Allergenic Products Advisory Committee (APAC) Meeting January 28, 2014

FDA Briefing Document

Biologics License Application (BLA) for *RAGWITEK™ [Standardized Allergen Extract, Short Ragweed (Ambrosia artemisiifolia)] sublingual tablet for oral use*

Applicant

Merck Sharp & Dohme Corp.

General Information

Product Proper Name:	Short Ragweed Pollen Allergen Extract Tablet for Sublingual Use
Proposed Trade Name:	RAGWITEK®
Description:	Sublingual tablet comprised of extract from short ragweed (*Ambrosia artemisiifolia*) pollen.
Formulation:	Each sublingual tablet contains 12 Amb a 1 units of the drug substance. The drug substance is an allergen extract from short ragweed pollen (*Ambrosia artemisiifolia*) sourced from the US.
Dosing Regimen:	The recommended dose of RAGWITEK for adults 18 years of age and older is 1 sublingual tablet daily.
Applicant:	Merck Sharp & Dohme Corp
Proposed Indication and Usage:	RAGWITEK is indicated as immunotherapy for diagnosed ragweed pollen induced allergic rhinitis, with or without conjunctivitis, in adults 18 years of age and older.

Abbreviations:

95% CI	95% confidence interval
95% CI UL	upper limit of the 95% CI
AC	allergic conjunctivitis
AE	adverse event (21 CFR 312.32)
Amb a 1-U	Amb a 1 units, a measure of potency of short ragweed allergen extract
AR	allergic rhinitis
ARC	allergic rhinoconjunctivitis
BLA	Biologics License Application
CSR	clinical study report
DMS	Daily Medication Score: see Table 2
DSS	Daily Symptom Score: sum of six RC symptoms (runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes), each scored daily by the patient using a 4-point scale from 0 to 3 where 0 = absent and 3 = severe symptoms.
FAS	full analysis set (essentially equal to the intent to treat subset)
IND	investigational new drug application
SAE	serious adverse event (21 CFR 312.32)
SCIT	subcutaneous allergen immunotherapy
SLIT	sublingual allergen immunotherapy
TCS	Total Combined Score: sum of DSS (maximum 18) and DMS (maximum 36). The maximum TCS is 54.

1.0 Introduction

Allergic rhinoconjunctivitis (ARC) affects over 500 million persons worldwide, including approximately 30 million persons in the US. While allergen avoidance and pharmacotherapy can provide significant relief, for many affected individuals symptoms remain. For some of these patients allergen immunotherapy is a reasonable alternative. Subcutaneous allergen immunotherapy (SCIT) has been practiced since the early 20th century; the administration of allergen extracts orally or sublingually is a more recent development, increasing in Europe and the US. To date, US-licensed allergen extracts for pollens, mold spores, animal danders, insects and inhalants are only approved for use in SCIT.

Merck Sharp & Dohme Corp. has submitted a Biologics License Application (BLA) to FDA for RAGWITEK®, a sublingual tablet comprised of extract from short ragweed (*Ambrosia artemisiifolia*) pollen. RAGWITEK is a sublingual tablet for oromucosal delivery. This tablet is intended to be administered for sublingual immunotherapy (SLIT) in adults (18 years of age and older) for treatment of allergic rhinitis with or without conjunctivitis due to sensitivity to short ragweed pollen. Short ragweed belongs to the taxonomic (botanical) family *Asteraceae* and grows throughout North America. Short ragweed pollen extract made by other manufacturers is licensed by FDA for SCIT of ARC and is distributed as extracts that are standardized according to potency in Amb a 1 units.[1]

Because the allergen Amb a 1 accounts for the great majority of allergenic activity in short ragweed extracts, the potency of the extracts is defined according to the concentration of this major allergen. The unitage is Amb a 1 units (Amb a 1-U), in which 1 Amb a 1-U is roughly equivalent to 1 mcg of Amb a 1. The current method of measurement is to compare an extract to a CBER reference with a defined potency by radial immunodiffusion assay.[1]

The dosage of the tablets proposed for use in the US is 12 Amb a 1-U of extract derived from short ragweed (*Ambrosia artemisiifolia*) pollen. The applicant proposes that patients initiate treatment with RAGWITEK at least 12 weeks prior to and throughout the ragweed pollen season. The first dose is taken at the healthcare provider's office, and the remaining doses are taken at home. RAGWITEK is not authorized for use outside the US, and to the knowledge of the Agency, the sponsor has performed no studies in addition to those described in this document.

2.0 Summary of Clinical Studies

The BLA includes clinical study reports (CSRs) of five clinical studies in adults.

- RT-01, a Phase 1 study conducted in the US of 53 subjects ages 18 to 50 years, who took placebo or RAGWITEK (3, 6, 12, 24, or 50 Amb a 1-U) for 28 days outside of ragweed season. RT-01 was completed in March, 2007.

- P06081, a Phase 2 safety study conducted in the US of 196 subjects ages 50 to 78 years, who took placebo or RAGWITEK (6 or 12 Amb a 1-U) for 28 days outside of ragweed pollen season. P06081 was completed in February, 2010.

[1] Slater JE. Standardized allergen extracts in the United States. *Clin Allergy Immunol.* 2008; 21:273-81.

- P05233 was a Phase 2/3 safety and efficacy study conducted in the US and Canada of 565 subjects ages 18 to 50 years who took placebo or RAGWITEK (6 or 12 Amb a 1-U) for approximately 52 weeks beginning ~16 weeks prior to the 2010 ragweed season. P05233 was completed in May, 2011.

- Protocol P05234 was a Phase 2/3 safety and efficacy study, similar in design to Study P05233, conducted in the US, Canada, Hungary, Ukraine, and Russia of 784 subjects ages 18 to 50 years, who took placebo or RAGWITEK (1.5, 6, or 12 Amb a 1-U) for approximately 52 weeks beginning ~16 weeks prior to the 2010 ragweed season. P05234 was completed in May, 2011.

- P05751 was a Phase 3 safety study conducted in the US and Canada of 914 subjects ages 18 to 85 years who took either placebo or RAGWITEK (12 Amb a 1-U) for 28 days outside of ragweed pollen season. P05751 was completed in April, 2012.

RAGWITEK has not been studied in subjects younger than 18 years of age.

Table 1 presents summaries of the clinical studies of RAGWITEK.

Table 1: RAGWITEK Clinical Studies

Study # Location (# of sites) Year conducted	Objectives	Study design	Study population age range	Treatment Dose	Number of subjects	Treatment Duration
RT-01 US (2) 2006, 2007	Safety	DB, PC	18-50y	RAGWITEK 1 Amb a 1-U RAGWITEK 6 Amb a 1-U RAGWITEK 12 Amb a 1-U RAGWITEK 24 Amb a 1-U RAGWITEK 50 Amb a 1-U Placebo	9 9 9 9 4 13	Each dose RAGWITEK and placebo: 7 days outside of ragweed pollen season
P06081 US (30) 2009, 2010	Safety	MC, R, DB, PG, PC	50-78y	RAGWITEK 6 Amb a 1-U RAGWITEK 12 Amb a 1-U Placebo	69 67 67	Each dose RAGWITEK and placebo: 28 days outside of ragweed pollen season
P05233 US (67) Canada (13) 2009-2011	Efficacy and Safety	MC, R, DB, PG, PC	18-50y	RAGWITEK 6 Amb a 1-U RAGWITEK 12 Amb a 1-U Placebo	190 187 188	Each dose RAGWITEK and placebo, 52 weeks: ~16 weeks prior to, during, and following the 2010 ragweed pollen season
P05234 US (72) Canada (12) Hungary (20) Ukraine (8) Russia (2) 2009-2011	Efficacy and Safety	MC, R, DB, PG, PC;	18-50y	RAGWITEK 1.5 Amb a 1-U RAGWITEK 6 Amb a 1-U RAGWITEK 12 Amb a 1-U Placebo	196 195 194 198	Each dose RAGWITEK and placebo, 52 weeks: ~16 weeks prior to, during, and following the 2010 ragweed pollen season
P05751 US (58) Canada (14) 2011-2012	Safety	MC, R, DB, PC, PG	18-85y	RAGWITEK 12 Amb a 1-U Placebo	609 304	RAGWITEK and placebo: 28 days outside of ragweed pollen season

Adapted from Original application, Module 2 (Common Technical documents), Folder 2.5 (Clinical Overview), Table 8, Page 39 of 69; DB = double-blind; MC = multicenter; PC = placebo-controlled; PG = parallel-group; R = randomized.

3.0 Summary of Efficacy

3.1 Clinical Scores for Assessment of Efficacy

Several clinical scoring algorithms have been developed to assess the efficacy of allergen immunotherapy. Some of these consider only symptoms or quality of life, some consider medication use, and some take into account both symptoms and medication use. To measure symptoms, the sponsors use the average rhinoconjunctivitis Daily Symptom Score (DSS). The DSS is the sum of six individual rhinoconjunctivitis symptom scores with possible values of 0 (absent) to 3 (severe). The six symptoms that are scored are: runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes. The maximum DSS is 18. Subjects recorded these efficacy assessments daily throughout the ragweed season on an electronic diary.

To measure medication use, the sponsors use the average rhinoconjunctivitis Daily Medication Score (DMS). The DMS is the sum of scores that are assigned to each medication as presented in Table 2.

Table 2: Scoring of Rescue Medication Usage for DMS calculation

Step	Rescue Medication	Score/ Dose Unit	Max Daily Score
1a	Loratadine syrup 1 mg/mL – 5 mL QD (5 to <6 yr)	6 (per 5 mL)	6
1b	Olopatadine hydrochloride 0.1% ophthalmic solution -1 drop in the affected eye BID	1.5 (per drop)	6
2	Mometasone furoate monohydrate nasal spray 50 mcg – 1 spray in each nostril QD (5 to <12 yr)	4 (per spray)	8
2	Mometasone furoate monohydrate nasal spray 50 mcg - 2 sprays in each nostril QD (≥12 yr)	2 (per spray)	8
3	Prednisone tablet 5 mg (Day 1 - 1 mg/kg/day, Max 50 mg/day)	1.6 (per tablet)	16[a]
3	Prednisone tablet 5 mg (Day 2+ - 0.5 mg/kg/day, Max 25 mg/day)	1.6 x 2 (per tablet)	
Maximum daily rhinoconjunctivitis medication score			36

[a]use of prednisone will be counted in the rhinoconjunctivitis medication score and/or the asthma medication score depending on the symptoms. In the combined score, use of prednisone was counted only once.
Extracted from BLA Application STN 125478/000; Module 5, CSR p05233, Vol 1, Page 65 of 3030

P05233 and P05234 were the two efficacy studies conducted by the applicant. The primary efficacy endpoint for each of the studies was the total combined score (TCS) over the peak of ragweed season. The TCS is the sum of DSS (maximum 18) and DMS (maximum 36). The maximum TCS is 54. Note that the TCS is weighted towards the use of rescue medication.

Key secondary endpoints are the DSS and DMS over the peak of ragweed season, and the TCS, DSS, and DMS over the entire ragweed season. The first day of the ragweed season was defined as "the first day of 3 consecutive recorded days with a ragweed pollen count of ≥10 grains/m^3." The end of the ragweed season was defined as "the last day of the last occurrence of 3 consecutive recorded days with a ragweed pollen count ≥10 grains/m^3." The peak ragweed season was defined as a "period of 15 consecutive recorded days with the highest moving average was defined as the peak RS."

3.2 Clinical Studies Efficacy Analyses

This section presents the analyses for the two placebo-controlled studies conducted to assess the efficacy of the RAGWITEK. Dosages chosen for evaluation in these studies were based on Study RT-01, a multiple dose safety study.

Study P05233

This study was conducted in North America from September 2009 to May 2011. Based on the sponsor's experience with GRASTEK, the Timothy grass pollen sublingual tablet, this study was powered to detect a difference of -1.80 (-25%) in the primary endpoint (TCS during peak ragweed season), and a difference of -1.45 (-23%) in the TCS over the entire ragweed season between an active dose group and the placebo group with 90% power at a 5% level of significance (2-sided test).

A total of 560 subjects 18 to 50 years of age were randomized 1:1:1 to receive placebo, RAGWITEK 12 Amb a 1-U, or RAGWITEK 6 Amb a 1-U (data using 6 Amb a 1-U not shown). Subjects were treated prior to the ragweed season (mean 14.8 weeks; median 17 weeks; range 0.1-20.9 weeks). Subjects were expected to take tablets for 367 consecutive days (actual range of number of tablets taken 1-401). The primary endpoint was the TCS in each group during the peak 2010 ragweed pollen season. The primary analysis for efficacy was the difference in TCS (12 Amb 1-U group minus placebo) during the peak season. Table 3 shows the primary and key secondary endpoint results.

Table 3: Study P05233 primary and secondary endpoints

	N	Adjusted Mean	Treatment Difference (RAGWITEK – Placebo) (95% CI)[a]	% difference relative to Placebo (95% CI)[b]	P-Value
TCS peak ragweed season (primary endpoint)					
12 Amb a 1-U	159	6.2	-2.24 (-3.41, -1.07)	-26.49 (-38.74, -14.59)	0.0002
Placebo	164	8.4	-	---	---
TCS entire ragweed season					
12 Amb a 1-U	160	5.2	-1.80 (-2.78, -0.82)	-25.66 (-37.55, -13.48)	0.0003
Placebo	166	7.0	-	---	---
DSS peak ragweed season					
12 Amb a 1-U	159	4.6	-0.94 (-1.70, -0.19)	-16.87 (-28.64, -4.62)	0.0144
Placebo	164	5.5	-	---	---
DSS entire ragweed season					
12 Amb a 1-U	160	4.0	-0.82 (-1.46, -0.18)	-16.85 (-28.47, -4.54)	0.0125
Placebo	166	4.8	-	---	---
DMS peak ragweed season					
12 Amb a 1-U	159	1.5	-1.30 (-1.95, -0.64)	-45.28 (-65.39, -26.99)	0.0001
Placebo	164	2.8	-	---	---
DMS entire ragweed season					
12 Amb a 1-U	160	1.16	-0.98 (-1.53, -0.44)	-45.86 (-65.53, -24.02)	0.0004
Placebo	166	2.15	-	---	---

a: Adjusted means, treatment differences, confidence intervals and p-values were based on an ANOVA model with baseline asthmatic condition, pollen region and treatment group as fixed effects; b. Percent reduction in ragweed AIT group compared to placebo: 100 x [(AIT-placebo)/placebo] Confidence intervals were obtained using the bootstrap method.

Study P05234

This study was conducted from September 2009 to May 2011 in the US, Canada, Hungary, Ukraine and Russia. Based on the sponsor's experience with GRASTEK, the Timothy grass pollen sublingual tablet, this study was powered to detect a difference of -1.80 (-25%) in the primary endpoint (TCS during peak ragweed season), and a difference of -1.45 (-23%) in the TCS over the entire ragweed season between an active dose group and the placebo group with 90% power at a 5% level of significance (2-sided test).

A total of 783 subjects 18 to 50 years of age were randomized 1:1:1:1 to receive RAGWITEK 12, 6, or 1.5 Amb a 1-U, placebo. Subjects were treated prior to the ragweed season (mean 15.9 weeks; median 17 weeks; range 0.1 to 22.3 weeks). Subjects were expected to take tablets for 367 consecutive days (actual range of number of tablets taken 1 to 414). The primary endpoint was the TCS in each group during the peak 2010 ragweed pollen season. The primary analysis for efficacy was the difference in TCS (12 Amb a 1-U group minus placebo) during the peak season. Table 3 shows the primary and key secondary endpoints for the 12 Amb a 1-U group.

Table 4: Study P05234 primary and secondary endpoints

Endpoint	N	Adjusted Mean	Treatment Difference (ragweed AIT-placebo) (95% CI)[a]	% change relative to Placebo (95% CI)[b]	P-Value
TCS peak ragweed season (primary endpoint)					
12 Amb a 1-U	152	6.41	-2.04 (-3.30, -0.79)	-24.16 (-36.47, -11.31)	0.0015
Placebo	169	8.46	---	---	---
TCS entire ragweed season					
12 Amb a 1-U	158	5.18	-1.92 (-2.95, -0.88)	-27.01 (-38.75, -14.07)	0.0003
Placebo	174	7.09	---	---	---
DSS peak ragweed season					
12 Amb a 1-U	152	4.43	-0.94 (-1.67, -0.21)	-17.51 (-29.20, -4.48)	0.0118
Placebo	169	5.37	---	---	---
DSS entire ragweed season					
12 Amb a 1-U	158	3.62	-0.96 (-1.57, -0.35)	-21.00 (-31.62, -8.81)	0.0021
Placebo	174	4.58	---	---	---
DMS peak ragweed season					
12 Amb a 1-U	152	1.99	-1.10 (-1.89, -0.32)	-35.73 (-55.82, -14.63)	0.0058
Placebo	169	3.09	---	---	---
DMS entire ragweed season					
12 Amb a 1-U	158	1.56	-0.95 (-1.57, -0.33)	-37.99 (-57.62, -16.39)	0.0026
Placebo	174	2.51	---	---	---

a: Adjusted means, treatment differences, confidence intervals and p-values were based on an ANOVA model with baseline asthmatic condition, pollen region and treatment group as fixed effects; b. Percent reduction in ragweed AIT group compared to placebo: 100 x [(AIT-placebo)/placebo] Confidence intervals were obtained using the bootstrap method.

In summary, P05233 and P05234 met the sponsor's pre-defined criterion for success of a difference in average TCS of -1.80 over the peak ragweed pollen season. These two studies also met the sponsor's key secondary criterion of a difference in average TCS of -1.45 over the entire ragweed pollen season.

In addition, the two studies met CBER's assessment of meaningful differences for allergen immunotherapy: a percent difference in average scores ≤ -15%, and a 95% CI UL ≤ -10% for the TCS during the peak of ragweed season and over the entire ragweed season.

4.0 Summary of Safety

4.1 Overall Clinical Studies Safety Database

Across the five clinical trials that comprised the pivotal clinical development program for RAGWITEK, a total of 2,517 participants were randomized to receive RAGWITEK (1,747 participants, all strengths) or placebo (770 participants).

Study RT-01 was a dose-ranging safety study of nine subjects in each of four doses (3, 6, 12, and 24 Amb a 1-U) for seven days. Because of the rate and severity of adverse events associated with the 50 Amb a 1-U dose, it was discontinued after administration to the first four subjects. There were thirteen placebo control subjects. The forty subjects who received RAGWITEK and the thirteen subjects who received placebo who participated in RT-01 are not included in the integrated safety analysis.

Data were integrated among P06081, P05751 (the two 28-day safety trials) and the first 28 days of P05233 and P05234 (the two 52-week efficacy trials). In addition, studies P05233 and P05234 collected safety data over 52 consecutive weeks and these safety data were integrated for analysis of administration over this time period. Three of these four studies had more than one dosage group, but there was no effect from the 1.5 Amb a 1-U dose, and the efficacy data from P05233 and P05234 suggested to the sponsors that the 12 Amb a 1-U may be more effective than 6 Amb a 1-U, but with similar rates and severity of adverse events. The final Phase 3 study, P05751, was a 28-day safety study that compared only the 12 Amb a 1-U dose to placebo (randomized 2:1).

Persons with a self-reported history of controlled asthma and an $FEV_1 \geq 70\%$ of predicted value at screening and randomization visits were allowed to enroll in the trials. Among subjects in the four studies, 441 of 2023 subjects (18%) had asthma. Subjects using low dose inhaled corticosteroids (ICS) were not excluded; 78 of the 441 subjects with asthma (18% of asthmatics) reported ICS use.

Safety Monitoring/Definitions

In studies P06081, P05233 and P05234, safety was monitored by observation in the physician's office for 30 minutes following the first three doses for three of the four studies, with telephone contact for the first four days of self-administration at home. In Study P05751, the subject was monitored in the physician's office on the first day, with telephone contact for the following two days of self-administration at home.

Each study included safety assessments at study visits. For P05233 and P05234 (the two 52-week efficacy trials), there were eleven study visits: the Screening visit; three visits for administration of Doses 1, 2, and 3; two additional visits between the start of treatment and before the start of ragweed season; one visit at peak ragweed season; and four visits after the end of ragweed season. One week after the last visit, subjects received a phone call for follow-up. Paper diary comment cards were collected at each study visit. Asthma-related events were captured in the same e-diaries that were used for efficacy until the end of ragweed season, after which the e-diaries were collected. These symptoms were recorded as adverse events on the e-diaries: asthma, chest tightness/discomfort, cough, dyspnea, and wheezing.

For the 28-day safety study P06081, there were five visits: one visit for screening; three visits for administration of Doses 1, 2, and 3; and a final visit one week after the final dose. One week after the last

visit, subjects received a phone call for follow-up. Paper diary comment cards were collected at the fifth visit.

For the 28-day safety study P05751, there were three visits: one visit for screening; one visit for administration of Dose 1; and a final visit one week after the final dose. One week after the last visit, subjects received a phone call for follow-up. Paper diary comment cards were collected at the third visit.

Treatment-related adverse events refer to those events considered by the investigator as possibly related (temporal association, but other etiologies were likely to be the cause; study drug involvement could not be excluded) or probably related (temporal association, other etiologies possible, but unlikely) to the study drug.

Severity of adverse events was graded as:

- Mild: awareness of sign, symptom, or event, but easily tolerated
- Moderate: discomfort enough to cause interference with usual activity and may have warranted intervention
- Severe: incapacitating with inability to do usual activities or significantly affected clinical status, and warranted intervention.

The sponsor defined a serious adverse event was any event that:

- was fatal
- was life-threatening (i.e., immediate risk of death from the event as it occurred)
- was significantly or permanently disabling
- required in-patient hospitalization, or prolonged hospitalization
- was a congenital abnormality or birth defect

Important medical events that did not result in death, were not life-threatening, or did not require hospitalization may have been considered serious when, on the basis of appropriate medical judgment, they jeopardized the subject or the subject required medical or surgical intervention to prevent one of the outcomes listed in the definition.

4.1.2 Clinical Studies Pooled Safety Analyses – Adults

Summary data for all TEAE, TEAE leading to study discontinuation, and serious adverse events are shown in Table 5. Note that Study RT-01, the short dose-ranging study, is excluded from this analysis. Also note the similar incidence of AE among the 6 and 12 Amb a 1-U dosage strengths.

Treatment-Related Adverse Events of 12 Amb a 1-U dose; 28 days of treatment

Treatment-related adverse events were reported at a higher frequency among the 1707 subjects treated over 28 days with RAGWITEK 12 Amb a 1-U compared to the 757 placebo subjects (56.5% RAGWITEK, 37.6% placebo). The most commonly reported treatment-related adverse events were oral pruritus (11.0% RAGWITEK; 2.0% placebo), ear pruritus (10.7% RAGWITEK; 1.1% placebo), throat irritation (17.0% RAGWITEK; 3.8% placebo), and mouth edema (6.1% RAGWITEK; 0.5% placebo).

Table 5. Adverse events: number (%) of subjects, pooled 28 day analysis from the two 28-day safety studies and the first 28 days of the two 52-week efficacy studies.

		RAGWITEK				Placebo n=757
		1.5 Amb a 1-U n=196	6 Amb a 1-U n=454	12 Amb a 1-U n=1057	Total RAGWITEK n=1707	
TEAE	All	97 (49.5)	261 (57.5)	597 (56.5)	955 (55.9)	285 (37.6)
	Treatment-Related	70 (35.7)	230 (50.7)	482 (45.6)	782 (45.8)	155 (20.5)
TEAE leading to study discontinuation	All	4 (2.0)	24 (5.3)	55 (5.2)	83 (4.9)	7 (0.9)
	Treatment-related	3 (1.5)	19 (4.2)	46 (4.4)	68 (4.0)	6 (0.8)
Serious Adverse Events	All	0	1 (0.2)	2 (0.2)	3 (0.2)	4 (0.5)
	Treatment-related	0	0	0	0	1 (0.1)

Treatment-Related Adverse Events of 12 Amb a 1-U dose; 52 weeks of treatment

Treatment-related adverse events were reported at a higher frequency among the 381 subjects treated over 52 weeks with RAGWITEK compared to the 386 placebo subjects (80.6% RAGWITEK, 68.4% placebo). The most commonly reported treatment-related adverse events were oral pruritus (17.3% RAGWITEK; 2.6% placebo), ear pruritus (14.2% RAGWITEK; 1.6% placebo), throat irritation (25.2% RAGWITEK; 5.4% placebo), mouth edema (9.7% RAGWITEK; 0.5% placebo) and eye pruritus (3.9% RAGWITEK, 1.3% placebo).

Additional AE that occurred in more than 2% of RAGWITEK subjects were oral paresthesia, swollen tongue, tongue pruritus, lip swelling, oropharyngeal pain, and cough.

Table 6. Adverse events: number (%) of subjects, from the two 52-week efficacy studies.

		RAGWITEK				Placebo n=386
		1.5 Amb a 1-U n=196	6 Amb a 1-U n=385	12 Amb a 1-U n=381	Total RAGWITEK n=962	
TEAE	All	148 (75.5)	296 (76.9)	307 (80.6)	751 (78.1)	264 (68.4)
	Treatment-Related	79 (40.3)	213 (55.3)	233 (61.2)	525 (54.6)	98 (25.4)
TEAE leading to study discontinuation	All	10 (5.1)	31 (8.1)	35 (9.2)	76 (7.9)	9 (2.3)
	Treatment-related	4 (2.0)	26 (6.8)	31 (8.1)	61 (6.3)	6 (1.6)
Serious Adverse Events	All	4 (2.0)	5 (1.3)	3 (0.8)	12 (1.2)	4 (1.0)
	Treatment-related	0	0	0	0	0

Time of onset for treatment-related local application site reactions in the 28-day and 52-week studies

The following application site reactions occurred in frequency greater than placebo, and the median day of onset was Day 1: ear pruritus, oral hypoesthesia, oral pruritus, and throat irritation. In addition, the median day of onset was Day 2 for throat tightness and oral discomfort, and Day 3 for tongue edema and oropharyngeal swelling.

Discontinuation due to Treatment-Related Adverse Events in the 28-day and 52-week studies
Ninety subjects were discontinued from Phase 2 and/or 3 studies in the first 28 days due to adverse events: placebo (n = 7/757; 0.9%), 1.5 Amb a 1-U (n = 4/196; 2.0%), 6 Amb a 1-U (n = 24/454; 5.3%) and 12 Amb a 1-U (n = 55/1057; 5.2%). Most of these discontinuations were considered treatment-related (74/90 subjects). The most common events (n > 3 subjects across all treatment groups) were dysphagia, lip swelling, edema mouth, oral pruritus, palatal edema, swollen tongue, tongue edema, pharyngeal edema, throat irritation, throat tightness, chest discomfort, lip edema, and nausea.

As with the 28-day safety data, most study discontinuations due to an AE reported through Week 52 were considered treatment-related among the study drug and placebo groups (67 of 85). Evidence for a dose response effect of these discontinuations was seen: placebo (n = 6/386; 1.6%), 1.5 Amb a 1-U (n = 4/196; 2.0%), 6 Amb a 1-U (n = 26/385 (6.8%) and 12 Amb a 1-U (n = 31/381; 8.1%).

The treatment-related adverse events that led to study discontinuation through Week 52 were largely similar to those that led to study discontinuation in the pooled 28-day analysis. The most commonly reported events, i.e., those occurring in more than three subjects across all treatment groups up to 52 weeks included: dysphagia, lip edema, lip swelling, edema mouth, oral pruritus, palatal edema, oral paresthesia, swollen tongue, tongue edema, chest discomfort, pharyngeal edema, nausea, pharyngeal erythema, and throat irritation.

TEAE of particular concern

The following subjects experienced TEAE of particular concern, either because they were systemic allergic reactions, were treated with epinephrine, or were considered by the investigator as serious adverse events.

Subjects who received RAGWITEK 12 Amb a 1-U:

1. Lip swelling, abdominal pain and diarrhea on Day 7 of treatment; all were considered mild in severity, but the abdominal pain and diarrhea persisted for subsequent days. No treatment was required, but the subject was discontinued from the trial.

2. Mild swollen tongue and dyspnea on Day 24 of treatment; the dyspnea was treated with albuterol and the subject was discontinued from the trial.

3. Mild wheezing and dyspnea on Day 162 of the trial; the events persisted for a few days and resolved. The subject continued in the trial and tolerated study medication.

4. Palatal edema and flushing on Day 1; no treatment was required. The subject developed palatal edema on subsequent administrations and ultimately discontinued from the trial.

5. Palatal edema and mild urticaria on Day 2; the subject did not require treatment and continued in the trial with resolution of the events.

6. Anaphylaxis on Day 41 in a subject who is allergic to almonds and ingested almonds shortly prior to the event.

7. Anaphylaxis in a 34 year-old male who developed local application site reactions starting at Day 1. The events persisted with subsequent tablet administrations and on Day 6, the subject developed local symptoms within 5 minutes of tablet administration followed by significant swelling in the throat, shortness of breath, nausea, and light-headedness 30 minutes after dosing. The subject self-administered epinephrine and proceeded to an emergency department where he received antihistamine therapy and corticosteroids. The relationship between the AE and RAGWITEK was considered probably related by the investigator. The subject fully recovered following treatment and was discontinued from the trial.

8. Severe throat tightness on Day 14 of treatment that resulted in self-injection of epinephrine by a 41 year old male. There was no history of respiratory compromise. The subject administered epinephrine approximately 2 hours following the event. The investigator assessed the event as a severe local reaction but did not assess epinephrine as necessary for treatment. This was judged by the investigator as probably related to RAGWITEK. The subject was discontinued from the trial.

9. Self-injection of epinephrine by a 71 year old male in response to persistent gastrointestinal symptoms (including abdominal pain, diarrhea, and vomiting) 26 hours after the second administration of study drug; the subject was evaluated by the site following the epinephrine administration. The events were assessed by the investigator as moderate in severity and unlikely related to study medication. This subject was discontinued from the trial.

10. Administration of epinephrine in a health care setting to a 22 year old female who developed local application events that began on Day 3 of treatment. Due to worsening of the events on Day 4, treatment was interrupted for two days so that the next dose of study drug could be administered under supervision in the investigator's office. Within 5 minutes of taking 12 Amb a 1-U, the subject developed mouth swelling and dysphagia. The subject was treated with epinephrine, albuterol and an antihistamine. This was judged by the investigator as probably related to study medication. The subject fully recovered following in-office treatment and discontinued from the trial.

11. Anaphylaxis in a peanut allergic subject with inadvertent exposure to peanut on Day 95.

Subjects who received RAGWITEK 6 Amb a 1-U

1. Syncope and urticaria on Day 121 of study drug administration. These symptoms were not considered severe, and were assessed by the investigator as unlikely related to the study drug. The subject completed the trial with local application side effects that were tolerated.

2. Administration of epinephrine in a health care setting to a 21 year old female in response to pharyngeal edema following administration of the study drug on Day 22. There were no signs of respiratory distress and the subject discontinued from the trial following the event.

Subjects in the Placebo group

1. Anaphylaxis in a 45 year old placebo subject with a history of latex allergy, within 5 minutes of taking the first dose of placebo. The subject required two doses of epinephrine and was transferred to an emergency facility. Since the subject took placebo, it is assumed that the event was due to inadvertent latex exposure.

Systemic Allergic Reactions

For an analysis of systemic allergic reactions, the sponsor searched the database for: anaphylaxis, anaphylactic reactions, and hypersensitivity reactions using specified MedDRA terms; events that could

indicate possible systemic allergic reactions when applying criteria proposed by the Food Allergy and Anaphylaxis Network (FAAN); and administrations of epinephrine.

The sponsor determined that there were three episodes of anaphylaxis: Placebo Subject 1, RAGWITEK 12 Amb a 1-U Subject 6 and RAGWITEK 12 Amb a 1-U Subject 7 discussed in the section above "*TEAE of particular concern."*

In addition, there were seven subjects who experienced symptoms that may be considered systemic. These include five subjects in the 12 Amb a 1-U treatment group (RAGWITEK 12 Amb a 1-U Subjects 1-5), and RAGWITEK 6 Amb a 1-U Subject 1 discussed in the section above "*TEAE of particular concern."*

Epinephrine use during RAGWITEK clinical trials
Each subject received self-injectable epinephrine as a safety precaution. Epinephrine was self-administered by five subjects. Two subjects self-injected the epinephrine after inadvertent exposure to a food allergen (almond and peanut; RAGWITEK 12 Amb a 1-U Subjects 6 and 11, respectively). The three other subjects who self-administered epinephrine were RAGWITEK 12 Amb a 1-U Subject 7, RAGWITEK 12 Amb a 1-U Subject 8, and RAGWITEK 12 Amb a 1-U Subject 9, discussed in the section above "*TEAE of particular concern."*

Three subjects were administered epinephrine in a health care setting: RAGWITEK 12 Amb a 1-U Subject 10, RAGWITEK 6 Amb a 1-U Subject 6, and Placebo Subject 1 discussed in the section above "*TEAE of particular concern."*

Asthma related events

In the 52-week studies, "asthma" recorded in either the eDiaries or diary record card surveys for adverse events were similar among the 6 Amb a 1-U (8/385, 2.1%), 12 Amb a 1-U (5/381, 1.3%), and placebo groups (6/386; 1.6%). Similar as well were the asthma symptoms of cough, dyspnea, and wheezing. There were no severe/life-threatening or serious events of asthma in the 28-day or 52-week pool.

Serious Adverse Events
At least one serious adverse event was reported in 20 of 1707 (1.5%) RAGWITEK recipients, and in 8 of 757 (1.1%) placebo recipients. Of note:

- In the 12 Amb a 1-U treatment group, there was one subject who experienced "hypersensitivity," who was hospitalized and recovered. This event followed ingestion of propolis, a bee product; the subject continued the study medication without additional treatment-related adverse events.

- One subject was hospitalized prior to randomization for hypoxia due to lobar pneumonia.

- Life-threatening adverse events through Week 52 in two 1.5 Amb a 1-U recipients: one who had a spontaneous abortion and one who developed breast cancer.

- Life-threatening adverse events were reported for two 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.

- There was one episode of anaphylaxis in the placebo subject discussed above with a history of latex allergy, within five minutes of taking the first dose of placebo. The subject required two

doses of epinephrine and was transferred to an emergency facility. Since the subject took placebo, it is assumed that the event was due to inadvertent latex exposure.

None of the adverse events categorized as serious by investigators or the sponsor are considered related to the study drug.

There were no deaths in any of the five clinical development trials of RAGWITEK.

4.1.3 Clinical Trials Studies Pooled Safety Analyses - Children and Adolescents

Discontinuation due to Treatment-Related Adverse Events

There were no studies that included subjects less than 18 years of age.

4.2 Post-Marketing Safety Data

RAGWITEK is not an approved product within or outside the US. There are no post-marketing safety data.

5.0 Allergenic Products Advisory Committee

The BLA includes data evaluating the safety and efficacy of RAGWITEK, 12 Amb a 1-U per dose, for immunotherapy of diagnosed short ragweed pollen induced allergic rhinitis, with or without conjunctivitis. The proposed treatment regimen is daily dosing with RAGWITEK for at least 12 weeks prior to the onset of grass pollen season, and to be continued through the duration of the season.

On January 28, 2014, the Allergenic Products Advisory Committee will be asked whether the available data support the safety and the efficacy of the product in persons 18 years of age and older.

The Committee will be asked to discuss recommendations regarding the need, if any, for additional studies.