, oxygen saturation decreased, oedema mouth, anxiety, oral discomfort	Antihistamine, corticosteroid, β-2 agonist, epinephrine	Recovered
9 y F	Oedema mouth, oral pruritus, dysphagia	Unknown	Recovered

1 Reports coded with any of the following preferred terms: choking sensation, dysphagia, dysphonia, laryngeal edema, larynx irritation, oropharyngeal swelling, pharyngeal edema, stridor, throat tightness and upper airway obstruction
From STN 125473.0.5, Safety Update, Appendix 6: CIOMS for Serious Local Reactions with Throat Symptoms from Spontaneous Post-Marketing Reports

Spontaneously reported serious adverse events reporting epinephrine use (safety update report)
Epinephrine was reported as a treatment for 8 patients experiencing serious adverse events as summarized in the following table.

Table 9: Spontaneously Reported Serious Adverse Events with Epinephrine Administration[1]
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Age/Sex	Event	Treatment	Outcome
20 y M	Angioedema, bronchospasm, dyspnea	Adrenaline, antihistamine	Recovering
65 y M	Anaphylactic shock, depressed level of consciousness, hypotension, heart rate increased, wheezing, urticaria, face edema, altered consciousness (no loss of consciousness)	Corticosteroid, epinephrine	Recovered
14 y M	Anaphylactic reaction, respiratory distress, dyspnoea, pruritus generalised, rash generalised, dysphonia, sensation of foreign body, urticaria, oral pruritus, throat irritation, drug ineffective	Antihistamine, corticosteroid, β-2 agonist, epinephrine	Recovered
36 y F	Anaphylactic reaction, throat tightness, wheezing, lip swelling, agitation	Antihistamine, corticosteroid, epinephrine	Recovered
7 y M	Allergic / anaphylactic reaction, swelling face, blood pressure decreased, feeling abnormal, lip swelling, oedema mouth, erythema	Antihistamine, corticosteroid, epinephrine	Recovered
14 y F	Anaphylactic reaction, bronchial obstruction, pharyngeal oedema, dyspnoea, chest discomfort, oxygen saturation decreased, oedema mouth, anxiety, oral discomfort	Antihistamine, corticosteroid, β-2 agonist, epinephrine	Recovered
17 y F	Anaphylactic reactions, dyspnoea, angioedema, local swelling, lip swelling, tremor	Antihistamine, corticosteroid, epinephrine	Recovered
16-18 yr. M	Anaphylactic reactions, angioedema, dyspnoea, swollen neck / lower lip, tremor, cardiovascular disorder	Antihistamine, corticosteroid, epinephrine	Recovered

1 Reports indicating epinephrine was used as treatment for a serious adverse event.
From STN 125473.0.5, Safety Update, Appendix 7: CIOMS for Serious Adverse Events treated w/ Epinephrine from Spontaneous Post-Marketing Reports

Postmarketing surveillance studies- safety update
One of the 4 ongoing non-interventional, observational, multicenter post-marketing surveillance trials, NI-GT-14, was completed during the safety update period, however, the clinical study report is not yet available.

Two subjects experienced SAEs from the on-going surveillance trials:

NI-GT-13
A 26 year old female with asthma experienced worsening local symptoms (oral cavity and throat discomfort and throat swelling) as well as skin pruritus and urticaria on Day 95. She self-treated with an antihistamine and was taken to an emergency unit by ambulance where she was noted to be extremely anxious, had normal vital signs and physical examination, and had no apparent respiratory difficulties. She was treated with IV antihistamine and IV hydrocortisone, but was not treated with epinephrine. The treating physician felt that an antecedent throat infection the previous week might have been a trigger to the adverse events.

NI-GT-10
A 13 year old male experienced a fractured forearm on an unknown date, requiring hospitalization and surgery.

3. Pharmacovigilance Plan Review

a. Clinical Safety Database – see Section 4, below

b. Safety concerns

POTENTIAL / ANTICIPATED SAFETY ISSUES
Specific anticipated or potential risks included systemic allergic reactions, including anaphylactic reactions and local allergic reactions with potential to compromise airway and acute worsening of asthma symptoms (exacerbation).

Anaphylaxis or systemic allergic reactions
Systemic allergic reaction(s), including anaphylactic reactions, Anaphylactic shock, and Hypersensitivity reactions; and local allergic reactions with potential to compromise airway were prospectively monitored in clinical studies. Safety analyses included review of anaphylactic reactions (PT) /anaphylaxis (LLT); Hypersensitivity (PT); systemic allergic reactions or allergic reactions (LLT); allergic adverse events as defined by Food Allergy and Anaphylaxis Network anaphylaxis criteria *(Sampson 2005)* and those involving epinephrine administration.

i. Important identified safety issues
The following events were observed in clinical studies and are common in the treatment population.

- Serious systemic allergic reactions, including anaphylactic reactions
- Local allergic reactions with potential to compromise airway

- Acute worsening of asthma symptoms (exacerbations)

ii. Important potential safety issues

Based upon the product class and postmarketing experience outside the US, potential safety concerns that should be considered for enhanced surveillance:

- Anaphylactic shock
- Severe laryngopharyngeal disorders

The sponsor additionally points out the potential for respiratory compromise in children due to their relatively smaller airway although such events have not been reported in the post-marketing setting to date.

- Autoimmune disorders

iii. Important missing information

- Pregnancy, lactation
- Use in children <5 years of age
- Co-administration with Ragweed (SLIT)

c. Sponsor's proposed actions and timelines

i. Enhanced pharmacovigilance activities proposed by sponsor

Table 10: Safety Concerns & Planned Pharmacovigilance Actions

	Routine pharmacovigilance	Follow-up questionnaire	PI & PPI information	Ongoing Phase 4 studies
Important Identified Risks				
Serious systemic allergic reactions, including anaphylactic reactions	X	X	X	X[1]
Local allergic reactions with potential to compromise airway	X	X	X	X[1]
Acute worsening of asthma symptoms exacerbations	X	X	X	X[1]
Important Potential Risks				
Anaphylactic shock (class risk for subcutaneous immunotherapy [SCIT])	X	X	X	X[1]
Use in Children Due to Relatively Smaller Airway	X	---	---	---
Important Missing Information				
Pregnancy, lactation	X		X	
Use in children <5 years of age	X		X	
Co-administration with Ragweed (SLIT)	X		X	X[2]

1. Phase 4 ongoing studies (Table 4); 2. Phase 4 Grass & Ragweed oral immunotherapy co-administration study
From 125473.0, Section 1.11.4, PVP, Section 1.2

ii. Review of Postmarketing Study proposal or protocol synopsis
No additional postmarketing studies are proposed by the sponsor.

4. Review of other information from the Managed Review process

a. Pertinent positive information suggesting a safety signal from the clinical or statistical reviewer: None to date

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

2.5 Clinical Overview
2.7.4 Summary of Clinical Safety
2.7.6 Synopses of Individual Studies

Clinical Safety Data

The clinical safety database includes 4700 subjects from 13 studies, including 2389 subjects randomized to MK-7243 (2114 to 2800 BAU) in Phase 2 and/or 3 studies. The mean subject age was 36 years in the adult cohort and 12 years in the pediatric cohort, most subjects were classified as Caucasian (88% of adults, 98% of adolescents and children) and most were from the US (57% of adults and 67% of adolescents and children).

Table 11: Overview of Clinical Studies[1]

Study	Phase	Outcomes	GRASTEK N	Placebo N	Age (years)
Adult Studies					
GT-01	1	Safety	39	8	20-57
GT-02 (dose-finding)	2/3	Safety / Efficacy	569	286	18-66
GT-03	1	Safety	63	21	20-61
GT-04	1	Safety	32	11	18-42
GT-07	2	Safety / Efficacy (allergic rhinitis and/or asthma)	74	40	18-64
GT-08[2] (Europe)	3	Safety / Efficacy	316 (yr. 1)	318 (yr. 1)	18-63[3]
			189 (yr. 2)	162 (yr. 2)	18-63[3]
			170 (yr. 3)	138 (yr. 3)	18-63[3]
			157 (yr. 4)	126 (yr. 4)	18-63[3]
			145 (yr. 5)	113 (yr. 5)	18-63[3]
GT-14 (US)	3	Safety / Efficacy	163	166	18-65
P05238 (N. America)	3	Safety / Efficacy	213	225	18-63
P08067 (N. America)	3	Safety / Efficacy	608	610	18-65
Total Adult Subjects (≤ 66 years of age)			**2077**	**1685**	**18 - 66**
Pediatric Studies					
GT-09	1	Safety	23	7	5 - 12
GT-11	1	Safety	22	8	5 - 12
GT-12 (Germany)	3	Safety / Efficacy	126	127	5 - 16
P05239 (N. America)	3	Safety / Efficacy	175	169	5 - 18[4]
P08067 (N. America)	3	Safety / Efficacy	144	139	5 - 18
Total Pediatric Subjects			**490**	**450**	**5 - 18**

1. Grastek recipients in Phase 2 and Phase 3 studies received a single daily dose of 2800 BAU, except study GT-02 (daily doses from 93-2800 BAU). Phase 1 dose regimens varied and are reported in SQ-U units which cannot be directly converted to BAUs. Please refer to the clinical review, the individual Phase 1 clinical study reports (Section 5.3.5.1), and study synopses, Section 2.7.6.
2. Includes long-term extension data from 3 treatment years and 2 follow-up years.
3. Age at screening
4. One subject classified as 18 years of age was actually 17 years of age at screening and randomization.
From STN 125473, Section 2.5 Table 1

The numbers of subjects exposed to active and to placebo treatment by age in Phase 2 and Phase 3 studies are summarized in the following table.

Table 12: Exposure in Phase 2 and 3 Studies (number of subjects)

	All Treatments	MK-7243	Placebo
All Ages	4465	2389	2076
> 18 years	3587	1944	1643
> 12 years to ≤ 18 years	481	237	244
≤ 12 years	397	208	189

Subjects are included if they received at least 1 dose of study product or placebo.
One subject in P05239 was 18 years old at randomization and is included in the >18 years age group for exposure but analyzed in the pediatric age group. Three placebo subjects were randomized but not treated in the adult population.
From STN 125374, Section 2.5, Table 9.

Overview

Phase 1

For adults ages 18 to less than 50 years old (N = 124), Phase 1 studies revealed a higher rate of AEs in the combined dose groups (90.3%) vs. placebo (58.1%), with some evidence of a dose-response: 933 BAU (55.6%), 2800 BAU (94.4%), 5600 BAU (83.3%), 11200 BAU (100%) and 18,666 BAU (100%), 28,194 BAU (87.5%), 37,592 (100%). Similar dose-responses were seen for throat irritation, ear pruritus, allergic conjunctivitis and eye pruritus, but no dose-response was seen for asthma, cough, dyspnea, throat tightness or wheezing.

There were only 3 subjects 50 to <65 years of age (1 in the 11,200 BAU group, 1 in the 28,194 BAU group and 1 in the placebo group), making comparisons of limited usefulness.

For children 5 to 18 years of age (N = 60), Phase 1 studies revealed the percentage of subjects experiencing AEs in the MK-7243 treatment group (82.2%) was higher than for subjects in the placebo group (66.7%). Dose ranging was not conducted in children, but the most common AEs were itching mouth, itchy throat, ear pruritus, oral pruritus, cough, and abdominal pain, all of which occurred in a greater proportion of subjects treated with MK-7243 than those treated with placebo. There were no reports of throat constriction or pharyngeal edema. Mouth edema occurred in 6 (13.3%) of the 45 MK-7243 subjects and in none of the 15 placebo recipients. Four subjects in the active treatment group developed dyspnea or difficulty breathing compared to none of the placebo recipients.

Phase 2 - Phase 3

Across the Phase 2 and 3 studies, the adult and pediatric subjects receiving GRASTEK reported similar rates of AEs (82.9% and 82.1%, respectively), which were higher than placebo recipients in the same age strata (68.0% and 79%, respectively), with pediatric placebo recipients reporting more AEs as compared to adult placebo recipients. AEs with the highest incidences in adults and children in Phase 2 and 3 studies included local allergic-type reactions: mouth edema, oral pruritus, tongue pruritus, nasopharyngitis, and throat irritation.

Deaths

Three deaths were reported in the 13 clinical studies included in the clinical development program. A 28 year old male MK-7243 recipient died due to a multiple drug overdose involving prescription and illegal drugs (and not including MK-7243); a 42-year old placebo recipient died due to unknown causes several weeks after completing the trial (autopsy report is pending); and a 31-year old male died due to a subarachnoid hemorrhage confirmed by CT scan.

Non-fatal serious adverse events

A total of 69 subjects experienced SAEs during the Phase 1-3 adult and pediatric pivotal clinical development program.

One non-fatal, life-threatening adverse event was reported as an asthmatic reaction 10 minutes after ingesting an herbal mixture and more than 24 hours after the last dose of MK-7243 in a pediatric subjects in study GT-12; one non-fatal life-threatening adverse event was reported as syncope and urticarial vasculitis in an adult subject in study P08067.

Note that one report of death, attributed to a drug overdose and reviewed in the section on deaths, immediately above, is also included in the SAE summary table.

Adult Studies - SAEs

No SAEs occurred in the pooled adult Phase 1 studies (GT-03 and GT-04).

Two of 1828 adults (0.1%) experienced one or more SAEs during the screening period, prior to randomization in Phase 2 and Phase 3 studies. These SAEs included, by PT: macrognathia, malocclusion, oedema peripheral and urticarial, and each PT was reported by only one of the two adults.

SAEs occurring, following randomization, in adult Phase 2 and Phase 3 studies are listed in the following table. The number of subjects in each cohort is too small to detect any potential differences, given the reporting rates for serious adverse events of ≤ 0.7 %.

Table 13: Serious Adverse Events from Adult Phase 2 and Phase 3 Studies[1]

	MK-7243 93 BAU	MK-7243 933 BAU	MK-7243 2800 BAU	Placebo
	N = 136	N = 139	N = 1669	N = 1645
Any serious adverse event	**2 (1.5)**	**2 (1.4)**	**25 (1.5)**	**22 (1.3)**
Cardiac disorders	**0**	**0**	**1 (0.1)**	**0**
Pericarditis	0	0	1 (0.1)	0
Congenital, familial and genetic disorders	**0**	**0**	**0**	**0**
Macrognathia	0	0	0	0
Gastrointestinal disorders	**1 (0.7)**	**0**	**1 (0.1)**	**1 (0.1)**
Abdominal pain	0	0	0	1 (0.1)
Abdominal pain upper	0	0	1 (0.1)	0
Colitis ulcerative	1 (0.7)	0	0	0
Malocclusion	1 (0.1)	0	0	0
General disorders and administration site conditions	**0**	**0**	**3 (0.2)**	**0**
Chest pain	0	0	1 (0.1)	0
Death	0	0	1 (0.1)	0
Device dislocation	0	0	1 (0.1)	0
Oedema peripheral	0	0	0	0
Immune system disorders	**0**	**1 (0.7)**	**0**	**0**
Drug hypersensitivity	0	1 (0.7)	0	0

Table 13: Serious Adverse Events from Adult Phase 2 and Phase 3 Studies[1]				
	MK-7243 93 BAU	**MK-7243 933 BAU**	**MK-7243 2800 BAU**	**Placebo**
	N = 136	N = 139	N = 1669	N = 1645
Infections and infestations	**0**	**0**	**4 (0.2)**	**6 (0.4)**
Appendicitis	0	0	2 (0.1)	2 (0.1)
Cholecystitis infective	0	0	0	1 (0.1)
Diverticulitis	0	0	1 (0.1)	1 (0.1)
Pelvic abscess	0	0	0	1 (0.1)
Pneumonia	0	0	1 (0.1)	1 (0.1)
Viral pericarditis	0	0	0	1 (0.1)
Injury, poisoning and procedural complications	**1 (0.7)**	**1 (0.7)**	**8 (0.5)**	**3 (0.2)**
Clavicle fracture	0	0	1 (0.1)	0
Epicondylitis	1 (0.7)	0	0	0
Foot fracture	0	0	0	2 (0.1)
Forearm fracture	0	0	1 (0.1)	0
Jaw fracture	0	0	1 (0.1)	0
Joint injury	0	0	1 (0.1)	` (0.1)
Laceration	0	0	1 (0.1)	0
Meniscus lesion	0	0	1 (0.1)	0
Multiple drug overdose	0	0	1 (0.1)	0
Road traffic accident	0	1 (0.7)	0	0
Upper limb fracture	0	0	1 (0.1)	0
Metabolism and nutrition disorders	**0**	**0**	**1 (0.1)**	**1 (0.1)**
Diabetic ketoacidosis	0	0	1 (0.1)	0
Hypokalemia	0	0	0	1 (0.1)
Musculoskeletal and connective tissue disorders	**0**	**0**	**3 (0.2)**	**1 (0.1)**
Intervertebral disc degeneration	0	0	1 (0.1)	0
Intervertebral disc protrusion	0	0	2 (0.1)	0
Osteoarthritis	0	0	0	1 (0.1)
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	**0**	**0**	**1 (0.1)**	**3 (0.2)**
Colon cancer	0	0	0	1 (0.1)
Lung adenocarcinoma	0	0	0	1 (0.1)
Malignant melanoma	0	0	1 (0.1)	0
Uterine leiomyoma	0	0	0	1 (0.1)
Nervous system disorders	**0**	**0**	**0**	**2 (0.1)**
Subarachnoid haemorrhage	0	0	0	1 (0.1)
Syncope	0	0	0	1 (0.1)
Pregnancy, puerperium and perinatal conditions	**0**	**0**	**1 (0.1)**	**0**
Abortion spontaneous	0	0	1 (0.1)	0
Psychiatric disorders	**0**	**0**	**0**	**2 (0.1)**
Alcohol abuse	0	0	0	1 (0.1)
Bulimia nervosa	0	0	0	1 (0.1)
Depression	0	0	0	1 (0.1)
Reproductive system and breast disorders	**0**	**0**	**1 (0.1)**	**2 (0.1)**
Dysmenorrhoea	0	0	0	1 (0.1)
Pelvic adhesions	0	0	0	1 (0.1)
Pelvic haematoma	0	0	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**1 (0.1)**	**1 (0.1)**
Asthma	0	0	1 (0.1)	1 (0.1)
Pulmonary embolism	0	0	0	1 (0.1)
Skin and subcutaneous tissue disorders	**0**	**0**	**0**	**1 (0.1)**
Leukocytoclastic vasculitis	0	0	0	1 (0.1)
Urticaria	0	0	0	0
Surgical and medical procedures	**0**	**0**	**1 (0.1)**	**2 (0.1)**
Caesarean section	0	0	0	1 (0.1)
Inguinal hernia repair	0	0	0	1 (0.1)
Toe operation	0	0	1 (0.1)	0
Vascular disorders	**0**	**0**	**0**	**2 (0.1)**
Deep vein thrombosis	0	0	0	1 (0.1)
Venous thrombosis	0	0	0	1 (0.1)

1. Studies GT-02, GT-07, GT-08, GT-14, P05238, P08067
From STN 125473.0, Section 2.7.4, Table 34

Pediatric Studies - SAEs

A single SAE was reported in pediatric Phase 1 studies – a 5 year old male in GT-09 experienced an asthmatic crisis 16 hours after table intake on Day 17 with dyspnea, shortness of breath, non-cardiac chest tightness, wheezing and dry cough. He was hospitalized and was reported to have recovered.

Two of 302 children (0.7%) experienced one or more SAEs during the screening period, prior to randomization in Phase 3 studies. These SAEs included, by PT: appendicitis, and status asthmaticus, each reported by one of the two children.

SAEs occurring in pediatric Phase 3 studies, following randomization, are listed in the following table. The number of subjects in each cohort is too small to detect potential differences, given the serious adverse event reporting rates of ≤ 0.7%.

Table 14: Serious Adverse Events from Pediatric Phase 3 Studies[1]

	MK-7243 2800 BAU	Placebo
	N = 447	N = 434
Subjects reporting:		
Any adverse event	**5 (1.1)**	**7 (1.6)**
Blood and lymphatic system disorders	**0**	**2 (0.5)**
Lymphadenitis	0	1 (0.2)
Thrombotic thrombocytopenic purpura	0	1(0.2)
Gastrointestinal disorders	**0**	**2**
Abdominal pain	0	1 (0.2)
Vomiting	0	1 (0.2)
Infections and infestations	**1 (0.2)**	**2 (0.5)**
Appendicitis	0	1 (0.2)
Pyelonephritis	0	1 (0.2)
Viral myocarditis	1 (0.2)	0
Injury, poisoning and procedural complications	**0**	**1 (0.2)**
Femur fracture	0	1 (0.2)
Musculoskeletal and connective tissue disorders	**1 (0.2)**	**0**
Synovitis	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	**3 (0.7)**	**0**
Asthma	3 (0.7)	0
Status asthmaticus	0	0

1. Studies GT-12, P05239, P08067
From STN 125473.0, Section 2.7.4, Table 35

Adverse Events Leading to Discontinuation

A total of 4 subjects were discontinued from Phase 1 trials – two adults (sting and blisters in the mouth; itching in the mouth, respectively) and two children (asthma exacerbation; ear pruritus, throat and non-cardiac chest pain and dysphagia, respectively).

A total of 146 adult subjects (4.1%) were discontinued from Phase 2 and 3 studies; with some evidence of a dose-dependent effect for treatment-related discontinuations: placebo group (n=15; 0.9%); 93 BAU treatment group (n=1; 0.7%); 933 BAU treatment group (n=3; 2.2%) and 2800 BAU treatment group (n=81; 4.9%). The most common treatment-related AEs leading to discontinuation were local allergic adverse events.

Six AEs that led to study discontinuation in the adult population were classified as serious: 1 subject treated with 93 BAU (colitis ulcerative), 1 subject treated with 2800 BAU (multiple drug overdose), and 4 subjects treated with placebo (subarachnoid hemorrhage, lung adenocarcinoma, colon cancer, bulimia nervosa). None of these SAEs were considered related to study medication.

Among the pooled pediatric Phase 3 studies, a total of 37 subjects discontinued from the trial, with 31 subjects (3.5%) discontinued due to AEs that were considered treatment-related. A higher percentage of subjects with treatment-related AEs leading to discontinuation were reported in the MK-7243 group (2800 BAU) as compared to placebo group (6.3% vs. 0.7%, respectively). The most common AEs leading to discontinuation overall were local allergic adverse events.

Only one AE in the pediatric population was classified as serious. This AE involved a 9-year old male treated with 2800 BAU who experienced an asthmatic reaction on Day 62.

Events of specific interest

Allergic reactions

The sponsor used several approaches to capture cases of possible allergic reactions, including serious, systemic reactions and/or anaphylaxis. Adverse events coded under MedDRA terms: Anaphylactic reaction (PT), Hypersensitivity (PT), Anaphylaxis (LLT) and Allergic reactions, anaphylaxis, and allergic reactions (LLT); any individual criterion from the list of Food Allergy and Anaphylaxis Network (FAAN) definition of anaphylaxis (which are used in an algorithm to determine an anaphylactic reaction); and epinephrine administration were used to screen for possible systemic allergic reactions.

<u>Food Allergy and Anaphylaxis Network (FAAN) Criteria</u>

The US NIH's National Institute of Allergy and Infectious Diseases and FAAN report on anaphylaxis (Sampson 2006), concluded that more than 95% of cases of anaphylaxis (i.e., administration of epinephrine indicated) will be captured when at least one of the following three criteria are met:

1. Acute onset (minutes to hours) with involvement of the 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 peak 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 occurring rapidly after exposure (minutes to hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen tongue-lips-uvula)

   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced 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 (minutes to hours)
   a. Infants / children: low systolic BP (age specific*) or >30% decrease

   *Age specific systolic blood pressure threshold values for pediatric subjects:
   1 month – <1 year: < 70 mm Hg
   1 – 10 years: < 70 mm Hg + (2 x age)
   11 – 17 years: < 90 mm Hg (11-17 years of age.

   b. Adults: systolic BP <90 mm Hg or >30% decrease from person's baseline

Epinephrine administration
Epinephrine use was monitored in clinical studies by evaluation of investigator reports of anaphylaxis, anaphylactic reaction, hypersensitivity, and systemic allergic reaction. While epinephrine auto-injectors were not provided to most study subjects, they were provided to all subjects (N=2283) in North American trials P05238, P05239, and P08067, at FDA's request.

A total of 13 subjects (11 MK-7243 recipients and 2 placebo recipients) were injected with epinephrine during the clinical trial program as summarized in the table below. In 3 cases the epinephrine was self-administered. Not surprisingly, 12 out of 13 administrations occurred in North American subjects.

<u>Allergic reactions of particular interest</u>
Allergic reactions of particular interest, including serious systemic reactions, anaphylaxis and adverse events requiring epinephrine use are summarized in the table below.

Table 15: Anaphylactic, Hypersensitivity, Systemic Allergic Reactions and/or Epinephrine Use in Clinical Studies

GT-02	7004[3]	933	22 M	Dyspnea, lip swelling, palatal edema	1	---
				Lip swelling	8; 83	---
	72015	2800	30 M	Swollen Tongue	74	Y
	82033[3]	2800	29 F	Urticaria, wheezing	114	---
P08067	2868[3]	2800	52 F	Lip swelling, urticarial	7	---
	3108[3]	PLC	51 M	Syncope, vomiting	50	---
	100056[3]	PLC	12	Anaphylactic reaction	1	---
	100963[1,2]	2800	65 F	Hypersensitivity	14	Y
	101062[2]	2800	45 F	Hypersensitivity	2	---
	101670	2800	18 M	Swelling, throat irritation	3	Y
	102364	2800	37 M	Idiopathic urticaria	2	Y
	102868[3]	2800	52 F	Lip swelling, urticarial	7	---
	103108	2800	52 M	Leukocytoclastic vasculitis	50	Y
	103134[2]	2800	22 M	Hypersensitivity	42	---
GT-08	474[3]	2800	46 F	Angioedema, dyspnea	1	---
	867[3]	PLC	55 M	Diarrhea, tachycardia	1	---
GT-12	175[3]	PLC	8 F	Allergic reaction	84	---
	274[3]	2800	12 M	Dyspnea, swollen tongue	16	---
GT-14	4005[1,2]	2800	25 F	Anaphylactic reaction	1	Y
	8010	2800	25 F	Lip swelling, mouth/tongue/throat pruritus, dysphagia	1	Y
	7004[3]	2800	22 M	Dyspnea, lip swelling, palatal edema	1	---
	10001[2]	2800	46 F	Anaphylactic reaction	1	---
	10003[2]	2800	37 F	Anaphylactic reaction	1	---
	10004[2]	2800	26 F	Anaphylactic reaction	1	Y
	27008[3]	2800	32 F	Diarrhea[5], urticaria	4	---
				Abdominal pain	6	---
	11387[2]	2800	50 F	Hypersensitivity	1	Y
P05238	12285	PLC	58 M	Anxiety	4	Y
	13971[3]	PLC	25 F	Diarrhea, urticarial	2	---
P05239	2180	2800	16 M	Viral infection	23	Y
	2327[3]	2800	11 F	Dyspnea, pruritus	8	---
	2482[3]	2800	13 unknown sex	Lip angioedema, dysphagia, intermittent cough	1	Y
	2818[3]	2800	8 M	Flushing, vomiting	1	---
	2873	2800	6 M	Wheezing	137	Y
	3078[3]	2800	11 M	Dyspnea, wheezing	144	---

1. Anaphylactic or hypersensitivity reaction, local symptoms only; 2. Coded under MedDRA LLT of systemic allergic reactions, anaphylaxis, or allergic reaction
3. From sponsor-selected systemic allergic events; 4. Age in years; 5. Diarrhea also reported on Day 8
PLC = placebo
From STN 125473.0, Section 2.5, Table 11; Section 2.7.4, Tables 36-38 and Section 2.7.4.2.1.4.1 Adverse events of anaphylactic reaction or possible systemic allergic reactions.

Local reactions with potential to compromise the airway

Local application site reactions were evaluated based upon the following terms: ear pruritus, edema mouth, swollen tongue, dysphagia, oral discomfort, tongue edema, glossodynia, oral pruritus, pharyngeal edema, hypoaesthesia oral, palatal edema, throat irritation, lip edema, paraesthesia oral, throat tightness, lip swelling, stomatitis, swelling face

Events associated with potential airway compromise included severe local allergic swellings in the mouth or throat, such as mouth edema, tongue edema/swelling, pharyngeal edema, palatal edema, and throat tightness.

There were no reported events leading to actual airway compromise. None of these events were classified as serious or life-threatening.

The rate of local reactions was clearly dose dependent, with rates from adult Phase 1 studies of 28.1% (placebo), 22.2% (933 BAU), 66.7% (2800 BAU), 83.3% (5600 BAU) and 94.4% (11,200 BAU). A similar effect was seen in the adult Phase 2 and 3 studies: 11.6% (placebo), 22.8% (93 BAU), 56.8% (933 BAU), and 58.9% (2800 BAU). Dose-ranging studies were not conducted in the pediatric population.

Airway compromise particularly in children due to relatively smaller airway

Due to the physically smaller airway, there is a potential difference in topical safety between adults and children. In the clinical trial program evaluating 940 pediatric subjects, there were no events of respiratory or oral/pharyngeal swellings described as leading to potential airway compromise in children.

Asthma exacerbation

Phase 1 studies

The number of subjects enrolled in Phase 1 studies was small (127 adults and 60 children). It is not clear that “asthma exacerbation” was defined or prospectively monitored in the Phase 1 studies. The review of safety in the Phase 1 studies is limited further by the relatively small sample sizes.

Asthmatic adults (18-50 years old) reported higher rates of AEs than non-asthmatic subjects in both combined treatment (100% vs. 85.2%, respectively) and placebo groups (90.9% vs. 38.1%, respectively).

In comparison to adults, in the pediatric population, asthmatic subjects reported lower overall rates of AEs (66.7% of active treatment recipients, 50% placebo recipients) as compared to non-asthmatic subjects (92.6% of active treatment recipients, 77.8% placebo recipients). Asthmatic crisis was reported in one asthmatic (5.6%) in the active treatment group and none in asthmatics in the placebo group or non-asthmatics in either the active or placebo groups.

Phase 2 and 3 studies

In Phase 2 and 3 studies, asthma was prospectively monitored by electronic diary (e-diary) symptoms: any wheezing, cough, chest tightness/discomfort, or exercise-induced symptoms, and AEs were reviewed for reports of asthma, dyspnea, wheezing, cough, chest tightness/discomfort, or exercise-induced symptoms. The analyses for Phase 2 and 3 studies were performed on adult Phase 2/3 and pediatric Phase 3 studies, as e-diary data were not collected in Phase 1 studies.

Asthma-related event in adults

In adults, the rates of asthma-related AEs were higher in the MK-7243 (2800 BAU) group as compared to the placebo group with the exception of wheezing; while in contrast the rates of symptoms reported by eDiaries were more similar. This relationship was seen in the overall population, the asthmatic subpopulation and the non-asthmatic subpopulation, although the non-asthmatic subpopulation also had low rates of asthma in both placebo and treated groups. These results are summarized in the following three tables.

Table 16: Asthma-related Symptoms During Adult Phase 2 & 3 Studies – all subjects

	MK-7243 93 BAU N=136		MK-7243 933 BAU N=139		MK-7243 2800 BAU N=1669		Placebo N=1645	
	n	%	n	%	n	%	n	%
eDiary	106	(77.9)	95	(68.3)	1063	(63.7)	1087	(66.1)
Chest Tightness/Discomfort	57	(41.9)	43	(30.9)	685	(41.0)	722	(43.9)
Cough	84	(61.8)	82	(59.0)	962	(57.6)	974	(59.2)
Exercise Induced	76	(55.9)	55	(39.6)	653	(39.1)	673	(40.9)
Wheezing	53	(39.0)	48	(34.5)	667	(40.0)	698	(42.4)
Adverse Events	4	(2.9)	12	(8.6)	151	(9.0)	113	(6.9)
Asthma	2	(1.5)	---	---	22	(1.3)	17	(1.0)
Chest Tightness/Discomfort	---	---	---	---	32	(1.9)	20	(1.2)
Cough	1	(0.7)	5	(3.6)	89	(5.3)	64	(3.9)
Dyspnoea	1	(0.7)	5	(3.6)	28	(1.7)	17	(1.0)
Wheezing	1	(0.7)	2	(1.4)	10	(0.6)	15	(0.9)

From STN 125473.0, Section 2.7.4, Table 59

Table 17: Asthma-related Symptoms During Adult Phase 2 & 3 Studies – asthmatics

	MK-7243 93 BAU N=12		MK-7243 933 BAU N=11		MK-7243 2800 BAU N=415		Placebo n=383	
	n	%	n	%	n	%	n	%
eDiary	10	(83.3)	9	(81.8)	317	(76.4)	332	(86.7)
Chest Tightness/Discomfort	6	(50.0)	7	(63.6)	258	(62.2)	296	(77.3)
Cough	8	(66.7)	6	(54.5)	285	(68.7)	302	(78.9)
Exercise Induced	8	(66.7)	7	(63.6)	251	(60.5)	274	(71.5)
Wheezing	5	(41.7)	5	(45.5)	259	(62.4)	285	(74.4)
Adverse Events	1	(8.3)	2	(18.2)	58	(14.0)	44	(11.5)
Asthma	---	---	---	---	19	(4.6)	13	(3.4)
Chest Tightness/Discomfort	---	---	---	---	17	(4.1)	5	(1.3)
Cough	---	---	---	---	25	(6.0)	19	(5.0)
Dyspnoea	---	---	1	(9.1)	10	(2.4)	4	(1.0)
Wheezing	1	(8.3)	1	(9.1)	4	(1.0)	5	(1.3)

From STN 125473.0, Section 2.7.4, Table 60

Table 18: Asthma-related Symptoms During Adult Phase 2 & 3 Studies – non-asthmatics								
	MK-7243 93 BAU n=124		MK-7243 933 BAU n=128		MK-7243 2800 BAU n=1254		Placebo n=1262	
	n	%	n	%	n	%	n	%
eDiary	96	(77.4)	86	(67.2)	746	(59.5)	755	(59.8)
Chest Tightness/Discomfort	51	(41.1)	36	(28.1)	427	(34.1)	426	(33.8)
Cough	76	(61.3)	76	(59.4)	677	(54.0)	672	(53.2)
Exercise Induced	68	(54.8)	48	(37.5)	402	(32.1)	399	(31.6)
Wheezing	48	(38.7)	43	(33.6)	408	(32.5)	413	(32.7)
Adverse Events	3	(2.4)	10	(7.8)	93	(7.4)	69	(5.5)
Asthma	2	(1.6)	---	---	3	(0.2)	4	(0.3)
Chest Tightness/Discomfort	---	---	---	---	15	(1.2)	15	(1.2)
Cough	1	(0.8)	5	(3.9)	64	(5.1)	45	(3.6)
Dyspnoea	1	(0.8)	4	(3.1)	18	(1.4)	13	(1.0)
Wheezing	---	---	1	(0.8)	6	(0.5)	10	(0.8)
From STN 125473.0, Section 2.7.4, Table 61								

Asthma-related events in children

In children enrolled in Phase 2 and Phase 3 studies, the rates of asthma-related AEs were not consistently higher in the MK-7243 (2800 BAU) group as compared to the placebo group, in the overall, asthmatic or non-asthmatic cohorts, as summarized for the Phase 3 pediatric studies in the following three tables. It is unclear if asthmatics in this study (who were able to tolerate a wash-out period for standard maintenance asthma medication several weeks prior to the start of the study) are representative of the general U.S. pediatric asthmatic population.

Table 19: Asthma-related Symptoms During Pediatric Phase 3 Studies – all subjects				
	MK-7243 2800 BAU n=447		Placebo n=434	
	n	%	n	%
eDiary	345	(77.2)	363	(83.6)
Chest Tightness/Discomfort	211	(47.2)	232	(53.5)
Cough	327	(73.2)	352	(81.1)
Exercise Induced	231	(51.7)	241	(55.5)
Wheezing	196	(43.8)	229	(52.8)
Adverse Events	70	(15.7)	69	(15.9)
Asthma	13	(2.9)	17	(3.9)
Chest Tightness/Discomfort	11	(2.5)	3	(0.7)
Cough	35	(7.8)	45	(10.4)
Dyspnoea	15	(3.4)	7	(1.6)
Exercise Induced	1	(0.2)	2	(0.5)
Wheezing	4	(0.9)	6	(1.4)
From STN 125473.0, Section 2.7.4, Table 62				

Table 20: Asthma-related Symptoms During Pediatric Phase 3 Studies – asthmatics				
	MK-7243 2800 BAU n=140		Placebo n=136	
	n	%	n	%
eDiary	121	(86.4)	129	(94.9)
Chest Tightness/Discomfort	91	(65.0)	95	(69.9)
Cough	118	(84.3)	125	(91.9)
Exercise Induced	100	(71.4)	104	(76.5)
Wheezing	89	(63.6)	104	(76.5)
Adverse Events	27	(19.3)	31	(22.8)
Asthma	9	(6.4)	16	(11.8)
Chest Tightness/Discomfort	7	(5.0)	1	(0.7)
Cough	8	(5.7)	15	(11.0)
Dyspnoea	6	(4.3)	3	(2.2)
Wheezing	2	(1.4)	2	(1.5)
From STN 125473.0, Section 2.7.4, Table 63				

	MK-7243 2800 BAU n=307		Placebo n=298	
	n	%	n	%
eDiary	224	(73.0)	234	(78.5)
Chest Tightness/Discomfort	120	(39.1)	137	(46.0)
Cough	209	(68.1)	227	(76.2)
Exercise Induced	131	(42.7)	137	(46.0)
Wheezing	107	(34.9)	125	(41.9)
Adverse Events	43	(14.0)	38	(12.8)
Asthma	4	(1.3)	1	(0.3)
Chest Tightness/Discomfort	4	(1.3)	2	(0.7)
Cough	27	(8.8)	30	(10.1)
Dyspnoea	9	(2.9)	4	(1.3)
Exercise Induced	1	(0.3)	2	(0.7)
Wheezing	2	(0.7)	4	(1.3)
From STN 125473.0, Section 2.7.4, Table 63				

In-season dosing

Experience with subcutaneous immunotherapy has shown that a decrease in dosage may decrease the risk of allergic reactions during the allergy season, and that initiation of a standard dose during the allergy season may result in an increased risk of AEs (Cox 2011).

As pre-seasonal treatment induction is important for the efficacy of GRASTEK, all efficacy trials with the exception of Study GT-18 were designed with a pre-seasonal treatment period. When treatment was commenced during the grass pollen season, in Study GT-18, subjects were reported to tolerate treatment without the need for dose adjustment. The safety profile appeared similar to that of other studies and no safety signals were identified by the sponsor (Reich 2011).

Tablet aspiration
Tablet aspiration was not reported in any clinical study, a risk which is reduced by the rapid disintegration (within a few seconds) of the tablet at mucosal contact.

Limitations of Clinical Safety Data

- The majority of subjects in the clinical studies were of Caucasian origin (~88%).

- The safety database included an adult cohort of subjects with a mean age of 36 years.

- Subjects with persistent and with moderate to severe asthma were excluded from the clinical studies and therefore, the safety of GRASTEK in this population has not been characterized. Also, individuals whose asthma is controlled with ICS or ICS/LABA combination therapy were not prospectively evaluated.

  Note: The sponsor states that sublingual immunotherapy in severe or uncontrolled asthmatics is a contraindication under current immunotherapy practice guidelines, but does not address their failure to study this product in individuals with moderate and/or persistent asthma who may use it. In addition, the asthmatic symptoms were identified by the sponsor as common features of serious treatment-related AEs in postmarketing observational studies, and risk identifiers included severe asthma, progressive / persistent local symptoms.

- Subjects with a history of anaphylaxis were excluded from the clinical studies.

- Subjects who had allergen immunotherapy within 5 years prior to enrollment were excluded from the clinical efficacy studies (a subset of the safety database).

- Children below the age of 5 were excluded from clinical studies as grass induced rhinitis or conjunctivitis is uncommon in children younger than 5 years, due to insufficient seasonal allergen exposure.

- 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 as this product was administered daily for 4-6 months, including periods prior to and during the relevant pollen season. Only study GT-08 evaluated adult subjects receiving active treatment for two or more successive annual pollen seasons as summarized in the following table.

Table 22: Duration of Treatment – Study GT-08			
	MK-7243 (2800 BAU)	Placebo	Total
	N	N	N
Randomized into Study GT-08 (1st Year)[a]	316	318	634
Completed Year 1[a]	274	272	546
Continued in Year 2	189	162	351
Continued in Year 3	170	138	308
Continued in Year 4	157	126	283
Continued in Year 5	145	113	258
Completed the Trial	135	103	238

a: A total of 195 subjects (85 active, 110 placebo) did not continue to Year 2 (closure of sites [n=68] and did not consent to participate in the extension [n=127]).

From STN 125473.0, Section 2.7.4, Table 65

- Safety experience with doses higher than 2800 BAU are limited as evidenced by the sponsor's disparate statements regarding this issue:

  - Section 2.7.4.5.5 Overdose:

    "The frequency of AEs was dose related, and if doses higher than the recommended daily dose (2800 BAU) are taken, the risk of AEs may increase, including the risk of systemic reactions or severe local application site reactions."

  - Section 2.5.5.10 (summarizing the safety experience in Phase 2 and 3 studies):

    "In general, there was no apparent dose-relationship among the MK-7243 treatment groups with respect to overall AEs reported. However, there was a trend toward an increased number of local application site reactions with increasing doses of MK-7243. In contrast, a dose response effect for possible systemic events was not observed in this pooled data set nor was there a dose response for serious adverse events."

5. Postlicensure Safety Review

a. Worldwide

i. Non U.S. postmarketing surveillance (e.g., UMC) – See postmarketing experience Section 2. b. iii., above
ii. Safety signals communicated by non-U.S. regulatory or public health authorities - None

b. U.S.

i. Prior safety changes to the label – N/A
ii. 921 postings – N/A
iii. 915 reviews – N/A
iv. Pediatric Advisory Committee presentations – N/A
v. U.S. postmarketing studies - N/A
vi. U.S. postmarketing surveillance (e.g. VSD or Mini Sentinel) – N/A
vii. Conclusions from periodic internal surveillance reports – N/A

6. 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 or persistent asthma
- Use of high-dose inhaled corticosteroids
- Use of long-acting beta agonists
- History of anaphylaxis and/or angioedema

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 in the reviewer's opinion:

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.

7. 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.

a. Routine pharmacovigilance as described by the sponsor appears adequate for use of GRASTEK in individuals 5 years of age and older.

b. Adequate labeling should reflect:

i. The potential for serious systemic allergic reactions, including anaphylactic reactions

ii. The potential for local allergic reactions that may compromise the airway

iii. The potential for asthma exacerbations following use of GRAZEX, particularly in subjects with uncontrolled asthma, based upon reported postmarketing experience

iv. The potential for airway compromise in children due to relatively smaller airway

v. Lack of information on the safety of co-administration with other sublingual immunotherapy

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