CBER Statistical Review
Merck Ragweed Extract, Ragwitek®: STN 125478

Application Type	Original BLA
STN	125478
CBER Received Date	March 8, 2013
Completion Goal Date	April 17, 2014
Division / Office	CBER/OBE/DB/VEB
Priority Review	n/a
Reviewer Name(s)	Tammy J. Massie, PhD
Review Completion Date / Stamped Date	
Supervisory Concurrence	A. Dale Horne, DrPH, Branch Chief VEB Lihan Yan, PhD, Team Leader BAT
Applicant	Merck Sharp & Dohme Corp.
Established Name	
(Proposed) Trade Name	Ragwitek®
Pharmacologic Class	Pollen Allergen Extract (Short Ragweed, *Ambrosia artemisiifolia*).
Formulation(s), including Adjuvants, etc	Tablet.
Dosage Form(s) and Route(s) of Administration	Sub-lingual (placed under tongue until dissolved).
Dosing Regimen	12 Amb a 1-U (Unit of *Ambrosia artemisiifolia*) the -----(b)(4)----- (per tablet), once per day.
Indication(s) and Intended Population(s)	The proposed indication for MK-3641, Short Ragweed (*Ambrosia artemisiifolia*) Pollen Extract, is as immunotherapy for diagnosed short ragweed pollen induced allergic rhinitis, with or without conjunctivitis in adults 18 through 65 years of age.

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GLOSSARY

AE	Adverse event
AIT	Allergy immunotherapy tablet
ALK	ALK-Abelló A/S
Amb a 1	*Ambrosia artemisiifolia* major allergen no. 1
Amb a 1-U	Unit of *Ambrosia artemisiifolia* major allergen no. 1
ANOVA	Analysis of variance
AR	Allergic rhinitis
ARC	Allergic rhinoconjunctivitis
ASaT	All Subjects as Treated
BLA	Biologic Licensing Application
CBER	Center for Biologics Evaluation and Research
CHMP	The Committee for Medicinal Products for Human Use (EMA)
CI	Confidence interval
CSR	Clinical Study Report
DMS	Daily medication score
DSS	Daily symptom score
EMA	European Medicines Agency
eDiary	Electronic diary
FAAN	Food Allergy and Anaphylaxis Network
FDA	Food and Drug Administration (US)
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IgG_4	Immunoglobulin G4
ITT	Intention-to-treat
LABA	Long-acting beta2-agonist
LDA	Longitudinal data analysis
LLT	Lower level term
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
Merck/Applicant	Merck Sharpe & Dohme, a subsidiary of Merck & Co.
MK-3641	SCH 039641; Ragweed AIT
NA	Not applicable
PP	Per protocol

PT	Preferred term
RQLQ(S)	Rhinoconjunctivitis quality of life questionnaire (with standardized activities)
RS	Ragweed season
SAE	Serious adverse event
SCIT	Subcutaneous Immunotherapy
TEAE	Treatment-emergent AE
TCS	Total combined score
US	United States
USP	United States Pharmacopeia
WAO	World Allergy Organization
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Merck conducted a multinational clinical development program for MK-3641/Ragwitek®, a short ragweed (*Ambrosia artemisiifolia*) pollen extract sublingual tablet for the treatment of allergic rhinoconjunctivitis in patients with clinical symptoms due to short ragweed pollen allergy.

MK-3641/Ragwitek ® contains allergen extracts of the short ragweed pollen *Ambrosia artemisiifolia*. As per the applicant, this product, MK-3641/Ragwitek®, is indicated for "*immunotherapy for diagnosed ragweed pollen induced allergic rhinitis, with or without conjunctivitis, in adults 18 years of age or older*."

Overall, approximately ~1750 subjects 18 to 65 years of age participated in the clinical development program of MK-3641, which consisted of a total of five (5) clinical trials in the MK-3641/Ragwitek® Clinical Development program. The effectiveness and safety of MK- MK-3641/Ragwitek® was evaluated in the following clinical trials from Phase I to Phase III:

- One 28-day Phase 1 safety trial in adults with ragweed-induced rhinoconjunctivitis without asthma (RT-01);
- One 28-day Phase 2 safety trial in adults 50 years and older with ragweed-induced rhinoconjunctivitis with or without asthma (P06081);
- Two 52-week Phase 2/3 dose-finding efficacy and safety trials in adults with ragweed-induced rhinoconjunctivitis with or without asthma (P05233, P05234); and
- One 28-day Phase 3 safety trial in adults with ragweed-induced rhinoconjunctivitis with or without asthma (P05751).

The clinical trials were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such trials, including the archiving of essential documents. All trials were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human subjects, that were in place at the time the trials were performed.

A summary of the 5 studies, including the purpose of the study, number of patients exposed to the doses of the Merck MK-3641/Ragwitek® ragweed product, is provided in the table below:

Table 1.1) Summary of Clinical Studies to Examine Merck's MK-3641 Short Ragweed Product, Ragwitek®

Type of Study	Study location	Study number	Study Objective	Design	Dose (Amb a 1-U)	No. of Subjects Randomized and Exposed	Age Range (years)	Planned Duration of Treatment
Phase 1: Safety	US	P007 (also referred to as RT-01)	Safety/ tolerability	Dose escalation, double blind, randomized, placebo controlled	3, 6, 12, 24, 50, placebo	Total=53 Active=40	18-50	28 days
Phase 2: Safety	US	P06081	Safety/ tolerability	Double blind, randomized, placebo controlled	6, 12, placebo	Total=203 Active=136	≥50	28 days
Phase 2/3: Safety/ efficacy	US, Canada	P05233	Primary endpoint: Total combined symptom score (TCS) over the peak ragweed season	Double blind, randomized, placebo controlled	6, 12, placebo	Total=565 Active=377	18-50	52 weeks
Phase 2/3: Safety/ efficacy	US, Canada, Hungary, Ukraine, Russia	P05234	Primary endpoint: TCS over the peak ragweed season	Double blind, randomized, placebo controlled	1.5, 6, 12, placebo	Total=783 Active=585	18-50	52 weeks
Phase 3: Safety	US, Canada	P05751	Safety/ Tolerability	Double blind, randomized, placebo controlled	12, placebo	Total = 913 Active = 609	≥18	28 days

Table summarizes data provided within applicant provided datasets:
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The studies provided in this submission appear to support the applicant's conjecture that the Ragwitek® 12 Amb a 1-U product is safe and effective in the treatment of allergic rhinoconjunctivitis caused by short ragweed pollen during the peak pollen season, using CBER's pre-specified criterion for efficacy based on the Combined Symptom Score that incorporates both rescue medication and symptom scores. Furthermore, similar positive trends are observed for the individual endpoints of Total Symptom Scores and the Total Rescue Medication Scores for both the peak and the entire ragweed pollen season, as well as the Total Combined Symptom Score during the entire ragweed pollen season.

Thus, based on the data submitted, reviewed and re-analyzed, Ragwitek® 12 Amb a 1-U per dose appears to be effective for immunotherapy treatment of allergic rhinoconjunctivitis due to sensitivity to the short ragweed pollen *Ambrosia artemisiifolia* included in the product for adults 18-50 years of age. Furthermore, the product appears to

be safe for adults 18-65 years of age, based on the statistical analyses examined and performed by the reviewing statistician.

2. CLINICAL AND REGULATORY BACKGROUND

Allergic rhinoconjunctivitis (ARC) is a worldwide disease affecting over 500 million people, including approximately 30 million Americans. Ragweed pollen is a major seasonal allergen in the Unites States. Untreated or inadequately treated ARC can cause sleep disturbance, daytime fatigue, and somnolence as well as depressed mood, irritability, and behavioral problems. Societal costs include absenteeism from work or school and decreased productivity when at work.

Currently, treatments for ARC include allergen avoidance, pharmaceutical treatment options including pharmacologic therapy such as oral antihistamines and nasal corticosteroids (which provide temporary relief from allergy symptoms but are not effective in all patients, and are not disease-modifying) and administration is subcutaneous injection (SCIT) (which is a treatment that modifies the immune response and treats the cause rather than the symptoms). An alternative to SCIT is sublingual immunotherapy (SLIT) in which treatment is administered orally rather than by injection.

As sublingual ragweed immunotherapy is novel, the clinical MK-3641 development program was based on the development experience with a similar sublingual formulation containing Timothy Grass Pollen. The program and study design was in accordance with the European Medicines Agency (EMA) and Food and Drug Administration (FDA) Guidelines on the clinical development of pharmaceutical products for the treatment of allergic rhinitis. Although no FDA guidance specific to the clinical development of allergen immunotherapy is available, the study designs incorporated guidance from the Center for Biologics Evaluation and Research (CBER) at the FDA, and recommendations from the World Health Organization (WHO) and World Allergy Organization (WAO) position papers for development of sublingual immunotherapy.

Based on the clinical studies provided in the BLA, the applicant proposes the following indication:

> "*Ragwitek® is an allergen extract indicated as immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for short ragweed pollen. Ragwitek® is approved for use in in adults 18 through 65 years of age*."

The dosage of the tablets to be used in the U.S. is (12 Amb a 1-U) daily, an in-house potency measurement which is discussed further in the product reviewer's and medical officer's review of this product.

Adults will initiate therapy at 12 Amb a 1-U per day (one tablet, sublingually administered per day) at least 12 weeks prior to the ragweed season. The first dose of Ragwitek® should only be administered in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. After

receiving the first dose, the patient should be kept under observation for 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the first dose is adequately tolerated, subsequent doses may be taken at home. Although treatment with Ragwitek® can be initiated at any time during the year, the applicant suggests that for optimal symptom improvement during the ragweed pollen season, initiate treatment with Ragwitek® at least 16 weeks prior to the season.

2.1 Disease or Health-Related Condition(s) Studied

Allergic rhinitis (AR) is characterized by red, itchy eyes, a blocked and runny nose, and sneezing. The most common causes of allergic rhinitis are different pollens (grass, tree, and ragweed), house dust mites, mold, and animal dander. Allergic rhinitis can be intermittent (such as hay fever) or persistent (all year round). Often AR is accompanied by allergic conjunctivitis (AC), and may be accompanied by allergic asthma. About 10% of adults and children in the United States have AR.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

A comprehensive listing of products that are approved to treat AR can be found in the medical officer's review. These include both pharmaceutical drugs (prescription as well as over the counter) as well as SCIT (subcutaneous injections).

2.3 Previous Human Experience with the Product (Including Foreign Experience)

There are allergenic products approved for SLIT administration of grass pollens; however, there are currently no ragweed products licensed or approved for administration in adults (or children) via SLIT in the U.S.

A total of five clinical studies comprise the MK-3641/Ragwitek® clinical program conducted to evaluate the efficacy and safety of MK-3641/Ragwitek®. This included one Phase 1 trial (P007 or RT-01); one Phase 2 trial (P06081); two Phase 2/3 (P05233 and P05234); and one Phase 3 (P05751) safety trial.

A comprehensive list of all studies including the location of the study, allocation of patients to treatment or placebo arm, as well as the age range of patients can be observed in the following table.

Table 2.3.1 Number of Subjects Included in the 13 Studies Comprising the MK-3641/ Ragwitek® Clinical Development Program by Study and Age Range
Clinical Studies in Adult Subjects

Study Number	Phase	Study Location	Objective	Number of Subjects Total	Number of Subjects Active	Number of Subjects Placebo	Age Range (Years)
P007 (*)	1	US	Safety	53	40	13	18-50
P06081	2	US	Safety	203	136	67	50+
P05233	2/3	US, Canada	Safety/ Efficacy	565	377	188	18-50
P05234	2/3	US, Canada Hungary, Ukraine, Russia	Safety/ Efficacy	783	585	198	18-50
P05751	3	US Canada	Safety	913	609	304	18+
Total				**2517**	**1747**	**770**	

Source: Table created by reviewing statistician utilizing data provided in:
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Note: (*) P0007 is also referred to as RT-01 by the applicant.

Additional experience can be found in the medical officer's review.

2.4 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Additional information related to the Pre- and Post-submission Regulatory Activity related to this submission can be found in the medical officer's and project manager's reviews.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

This submission includes the summary of five (5) pre-marketing studies, of which two (2) studies included efficacy endpoints and all five (5) pre-marketing studies gathered safety data. These studies included approximately 1,750 subjects exposed to various doses of the Ragwitek® product, of which 1066 were exposed to the 12 Amb a 1-U dosage administered prior to allergy season; then efficacy data were collected up to a year post dose in both US and non-US study sites.

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review. The efficacy and safety data were presented within the Integrated Summary of Safety (ISS) section of the submission, which is unusual. Additionally, the applicant elected not to provide an integrated summary of efficacy that pooled the results of the two efficacy studies. Thus, a sense regarding the totality of effect based on all efficacy data had to be gleaned from each individual study report.

3.2 Compliance with Good Clinical Practices and Data Integrity

Based on the submitted material and current analysis, it appears the clinical trials were conducted in accordance with acceptable ethical standards.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

No issues have been identified that would impact the statistical review or influence the conclusions made based on the studies which examined this product.

5. Sources of Clinical Data and Other Information Considered in the Review

The BLA submission provided by Merck can be found in the following location:
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This filepath includes the clinical overview, summary of safety, summary of efficacy, as well as datasets for the 2 efficacy studies and 5 safety studies that were examined and analyzed by the Agency statistician in the review of this product.

5.1 Review Strategy

The applicant provided a summary of and detailed results for the safety and efficacy analysis. Within the BLA submission, the applicant provided the datasets of 2 efficacy studies as well as the 5 safety studies. The primary studies of interest include both of the Phase II/III Safety and Efficacy Studies and the Phase III safety study, all performed under US IND. The data and the detailed and comprehensive write-up of the studies are found within Module 2 and Module 4 of the original submission of this BLA, 125478 amendment 0, submitted to CBER on March 8, 2013.

Individual study results were provided for both safety and efficacy; however, pooled results were also examined, particularly for safety/tolerability and adverse events.

This BLA includes the following 5 clinical trials that comprise the clinical program which were conducted to evaluate the efficacy and safety of MK-3641/ Ragwitek®:

- One Phase I
  - Adults
    - P007 (or RT-01) US

- One Phase II safety trial in
  - Older Adults (50+)
    - P06081 US
- Two Phase II/III efficacy and safety trials in
  - Adults
    - P05233 US/Canada
    - P05234 US/Russia/Hungary/Ukraine
- One Phase III safety trial:
  - Adults:
    - P05751 US & Canada

The Phase I/II studies contribute data and information to the overall safety of this product and will be discussed briefly only in the safety section of this review.

The Phase II/III studies that are of most interest were the studies performed under US-IND, and examined both the safety and efficacy of this product during the pre-treatment phase, the treatment phase, the pollen season, and a 52-week follow-up. These studies include P05233 and P05234.

5.2 BLA/IND Documents that Serve as the Basis for the Statistical Review

The BLA submitted by the applicant is stored in the following location:

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This includes the clinical and non-clinical information, background material, protocol(s), case report forms, and datasets of all studies submitted by the applicant.

The datasets are located in the file paths:

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Additionally, the applicant provided several publications related to the studies submitted within this BLA, as well as references and publications of similar seasonal allergenic products.

5.3 Table of Studies/Clinical Trials

The following table lists a brief summary of the efficacy studies provided within this submission:

Table 5.3.a. Summary of Efficacy Studies Performed to Examine the Effect of Merck Ragwitek®: 1.5, 6, and 12 Amb a 1-U dose (in which 12 Amb a 1-U is dose of interest)

Study #	Location	Years/ Age Range	Study Type	Treatment Dose	Number of Subjects
P05233	US Canada	18-50yr	Phase II/III	6 Amb a 1-U 12 Amb a 1-U Placebo	188 187 188
P05234	US, Canada, Hungary, Ukraine, Russia	18-50yr	Phase II/III	1.5 Amb a1-U 6 Amb a1-U 12 Amb a 1-U Placebo	197 195 194 198

Table summarizes data provided within applicant provided datasets:
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All studies examined within this submission were single-season field studies that examined subjects' responses for one single allergy season.

The Phase II/III efficacy studies, P05233 and P05234, collected safety data for 52 weeks after treatment initiation; however, there were several additional studies explicitly designed to provide insight into safety/tolerability of this product. A summary of the safety studies can be examined in the following table.

Table 5.3.b. Summary of Safety Studies Performed to Examine the Effect of Merck Ragwitek®: 1.5, 6, and 12 Amb a 1-U dose (in which 12 Amb a 1-U is the primary dose of interest)

Study #	Location	Years/ Age Range	Study Type	Treatment Dose	Number of Subjects
P007	US	18-50 years	Phase I	3 Amb a1-U 6 Amb a1-U 12 Amb a 1-U 24 Amb a1-U 50 Amb a1-U Placebo	9 9 9 9 4 13
P06081	US	50+ years	Phase I/II	6 Amb a1-U 12 Amb a 1-U Placebo	69 67 67
P05233	US Canada	18-50 years	Phase II/III	6 Amb a 1-U 12 Amb a 1-U Placebo	188 187 188
P05234	US, Canada, Hungary, Ukraine, Russia	18-50 years	Phase II/III	1.5 Amb a1-U 6 Amb a1-U 12 Amb a 1-U Placebo	197 195 194 198
P05751	US, Canada	18+ years	Phase III Safety	12 Amb a 1-U Placebo	609 304

Table summarizes data provided within applicant provided datasets:
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A summary of the analyses based on the primary efficacy variable of interest for the optimal dosage proposed (12 Amb a 1-U), the Total Combined Score (CS), for the first year of all efficacy studies is provided in Table 5.3.c, below.

Table 5.3.c. Ragwitek® Summary of Primary Efficacy Results Based on Combined Medication and Symptom Score

Study #	Location	Years/ Age Range	Treatment Dose	Number of Subjects	Met US-FDA Criteria for Efficacy*	% Difference TCS Pt Est (95% CI)
P05233	US Canada	18-50yr	12 Amb a 1-U Placebo	187 188	Yes	-27% (-39%, -15%)
P05234	US, Canada, Hungary, Ukraine, Russia	18-50yr	12 Amb a 1-U Placebo	194 198	Yes	-24% (-37%, -11%)

Table summarizes data provided within applicant provided datasets:
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Other efficacy endpoints of interest included the Daily Rescue Medication Score (DMS), as well as the Daily Symptom Score (DSS) which examined the specific endpoints that contributed to the TCS. The daily symptom scores are a summation of a variety of rhinoconjunctivitis symptoms that were rated on a scale of 0 to 3. The daily rescue medication score is a score assigned to any rescue medication self-administered by the subject to alleviate allergenic symptoms. The results of analysis comparing the TCS, DSS, and DMS scores for individuals treated with Ragwitek versus placebo can be seen in the following tables.

Table 5.3.d.1. Ragwitek® Summary of Primary and Secondary Efficacy Results Based on Combined Medication and Symptom Score, Daily Symptom Score, and Daily Medication Score for Peak and Entire Ragweed Pollen Season

Study P05233

Endpoint	N	Adjusted Mean	Treatment Difference (MK-3641 – Placebo) (95% CI)	% Relative to Placebo (MK-3641 – Placebo) (95% CI)	p-Value
TCS Peak					
12 Amb a 1-U	159	6.22	-2.24 (-3.41, -1.07)	-26.49 (-38.74, -14.59)	0.0002
6 Amb a 1-U	150	6.70	-1.76 (-2.95, -0.57)	-20.82 (-34.06, -7.08)	0.0039
Placebo	164	8.46	—	—	—
TCS Entire RS					
12 Amb a 1-U	160	5.21	-1.80 (-2.78, -0.82)	-25.66 (-37.55, -13.48)	0.0003
6 Amb a 1-U	152	5.92	-1.09 (-2.08, -0.09)	-15.50 (-29.55, -1.65)	0.0320
Placebo	166	7.01	—	—	—
DSS Peak					
12 Amb a 1-U	159	4.65	-0.94 (-1.70, -0.19)	-16.87 (-28.64, -4.62)	0.0144
6 Amb a 1-U	150	4.81	-0.78 (-1.54, -0.01)	-13.89 (-26.51, - 0.04)	0.0472
Placebo	164	5.59	—	—	—
DSS Entire RS					
12 Amb a 1-U	160	4.05	-0.82 (-1.46, -0.18)	-16.85 (-28.47, -4.54)	0.0125
6 Amb a 1-U	152	4.41	-0.46 (-1.11, 0.19)	-9.39 (-22.67, 4.28)	0.1686
Placebo	166	4.87	—	—	—
DMS Peak					
12 Amb a 1-U	159	1.57	-1.30 (-1.95, -0.64)	-45.26 (-65.39, -26.99)	0.0001
6 Amb a 1-U	150	1.89	-0.98 (-1.65, -0.32)	-34.28 (-54.97, -13.31)	0.0039
Placebo	164	2.87	—	—	—

TCS (total combined score) is the sum of DSS (daily symptom score) and DMS (daily medication score) and ranges from 0-54. RS=ragweed season; CI=confidence interval; Difference is compared to placebo;
% Relative to Placebo= (MK-3641-placebo)/ 100.
Due to GCP non-compliance, 5 subjects from Site 63 are excluded from the efficacy analysis.

Source: sBLA 125478/000; Summary of Clinical Efficacy, Page 29 (results of the 12 Amb a 1-U dose verified by statistical reviewer)

Table 5.3.d.2. Ragwitek® Summary of Primary and Secondary Efficacy Results Based on Combined Medication and Symptom Score, Daily Symptom Score, and Daily Medication Score for Peak and Entire Ragweed Pollen Season

Study P05234

Endpoint	N	Adjusted Mean	Treatment Difference (MK-3641-placebo) (95% CI)	% Relative to Placebo (MK-3641-placebo) (95% CI)	p-Value
TCS Peak					
12 Amb a 1-U	152	6.41	-2.04 (-3.30, -0.79)	-24.16 (-36.47, -11.31)	0.0015
6 Amb a 1-U	167	6.88	-1.58 (-2.80, -0.36)	-18.67 (-31.48, -3.57)	0.0113
1.5 Amb a 1-U	169	7.70	-0.76 (-1.98, 0.45)	-8.99 (-22.04, 7.90)	0.2192
Placebo	169	8.46	---	---	---
TCS Entire RS					
12 Amb a 1-U	158	5.18	-1.92 (-2.95, -0.88)	-27.01 (-38.75, -14.07)	0.0003
6 Amb a 1-U	172	5.81	-1.28 (-2.29, -0.28)	-18.09 (-31.37, -3.05)	0.0125
1.5 Amb a 1-U	171	6.22	-0.88 (-1.88, 0.13)	-12.35 (-25.20, 3.59)	0.0878
Placebo	174	7.09	---	---	---
DSS Peak					
12 Amb a 1-U	152	4.43	-0.94 (-1.67, -0.21)	-17.51 (-29.20, -4.48)	0.0118
6 Amb a 1-U	167	4.87	-0.50 (-1.21, 0.21)	-9.25 (-21.95, 4.95)	0.1695
1.5 Amb a 1-U	169	5.11	-0.26 (-0.96, 0.45)	-4.75 (-16.98, 10.08)	0.4781
Placebo	169	5.37	---	---	---
DSS Entire RS					
12 Amb a 1-U	158	3.62	-0.96 (-1.57, -0.35)	-21.00 (-31.62, -8.81)	0.0021
6 Amb a 1-U	172	4.19	-0.40 (-0.99, 0.20)	-8.64 (-21.44, 5.69)	0.1914
1.5 Amb a 1-U	171	4.24	-0.34 (-0.93, 0.25)	-7.41 (-19.50, 7.10)	0.2622
Placebo	174	4.58	---	---	---
DMS Peak					
12 Amb a 1-U	152	1.99	-1.10 (-1.89, -0.32)	-35.73 (-55.82, -14.63)	0.0058
6 Amb a 1-U	167	2.01	-1.08 (-1.84, -0.32)	-35.03 (-54.41, -10.06)	0.0053
1.5 Amb a 1-U	169	2.58	-0.51 (-1.26, 0.25)	-16.36 (-38.29, 13.74)	0.1900
Placebo	169	3.09	---	---	---

TCS (total combined score) is the sum of DSS (daily symptom score) and DMS (daily medication score) and ranges from 0-54. RS=ragweed season; CI=confidence interval; Difference is compared to placebo; % Relative to Placebo= (MK-3641-placebo/placebo)*100.

Source: sBLA 125478/000; Summary of Clinical Efficacy, Page 30 (results of the 12 Amb a 1-U dose verified by statistical reviewer)

From the above tables and analysis of data provided in this submission, it appears that the applicant's conjecture that the Ragwitek® 12Amb a 1-U product is safe and effective in the treatment of allergic rhinoconjunctivitis caused by short ragweed pollen is supported, using CBER's pre-specified criterion for efficacy based on the Combined Symptom Score that incorporates both rescue medication and symptom scores. Furthermore, similar positive trends are observed for the individual endpoints of Total Daily Symptom Scores as well as the Total Daily Rescue Medication Scores for the selected dose.

5.4 Consultations

5.4.1 Advisory Committee Meeting
An Advisory Committee meeting was held on January 28, 2014 to discuss Merck's Ragwitek® product. The Advisory Committee voting results suggested that the data for this product support the contention of adequate safety and efficacy in individuals 18-65 years of age.

5.5 Literature Reviewed

Within this submission, the applicant provides several articles related to the studies performed. These articles have extensive references, of which the statistician utilized several journal articles as well as websites (in particular World Allergy Organization-WAO published suggested standards).

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

This submission included the results of five randomized, double blind, placebo controlled clinical trials to examine the safety/tolerability and efficacy of Ragwitek®.

Specifically, the applicant submitted the data and summaries of the following safety/tolerability and efficacy studies:

- P0007 (Phase I: US safety/tolerability study in Adults Ages 18-50 years)
- P06081 (Phase II: US safety/tolerability study in Adults Ages 50+ years)
- P05233 (Phase II/III: US/Canada efficacy and safety trial in Adults 18-50)
- P05234 (Phase II/III: US/ Russia/Hungary/Ukraine/Canada efficacy and safety trial in Adults 18-50)
- P05751 (Phase III: US & Canada safety trial in Adults 18+ years)

The studies of primary interest in the examination of the efficacy of this product, Ragwitek®, are the Phase II/III studies performed under US-IND:

- P05233 (Phase III: North American-US/Canada safety/tolerability and efficacy study in Adults)
- P05234 (Phase III: US/ Russia/Hungary/Ukraine/Canada safety/tolerability and efficacy study in Children)

Key design features for the studies that were consistent among the efficacy studies include the following components.

Data were to be collected to determine the safety and the efficacy of this product. This included efficacy endpoints related to Total Daily Symptom Scores (DSS), Total Daily Rescue Medication Scores (DMS), and Total Combined Symptoms (TCS) which combines the Daily Symptom Scores and Daily Rescue Medication Scores. Additionally, the total Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was to gather scores related to general lifestyle prior to and during the pollen season.

Randomization

In all studies, patients who fulfilled all the inclusion criteria and none of the exclusion criteria were randomized to active therapy or placebo, with a treatment assignment ratio (or allocation ratio) typically leading to groups of equal size (ratio 1:1:1, 1:1:1:1 for studies with placebo and two, or three dosage levels of active treatment, respectively). A computer-generated randomization list was prepared for each study. All multicenter studies were stratified by study center by allocating complete blocks to each center.

Control treatment

The efficacy studies were placebo-controlled.

The placebo tablets appeared identical to all doses of the active treatment tablets with respect to physical characteristics (i.e., color, weight, taste, size, and shape), the number of tablets per treatment box, and the number of tablets to be taken daily. The excipients were also the same as those used in the active treatment tablets. Furthermore, both the treatment and placebo dose were quick-release tablets that would dissolve within 5 seconds on the tongue, ensuring a similar feel and dissolution rate for both placebo and treatment tablets.

Blinding

All studies addressed in this document were double-blind.

The issue of blinding specific immunotherapy studies is raised in the Food and Drug Administration (FDA) Guidance for Industry: Allergic Rhinitis, Clinical Development Programs for Drug Products (April 2000) and in the EMA Guideline [EMA, 2008]: ". . . superiority versus placebo or any other comparator has to be shown. Since local allergic adverse events are frequent in specific immunotherapy, a placebo preparation with histamine may be considered to keep the blinding."

Treatment Schedules

The various study treatment schedules were fairly similar between all studies, particularly the Phase II/III dose finding safety/efficacy studies; however, separate discussions of individual studies will be provided when examining specific studies. In general, there was a baseline time period in which subjects' allergic symptoms were collected. Subsequent administration of product occurred approximately 16 weeks prior to the anticipated ragweed pollen season; during the pollen season, subjects noted their allergic symptoms on daily diary cards. Additionally, during and after the treatment dosing time frame for both the safety and efficacy studies, adverse events were collected on diary cards or during clinic visits.

Patient population

The patients enrolled in the clinical development program included adults varying in age from 18 to 50 years of age or 18 to 65 years of age, depending on the study, and were consistent with the population consulting allergy practices for treatment of ragweed pollen-related allergic rhinoconjunctivitis.

Choice and description of study endpoints

The clinical development program of Ragwitek® sublingual tablet began by Merck (originally ALK Abello) in 2006.

The efficacy endpoints chosen for the Phase 3 program were in accordance with FDA and EMA guidance's on evaluations for AR and the EMA guideline on the clinical development of products for specific immunotherapy for the treatment of allergic disease.

According to these guidelines, an accepted demonstration of efficacy in rhinoconjunctivitis is based on alleviation of symptoms as measured by subject symptom score, use of rescue medication, and in vitro parameters. However, based on advice provided during the May 2011 Allergenic Product Advisory Committee (APAC), endpoints were utilized that reflect symptoms adjusted by rescue medication usage. Thus, the efficacy endpoints chosen for the Phase 3 program were in accordance with these guidelines on evaluations for AR trials and included rhinoconjunctivitis daily symptom score (DSS), daily medication score (DMS), and the total combined symptom and medication score (TCS: the sum of DSS and DMS). The total Rhinoconjunctivitis Quality of Life Questionnaire with standardized activities (RQLQ) score was a key secondary endpoint.

Throughout the program, the applicant designed the studies in line with appropriate health authority guidelines, including the US-FDA with respect to the studies performed under US-IND. The field exposure studies provided in this submission had similar endpoints and time frames for administration and data collection, while the safety studies had similar endpoints with safety data collected over time spans consisting of 28 days from initial exposure to Ragwitek® through up to 1 year post-exposure to the product.

Symptom Score

Daily rhinoconjunctivitis symptoms, including the four nasal symptoms of runny nose, stuffy nose, sneezing, and itchy nose, and the two non-nasal symptoms of gritty/itchy eyes and watery eyes, were measured on a scale of 0 (none) to 3 (severe), in accordance with the FDA and EMA guidance, as well as clinical guidance from the WAO. A description of the score to be reported by patients is provided in the following table.

Table 6.a. Daily Symptom Score

Score	Severity	Description
0	Absent symptoms	No sign/symptom evident
1	Mild symptoms	Sign/symptom clearly present, but minimal awareness; easily tolerated
2	Moderate symptoms	Definite awareness of sign/symptom, which is bothersome but tolerable
3	Severe symptoms	Sign/symptom that is hard to tolerate, may cause interference with activities of daily living and/or sleeping

Table summarizes the definition of symptom scores based on definitions provided within summary of clinical efficacy:
----------(b)(4)----------

Daily Medication Score

In natural field studies, in order to manage severe rhinoconjunctivitis symptoms, patients were permitted to take rescue medication according to a stepwise regimen described in each protocol. The Daily Rescue Medication Score (DMS) was defined by Merck based on the hypothesis that a nasal corticosteroid is more efficient than an antihistamine, and an oral corticosteroid is more efficient than a nasal corticosteroid, leading to a derived ordinal score that can be seen in the following table. Additionally, it was suggested to the randomized patients to utilize rescue medication based on a stepwise manner that would escalate the use of rescue medication as the symptoms developed and became more severe.

Table 6.b. Daily Rescue Medication Score

Rescue Medication for Rhinoconjunctivitis symptoms	Score/Dose Unit	Maximum Daily Score
Loratadine syrup 1 mg/mL – 5 mL QD (5 to <6 years)	6 (per 5 mL)	6
Loratadine RediTabs tablet 10 mg – 1 tablet QD ≥ 18 years); Claritin syrup 1 mg/mL – 10 mL QD (≥6 to <18 years)	6 (per tablet or 10 mL)	6
Olopatadine hydrochloride 0.1% ophthalmic solution - 1 drop in the affected eye BID	1.5 (per drop)	6
Mometasone furoate monohydrate nasal spray 50 mcg – 1 spray in each nostril QD (5 to <12 years of age)	4 (per spray)	8
Mometasone furoate monohydrate nasal spray 50 mcg - 2 sprays in each nostril QD (≥12 years of age)	2 (per spray)	8
Prednisone tablet 5 mg (Day 1 - 1 mg/kg/day, Max 50 mg/day)	1.6 (per tablet)	16
Prednisone tablet 5 mg (Day 2+ - 0.5 mg/kg/day, Max 25 mg/day)	1.6 x 2 (per tablet)	16
Maximum daily rhinoconjunctivitis medication score		36

Source: Adapted from applicant's Table 4 Clinical Overview Page 25

Total Combined Symptom and Medication Score

This combined score incorporated both the daily symptom scores and the combined symptom score. The daily Total Combined Score (TCS) is a score taking into account the DSS and DMS and assuming equivalent importance of symptoms and medications scores. This score is the combination of the daily symptom score and daily rescue medication score and is calculated for each day for each patient as:

TCS = DSS + DMS.

General Statistical approach

For each study in the clinical development program, all analyses were pre-specified in the respective protocol and detailed in the associated Statistical Analysis Plan (SAP) and its amendments. Each SAP also described the models to be used for the endpoint analyses, validity assumptions, handling of missing data, and how potential statistical issues were to be addressed.

In the Phase 2/3 studies of Ragwitek®, the key efficacy endpoints of clinical interest, TCS, DSS, and DMS, were computed as the average of the available daily scores over specified RPS (entire or peak RPS). The daily TCS was computed as the sum of daily DSS and DMS scores.

In both Phase II/III efficacy studies, the applicant examined multiple dosages to determine the optimal dose. The criterion for selecting the optimal dose for efficacy was to be based on a hierarchical stepwise model in which comparisons were to be made examining the highest dose compared to placebo. Upon meeting the pre-specified criteria for efficacy for each dosage level, the next lower dosage would be examined and compared to the placebo dosage. This stepwise procedure would control the type I error.

In the two studies that included efficacy endpoints, the key efficacy endpoints were to be analyzed using linear (b)(4) models. The specific model to be utilized for each study adjusted for factors such as site/region effect, asthma status, and baseline scores, and these details are outlined in each individual study report. The least squares mean and 2-sided 95% confidence interval (CI) for the between-treatment differences were estimated from the models, with the associated p-values reported. In addition, the percentage reduction relative to placebo effect was calculated as (Ragwitek®-placebo) / placebo x 100% using the within-group least squares means for the Ragwitek® group and the placebo group.

The normality assumption of the ANOVA model was examined for the key efficacy endpoints. When the normality assumption was severely violated, analysis based on appropriate parametric methods (e.g., square root and log transformation of the data, and a ----(b)(4)------- log-normal model) or nonparametric analysis (e.g., ----------(b)(4)---------- analysis of median differences) was adopted as the primary efficacy analysis. In addition, when ANOVA remained as the primary analysis approach,

sensitivity analyses using such transformed data or non- parametric methods were utilized to corroborate the results for the primary ANOVA analysis approach. Further, the interaction of treatment with other model covariates was examined via subgroup analyses by each level of the covariates.

The efficacy analyses were based on the full analysis set (FAS), which generally includes all randomized subjects in accordance with the International Conference on Harmonization (ICH) intention-to-treat principles. Additional analyses based on a per-protocol approach were also performed to corroborate the results of the key efficacy endpoints.

In the Phase 2/3 studies of Ragwitek®, the safety analyses were performed based on all randomized subjects. Subjects were counted in the treatment group for which treatment they actually received. The adverse experiences were summarized by treatment group for the frequency distribution (number and percentage). The vital signs were summarized by treatment group, including the means and standard deviations for changes from baseline. Additional details are provided in individual study reports.

In addition to the safety summary of the individual studies, the data were pooled across studies, separately for the adult and pediatric populations, to provide an integrated summary of safety profile of Ragwitek® treatment.

Analysis sets

In the natural field studies, consistent with the ICH E9 Guideline (*Statistical Principles for Clinical Trials*), the applicant planned to utilize the analysis set which is as complete as possible and as close as possible to the intention-to-treat ideal of including all randomized subjects. The primary efficacy analysis included data from all patients who received at least one dose of the investigational product and had recorded the primary efficacy measure on at least one day during the pollen period while on treatment. Thus, the primary analysis set is appropriately termed "Full Analysis Set" (FAS).

6.1 Trial #1: Study P05233

Merck's trial P05233 was submitted to CBER under US-IND to be "a multi-center, double-blind, randomized, placebo controlled, parallel-group study evaluating the efficacy and safety of Short Ragweed, (*Ambrosia artemisiifolia)* sublingual tablet (SCH 039641) in adult subjects with a history of ragweed pollen induced rhinoconjunctivitis with or without asthma."

This double-blind, randomized, multicenter, parallel-group, placebo-controlled Phase 2/3 study design was used to evaluate the efficacy and safety of treatment with ragweed AIT sublingual tablets in adult subjects (18 to 50 years of age) with a history of ragweed pollen-induced rhinoconjunctivitis, with or without asthma and an IgE mediated response to short ragweed. A placebo was included as an ineffective agent against which to compare the response to ragweed AIT (6 or 12 Amb a 1-U of *Ambrosia artemisiifolia* extract).

6.1.1 Objectives (Primary, Secondary, etc.)

The objectives of this study were to evaluate the efficacy and safety of sublingual tablets of ragweed pollen allergen extract compared with placebo for reduction of rhinoconjunctivitis symptoms and rescue medication usage.

Primary Objective:

To evaluate the efficacy of ragweed sublingual tablet (MK-3641, Ragwitek®) versus placebo in the treatment of ragweed pollen-induced rhinoconjunctivitis based on the combined sum (CS) of rhinoconjunctivitis daily symptom scores (DSS) and rhinoconjunctivitis daily medication scores (DMS) averaged over the entire ragweed pollen season (RPS). Furthermore, since the applicant examined multiple dosages, 6 Amb a 1-U and 12 Amb a 1-U, in addition to establish the efficacy of this product, a second and important goal of this study was to determine the optimal dosage. The criterion for selecting the optimal dose for efficacy was to be based on a hierarchical stepwise model in which comparisons were to be made examining the highest dose compared to placebo. Upon meeting the pre-specified criteria for efficacy for each dosage level, the next lower dosage would be examined and compared to the placebo dosage. This stepwise procedure would control the type I error.

Key Secondary Objectives:

To assess overall safety and to compare the following between the Ragwitek® and placebo groups:

- The average rhinoconjunctivitis DSS for the entire RPS.
- The average rhinoconjunctivitis DMS for the entire RPS.
- The average weekly rhinoconjunctivitis quality of life total score for the entire RPS.

6.1.2 Design Overview

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study in subjects 18 to 50 years of age, of either sex and of any race, with a history of ragweed pollen-induced rhinoconjunctivitis with or without asthma.

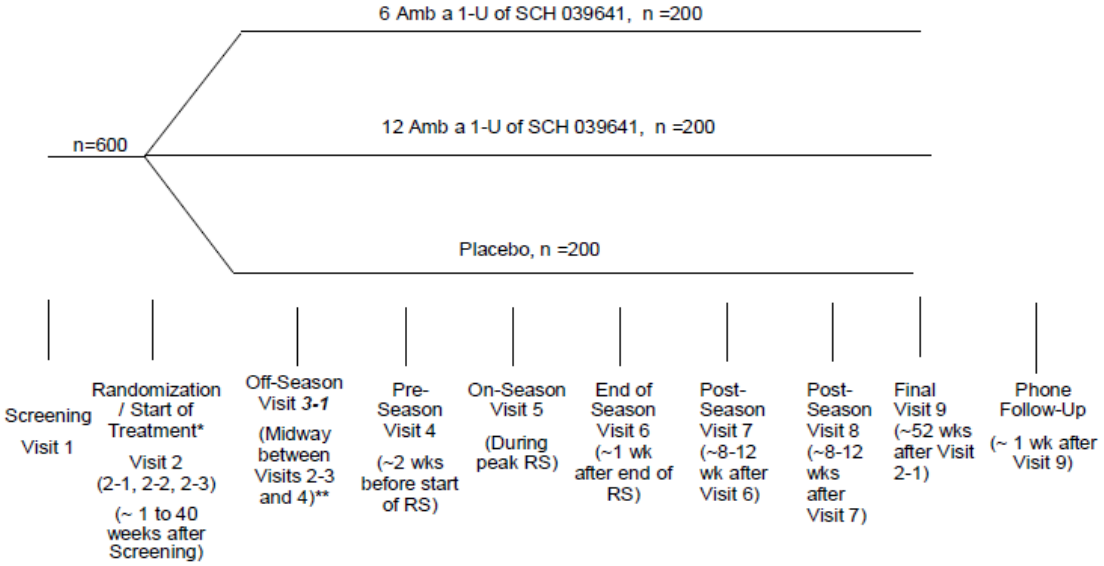
Eligible subjects were to visit the study site for at least 6 visits: Screening, Post-screening, Pre-season, On-season, End-of-season, and Off-season Visits, and at Unscheduled Visits as appropriate. Additional Off-season Visits were scheduled depending on the timing of the Randomization Visit in relation to the anticipated start of the Ragweed Pollen Season (RPS). Qualified subjects were to be randomized into the treatment period.

In the treatment period, the subjects were treated once daily with either Ragwitek® (Short Ragweed allergy immunotherapy tablet [ragweed AIT]) or placebo for approximately 16 weeks prior to the RPS and during the RPS.

At the Randomization Visit, subjects were supplied with self-injectable epinephrine together with instructions on how and when to use it. Open-label rescue medications for the rhinoconjunctivitis and asthma symptoms were to be provided. Subjects were to visit the study site for at least 9 visits: Screening (2 visits), Randomization/Start of Treatment (3 visits), Off-season, Pre-season, On-season, and End-of-season Visits, and at Unscheduled Visits as appropriate.

The first three consecutive daily doses of IMP were administered at the study site (entitled Visit 2-1, 2-2, and 2-3 by the applicant) , and the subjects were monitored at the site for 30 minutes following dosing. Subsequent administration of IMP was done once daily at home at approximately the same time each day. A telephone contact between the investigator/designee and the subject occurred once daily for the first 4 days of at-home administration of IMP to monitor adverse events (AEs) and once approximately 1 week after the End-of-season Visit. A summary of the study visits and data collection points for this study are illustrated in the following study design diagram.

Figure 6.1.2.a. Study Design Diagram



Source: Original BLA 125478/000 Clinical Study Report P05233 page 43

This study was conducted in conformity with Good Clinical Practice. A data safety monitoring committee (DSMC) was established prior to the start of the treatment period. The purpose of the DSMC was to evaluate adverse event data and to provide recommendations regarding the conduct of the study to ensure the safety of the subjects.

6.1.3 Population

The treatment population consisted of male or female patients aged 18 to 50 years (inclusive) in the United States and Canada with documented ragweed pollen-related allergic rhinoconjunctivitis, based on a clinical history of significant allergic rhinoconjunctivitis to ragweed (with or without asthma) diagnosed by a physician and who had received treatment for their disease for the previous ragweed pollen season, had a positive skin prick test (SPT) to Ragweed, and were positive for short ragweed-specific IgE at the screening visit.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Ragweed AIT (6 and 12 Amb a 1-U) and placebo were supplied to the study site by the applicant in the US sites. Similarly, Ragweed AIT and placebo were distributed to the Canadian sites by Canadian country operations. The active treatment (ragweed AIT [SCH 39641]) was a ragweed (*Ambrosia artemisiifolia*) pollen allergen extract formulated as a rapidly dissolving tablet administered sublingually once daily. The placebo treatment was identical to the active treatment, except that no allergen extract was included in the placebo rapidly dissolving tablet. Both the active treatment and placebo were to be administered sublingually (under the tongue) every day at the same time during the approximate 4 to 6-month treatment period, depending on the location of the treatment site.

6.1.5 Sites and Centers

This study was to include 67 centers located in the United States of America and 13 centers in Canada with expected exposure to ragweed pollen.

6.1.6 Surveillance/Monitoring

A detailed synopsis of the surveillance and monitoring of the study can be found in the medical officer's and epidemiologist's reviews. However, a data safety monitoring committee (DSMC) was set up to ensure adequate safety monitoring of the study with pre-specified plans to examine and stop the study in case of unexpected safety issues.

6.1.7 Endpoints and Criteria for Study Success

There are several primary and secondary endpoints in this study that were utilized to assess how well the Ragwitek® product reduced symptoms related to ragweed allergies, as well as reduced the need to take medications to treat or prevent symptoms associated with ragweed allergies. The primary criterion for success was the combined symptom score (CS), which consisted of the patient's daily symptom scores (DSS) and daily rescue medication scores (DMS).

<u>Primary efficacy variable</u>:

The primary efficacy endpoint was the combined (sum of) rhinoconjunctivitis DSS and DMS averaged over the peak RS.

The combined score for each subject was calculated as the sum of rhinoconjunctivitis DSS and DMS during the peak RS, divided by the duration of the peak RS. Endpoints that are average scores for a specific period (e.g., during peak RS or during the entire RS, etc.) were defined based on the available number of days with data (non-missing values) in that period. This endpoint is also commonly referred to as the combined symptom score (CS) and is calculated as follows:

TCS = DSS + DMS.

Both the DSS and DMS are described in Section 6, including tables that specifically provide the scoring mechanisms and methods.

Secondary efficacy variables:
The key secondary endpoints consisted of

1. The combined (sum of) rhinoconjunctivitis DSS and DMS during the entire RS, divided by the duration of the entire RS.
2. The average rhinoconjunctivitis DSS during the peak RS, calculated for each subject as the sum of the rhinoconjunctivitis DSS during the peak RS, divided by the duration of the peak RS.
3. The average rhinoconjunctivitis DSS during the entire RS.
4. The average rhinoconjunctivitis DMS during the peak RS, calculated for each subject as the sum of the rhinoconjunctivitis DMS during the peak RS, divided by the duration of the peak RS.

In addition to examining the various scores, TCS, DSS, DMS, during the entire ragweed pollen season, these scores were also computed and compared for the worst pollen period while the patient was on treatment. Additionally, the following tertiary endpoints were examined:

- The proportion of patients who used rescue medication during the pollen period and worst pollen period while on treatment.
- The proportion of days rescue medication was used during the pollen period and worst pollen period while on treatment.
- Change in the Work Productivity and Activity Impairment-Allergy Specific Questionnaire (WPAI-AS) 7 individual outcomes from randomization to on-season and end-of-season visits.
- Proportion of Symptom-Controlled Days (PSCD) as defined by a DSS score of "0."
- Overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score.
- Global assessment and evaluation of the efficacy of the treatment by the patient.
- Asthma status and severity.
- Immunological markers (IgE specific for ragweed pollen allergen) and Skin Prick Test (SPT) results.

Safety variables:
- Adverse events (AEs).
  - Laboratory assessments.
  - Physical examinations.
  - Vital signs.

Reviewer Comment: *The study design and methods of data collection and evaluation are standard for the indication studied. Subjective symptom reporting and assessment of the nasal and non-nasal symptoms are standard efficacy measurements in rhinoconjunctivitis trials for the ragweed product being studied in this BLA, as well as for other products examining the effect of SLIT in reduction of pollen inducing symptoms.*

6.1.8 Statistical Considerations & Statistical Analysis Plan

Analysis sets:
For the purpose of this study, three analysis sets were defined, namely, the Safety Set, the Full Analysis Set (FAS), and the Per Protocol Analysis Set (PPS), which were pre-specified and defined as follows:

- The Safety Set includes all patients who received at least one dose of the investigational product.
- The FAS includes all patients who received at least one dose of investigational product and had at least one TCS while on treatment during the ragweed pollen season (RPS). The FAS was regarded as the primary population for the efficacy analyses.
- The PPS includes all patients from the FAS who had valid TCS during the RPS while on treatment and who completed the study according to the protocol and had no major protocol deviations.

Primary efficacy endpoints:

The primary efficacy endpoint of average TCS during the peak RS was evaluated using an analysis of variance (ANOVA) model with baseline asthmatic condition (yes/no), pollen region, and treatment group as fixed effects. Pollen region was defined based on pollen station, and included several sites within an acceptable distance from the pollen counters.

For each dose comparison against placebo, a 2-sided 95% confidence interval (CI) of the difference in adjusted means between the two treatment groups was presented. Also, the difference in adjusted means between the two treatment groups relative to the adjusted mean of the placebo group was presented as a percentage (i.e., 100*[ragweed AIT-placebo]/placebo) with a corresponding 2-sided 95% CI, where the 95% CI was derived using the -(b)(4)--- method with 10,000 repetitions ----(b)(4)--------. This was further examined utilizing the difference based on the adjusted means computed utilizing the pre-specified model and the ----------(b)(4)----------.

Secondary Efficacy Endpoints:

The key secondary endpoints were evaluated using the same ANOVA model defined for the primary efficacy endpoint as described above.

The following additional secondary endpoints were evaluated using the same ANOVA model defined for the primary efficacy analysis: DMS, Minimal Symptom Days, VAS and asthma DSS over the entire RS, RQLQ, VAS and asthma DSS during peak RS, and WPAI-AS (each individual domains) change from randomization to Visits 5 (on-season) and 6 (end-of-season). The reviewing statistician also performed sensitivity analysis on select secondary endpoints using both the peak pollen season as well as the entire pollen season.

Safety Analysis:

The number of subjects reporting any adverse events, the incidence of specific adverse events, and discontinuations due to adverse events were tabulated by treatment group. Laboratory and vital sign data were listed and summarized, and values outside the reference ranges were flagged.

Missing Data:

For the primary analysis, there was no imputation of missing data. The combined average score was based on the available data. However, the primary analysis was supplemented by sensitivity analyses using various imputation techniques to ensure the robustness of the conclusions made via the primary analysis methods.

Determination of the sample size:

For Study P05233, approximately 600 subjects will be randomized in an equal ratio to one of three treatments: 6 and 12 Amb a 1-U of the ragweed sublingual tablet, and placebo.

Based on the original protocol primary endpoint of TCS average over the entire RS, with approximately 200 subjects per group, the study would be able to detect a difference of - 1.63 in the primary endpoint between an active dose group and the placebo group with 92% power at a 5% level of significance (2-sided test). The calculation was based on the original assumptions on the estimates of the standard deviation (SD=4.77) and treatment effect (-1.63) derived from ALK-Abello study GT-08 (grass sublingual tablet).

Based on the current (revised) protocol the primary endpoint of interest, the TCS during the peak RS, with approximately 200 subjects per group, the study would be able to detect a difference of -1.80 in the primary endpoint between an active dose group and the placebo group with 90% power at a 5% level of significance (2-sided test). The assumptions used in the power calculations were derived from the data across two US studies P05238 and P05239 (grass sublingual tablet).

Table 6.1.8.1 Estimates and Differences, Standard Deviation, and Power

	Differences of Effect (%) from Placebo to be Detected	Estimates of		Power
		Mean Placebo Effect	Standard Deviation	
Primary Endpoint				
Average TCS Over the Peak RS[a]	-1.80 (25)	7.10	5.51	90%
Key Secondary Endpoints				
Average TCS Over the Entire RS[a]	-1.45 (23)	6.40	4.38	90%
Average DSS Over the Peak RS[a]	-1.26 (24)	5.20	3.53	95%
Average DSS Over the Entire RS[a]	1.01 (21)	4.80	3.12	90%

a: Estimates of standard deviations and placebo effects are derived from the two US studies P05238 and P05239 (grass sublingual tablet).

Source: Original BLA 125478/000 Clinical Study Report P05233 page 72

Reviewer comment: *The applicant initially proposed utilizing a point estimate in which an improvement of greater than 20% based on the combined score of the Ragwitek® treated individuals over the placebo comparator was to be considered the primary endpoint. This was agreeable to CBER; however, it was suggested that the study also meet a clinically meaningful margin of -10% for the upper bound of the 95% CI. This study sample size calculation was revised based on additional information gleaned through the grass studies, which was agreeable to the Agency.*

6.1.9 Study Population and Disposition

The study population and baseline demographics of the enrolled patients are similar for both treatment groups.

In this study, 565 patients were randomized to treatment. Of a total of 565 randomized subjects, 560 subjects were included in the safety and efficacy analyses, treated with either 12 Amb a 1-U ragweed AIT (n=186) or 6 Amb a 1-U ragweed AIT (n=188) or placebo (n=186).

A total of 423 (74.9%) randomized subjects completed the protocol-specified, double-blind treatment period. The median pre-seasonal duration of treatment was approximately 17 weeks. Demographic and Baseline characteristics were well matched between the treatment groups. Overall, the median age was 37 years, 51% of subjects were female, and approximately 78% were white. Twenty-one percent of subjects had a diagnosis of asthma. Median duration of ragweed allergy at Baseline was approximately 18 years. All subjects tested positive by serum specific IgE measurements to short ragweed pollen (*Ambrosia artemisiifolia)* and all subjects tested positive for short ragweed pollen (*Ambrosia artemisiifolia*) by skin prick testing at Screening. In addition, 85.1% of all subjects were multi-sensitized to additional allergens, with notable trends in sensitization to other pollens such as grasses and/or trees. Approximately, one third of subjects were sensitized to perennial allergens including dander and dust mites.

6.1.9.1 Populations Enrolled/Analyzed

The following table illustrates the population distribution in study P05233.

Table 6.1.9.1.1. Summary of Patient Population

	Ragwitek AIT 6 Amb a 1-U **N (%)**	**Ragwitek AIT 12 Amb a 1-U** **N (%)**	**Placebo** **N (%)**	**Total** **N (%)**
Patients Randomized	190 (100%)	187 (100%)	188 (100%)	565 (100%)
Patients in Safety Set	188 (98.9%)	185 (98.9%)	186 (98.9%)	559 (98.9%)
Patients in Full Analysis Set	188 (98.9%)	185 (98.9%)	186 (98.9%)	559 (98.9%)
Protocol Evaluable Data Set	149 (78.4%)	158 (84.5%)	157 (83.5%)	464 (82.1%)

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

6.1.9.1.1 Demographics

The demographics of the individuals included in this study can be seen in the following table. Since the optimal dose for the product is 12 Amb a 1-U, the focus of the data and results observed within study P05233 will be based on the 12 Amb a 1-U dose and the placebo comparator. Within the table, the number of individuals and percent of individuals is noted for each treatment group, based on the demographic variables of gender, age, and race. This table illustrates that the baseline characteristics were similar for both treatment groups for nearly all baseline characteristics except gender. In the 6 Amb a 1-U treatment group, there were more male subjects when compared to female subjects, while in the 12 Amb a 1-U treatment group, there were more female subjects when compared to male subjects. The placebo treatment group had similar numbers of males and female subjects randomized, and the total number of subjects overall were fairly well balanced. Examining the CRFs and the datasets provided did not provide any insight as to what may have led to this slight imbalance in gender within this study; however, no stratification for gender was utilized within the randomization scheme to prevent any imbalance in gender or any other baseline variable.

Table 6.1.9.1.1 Baseline Demographics of the Patient Population

Baseline Demographic	**Ragwitek AIT 6 Amb a 1-U N=190**	**Ragwitek AIT 12 Amb a 1-U N=187**	**Placebo N=188**	**Total N=565**
Gender [n (%)]				
Female	84 (44%)	109 (59%)	93 (49%)	286 (51%)
Male	106 (56%)	78 (41%)	95 (51%)	279 (49%)
Age (years)				
Mean (SD)	35.3 (9.0)	34.9 (9.4)	35.9 (9.1)	34.5 (9.2)
Range	18-50	18-51	18-50	18-51
Race [n (%)]				
White/Caucasian	151 (80%)	153 (81%)	139 (74%)	443 (78%)
Black or African American	18 (9%)	21 (11%)	27 (14%)	66 (12%)
Asian	16 (8%)	10 (5%)	19 (10%)	45 (8%)
American Indian/Alaska	2 (1%)	1 (0%)	0 (0%)	3 (1%)
Other	4 (2%)	2 (1%)	3 (2%)	9 (2%)

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

6.1.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

The medical/behavioral characteristics of the individuals included in this study can be seen in the following table. Within the table, the mean and standard deviation of various relevant medical/behavioral characteristics are noted for each treatment group based on the BMI, height, and weight. This table illustrates that these characteristics were similar for both treatment groups.

Table 6.1.9.1.2 Baseline Medical/Behavioral Characteristics of the Patient Population

Baseline Demographic	**Ragwitek AIT 6 Amb a 1-U N=190**	**Ragwitek AIT 12 Amb a 1-U N=187**	**Placebo N=188**	**Total N=565**
BMI (kg/m^2)				
Mean (SD)	28 (5.5)	28 (6.3)	27 (5.5)	27 (5.9)
Range	18.7-47.5	17.7-52.9	17.0-44.8	17-52.9
Asthma Status [n (%)]				
Asthmatic	37 (19%)	42 (22%)	43 (23%)	122 (22%)
Non-Asthmatic	153 (81%)	145 (78%)	145 (77%)	443 (78%)
Sensitization [n (%)]				
Ragweed	26 (14%)	28 (15%)	28 (15%)	82 (15%)
Other Allergens	164 (86%)	159 (85%)	160 (85%)	483 (85%)

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

6.1.9.1.3 Subject Disposition

The following table illustrates the randomization, allocation, and withdrawal of patients for this study. This table notes which treatment arm subjects were randomized to and

subsequently lists the reason for dropout, including the number of subjects and percentage of subjects that withdrew prior to study completion. It is of interest to note the adverse event rate is slightly higher in the active treatment group; however, other reasons for dropout were fairly similar between the placebo and active treatment groups (both the 6 Amb a 1-U as well as the 12 Amb a 1-U doses). Considering this is an allergen extract administered via SLIT in subjects that are sensitive to the allergen, this is reasonable and expected.

Table 6.1.9.1.3.2. Patient Disposition after Randomization

	Number (%) of Subjects			
Disposition of Subjects	**Ragweed AIT 6 Amb a 1-U (n=190)**	**Ragweed AIT 12 Amb a 1-U (n=187)**	**Placebo (n=188)**	**Total (n=565)**
Randomized	190	187	188	565
All Subject as Treated (n,%)	188 (98.9)	186 (99.5)	186 (98.9)	560 (99.1)
Full Analysis Set (n,%)	188 (98.9)	185 (98.9)	186 (98.9)	559 (98.9)
Per Protocol Set (n, %)	149 (78.4)	158 (84.5)	157 (83.5)	464 (82.1)
Included in the Analyses of TCS, DSS, DMS during the Peak RS	150 (78.9)	159 (85.0)	164 (87.2)	473 (83.7)
Included in the Analyses of TCS, DSS, DMS during the Entire RS	152 (80.0%)	160 (85.6%)	166 (88.3%)	478 (84.6%)
Discontinued Treatment (n,%)	57 (30.0%)	43 (23.0%)	42 (22.3%)	142 (25.1%)
Adverse Event	15 (7.9%)	19 (10.2%)	3 (1.6%)	37 (6.5%)
Lost to follow-up	11(5.8%)	1 (0.5%)	7 (3.7%)	19 (3.4%)
Subject did not wish to continue for reasons unrelated to assigned study treatment	22 (11.6%)	14 (7.5%)	20 (10.6%)	56 (9.9%)
Noncompliance with protocol	7 (3.7%)	7 (3.7%)	10 (5.3%)	24 (4.2%)
Did not meet protocol eligibility	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Administrative	2 (1.1%)	1 (0.5%)	2 (1.1%)	5 (0.9%)
Completed Treatment (n,%)	133 (70.0)	144 (77.0)	146 (77.7)	423 (74.9)

Source: Original BLA 125478/000 Clinical Study Report P05233 page 82

6.1.10 Efficacy Analyses

In this study the applicant examined the efficacy response to multiple dosages and sought to determine the optimal dose. The criterion for selecting the optimal dose for efficacy was to be based on a hierarchical stepwise model in which comparisons were to be made examining the highest dose compared to placebo. Upon meeting the pre-specified criteria for efficacy for each dosage level, the next lower dosage would be examined and compared to the placebo dosage. This stepwise procedure would control the type I error.

The applicant proposed and implemented efficacy analysis based on the various efficacy endpoints including TCS, DSS, DMS, and other allergenic symptom scores and responses within this study. Although the applicant did examine the 6 Amb a 1-U and 12 Amb a 1-U dosages in this study, it was determined that the 12 Amb a 1-U dosage was the optimal dose based on the results of safety and efficacy analysis. Based on the results provided by the applicant and confirmed by the statistical reviewer, the optimal dose was determined to be 12 Amb a 1-U. Thus, in most cases these results will be presented and discussed in the remainder of this section, Section 6.1., of this review.

Primary Efficacy Analysis

The primary efficacy variable to address the treatment effect for this study was the Total Combined Score (TCS) based upon the combined (sum of) rhinoconjunctivitis daily symptom score (DSS) and daily medication score (DMS) averaged over the peak Ragweed Pollen Season (RPS).

For the treatment period, the primary efficacy endpoint of the combined (sum of) rhinoconjunctivitis DSS and DMS averaged over the peak RPS was to be evaluated using a linear model with asthma status, study site, and treatment group as fixed effects. This model was to allow for heterogeneous variance estimates for the treatment groups, with appropriate adjustments made. For the primary endpoint, subjects with at least one post-baseline diary record with DSS and DMS within the defined pollen season were to be included. The combined average score was to be based on all available data during the RPS for each subject.

A 2-sided 95% confidence interval for the difference in the adjusted means (adjusted for asthma status, and study site) between the two treatment groups was to be presented. Also the difference in adjusted means between the two treatment groups relative to the adjusted mean of the placebo group was to be presented as a percentage with corresponding confidence interval.

Secondary Efficacy Analysis

The secondary efficacy variable to address the treatment effect for this study was the DSS and DMS over the peak RPS, as well as these endpoints and TCS for the entire RPS.

The DSS is composed of six rhinoconjunctivitis symptoms recorded daily, including runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes; the symptoms were measured on a scale of 0 (no symptoms) to 3 (severe symptoms), and a higher score indicated a higher level of symptoms. The DMS is composed of a sum of the scores associated with rescue medication use per day, where a lower medication score indicated less use of rescue medication. The DSS and DMS data were collected during the RPS in which the duration of the RPS was defined as the total number of days for which a subject had data during the RPS.

Safety Analysis

The safety endpoints (treatment-emergent, treatment-related AEs; local AEs; discontinuations due to AEs) were to be based on the All-Treated set, and were to be summarized by treatment group and asthma status for the frequency distribution (N and percentage).

6.1.10.1 Analyses of Primary Endpoint(s)

The primary efficacy endpoint is the Total Combined Score (TCS) during the ragweed pollen season (RPS) while on treatment. The primary analysis was performed for the Full

Analysis Set (FAS), which included all patients who received at least one dose of the investigational product.

The TCS was analyzed using a linear model with asthma status, study site, and treatment group as fixed effects and also adjusting for heterogeneous variance between treatment groups. The TCS score was based on all available data during the RPS for each subject within the FAS.

A 2-sided 95% confidence interval for the difference in adjusted means between the two treatment groups was provided. Also, the difference in adjusted means between the two treatment groups relative to the adjusted mean of the placebo group was presented as a percentage with corresponding confidence interval.

The linear model results for the primary efficacy analysis of the TCS during the pollen period for the FAS are summarized below. The point estimate is the LS Means difference between 12 Amb a 1-U dose and placebo, and the relative LS Means difference is equal to (LS Mean difference/LS Mean for the Placebo group) x 100.

For the tables provided in this review the calculations were performed utilizing -----(b)(4)-, with the specific model noted within the footnotes. If additional methods were used to compute the 95% CI to verify and confirm the robustness of results, the methods are noted in the table footnotes.

The (b)(4) model is a combination of fixed and random effects parameters and is written as follows:

-------(b)(4)----

----------(b)(4)----------
----------.

The results in the third and fourth columns of Table 6.1.11.1.a. below are the estimates from the (b)(4) model, including the linear estimate for the -----(b)(4)---------- and the approximate standard error for the LS Mean (computed as the square root of ----------
----------(b)(4)----------.

As an additional method to ensure robustness of results, the reviewing statistician utilized the delta method to estimate the 95% CI for the difference between the treatment and placebo group. Additionally, the reviewing statistician also utilized different variance/covariance structures within the model to ensure robustness of the results of the statistical tests and conclusions drawn from them.

These results of statistical analysis of the primary endpoint, which can be seen in the below table, confirmed the applicant's results and provided an additional analysis

supporting the applicant's conjecture that this product reduces the combined symptom and rescue medication score when compared to placebo.

Table 6.1.10.1.a. Primary Efficacy Analysis: ANCOVA of the TCS during the Peak Ragweed Pollen Period – FAS Comparing the 12 Amb a 1-U Dosage to Placebo

Treatment	n	LS Mean	LS Mean difference vs Placebo Point Est	LS Mean difference vs Placebo 95% CI	Relative LS Mean difference (%) Point Est	Relative LS Mean difference (%) 95% CI	Relative LS Mean difference (%) 95% CI (using the delta method)
Ragwitek®	159	6.2	-2.2	(-3.4, -1.1)	-26.5%	(-39.7%, -14.6%)	(-39.2%, -15.0%)
Placebo	164	8.5					

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, asthma status, and treatment group using SAS: ---(b)(4)------ procedure. As an additional analysis method, the delta method was used to calculate the confidence intervals.

The difference in LS means of the daily TCS during the entire ragweed pollen period between the 12 Amb a 1-U group and the Placebo group was statistically significant. The treatment effect was estimated as the difference in LS means of -2.2, corresponding to a relative LS Mean difference of -26.5% from placebo. The 95% CI expressed as percentages was [-39.7%, -14.6%]. Furthermore, utilizing the delta method, the 95% CI expressed as percentages was [-39.2%, -15.0%], which satisfies CBER's suggested criterion of meeting a -10% threshold for reduction of combined symptom scores. Additionally it meets the applicant's pre-specified treatment difference of 15% ,supporting the applicants conjecture that Ragwitek® reduces the combined symptoms and rescue medication score when compared to placebo.

6.1.10.2 Analyses of Secondary Endpoints

In addition to the primary endpoint of interest, the total combined symptom and rescue medication score (TCS) during the entire RPS, several secondary endpoints were of interest. These include but are not limited to the daily symptom scores, as well as use of rescue medication during the pre-specified ragweed pollen season and the TCS during the peak pollen season.

Table 6.1.10.2.a. illustrates the difference between the placebo and treatment groups for the peak ragweed pollen season. Within this table, the DSS and DMS sample size in each treatment arm, point estimate of the LS Mean per treatment arm as well as LS Mean difference, 95% CI of the LS Mean, and relative LS Mean Difference are presented.

Table 6.1.10.2.a Secondary Efficacy Analysis: ANCOVA of the DSS and DMS during the Peak Ragweed Pollen Season (RPS) – FAS

Treatment	n	LS Mean	LS Mean difference vs Placebo Point Est *(95% CI)*	Relative LS Mean difference vs Placebo (%) Pt Est	Relative LS Mean difference vs Placebo (%) 95% CI
DSS					
Ragwitek®	160	4.6	-1.0	-16.9%	(-28.7%, -4.6%)
Placebo	166	5.6	*(-1.7, -0.2)*		
DMS					
Ragwitek®	160	1.6	-1.3	-45.3%	(-65.4%, -28.0%)
Placebo	166	2.9	*(-2.0, -0.6)*		

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------
Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, asthma status using SAS --(b)(4)-- procedure.

Table 6.1.10.2.b. illustrates the difference between the placebo and treatment groups for the entire ragweed pollen season. Within this table, the TCS, DSS, and DMS sample size in each treatment arm, point estimate of the LS Mean per treatment arm as well as LS Mean difference, 95% CI of the LS Mean, and relative LS Mean Difference are presented. This is a secondary analysis for which the study was not powered to detect differences between treatment groups, nor were alpha adjustments made for these multiple hypothesis tests. However, the trends observed within the table suggest that the treatment reduces the symptoms, use of rescue medication, or the combination of both when compared to individuals randomized to the placebo treated group.

Table 6.1.10.2.b. Secondary Efficacy Analysis: ANCOVA of the DSS and DMS during the Entire Ragweed Pollen Season (RPS) – FAS

Treatment	n	LS Mean	LS Mean difference vs Placebo Point Est *(95% CI)*	Relative LS Mean difference vs Placebo (%) Pt Est	Relative LS Mean difference vs Placebo (%) 95% CI
TCS					
Ragwitek®	160	5.2	-1.8	-25.7%	(-37.6%, -13.5%)
Placebo	166	7.0	*(-2.8, -0.8)*		
DSS					
Ragwitek®	160	4.0	-0.8	-16.9%	(-28.5%, -4.5%)
Placebo	166	4.9	*(-1.5, -0.2)*		
DMS					
Ragwitek®	160	1.2	-1.0	-45.9%	(-65.5%, -24.0%)
Placebo	166	2.2	*(-1.5, -0.4)*		

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------
Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, asthma status using SAS --(b)(4)-- procedure.

Reviewer Comment: *The applicant proposed to meet a clinically meaningful margin of -10% for the upper bound of the 95% CI when comparing the difference between the treatment and placebo treated individuals for the primary endpoint of TCS.*

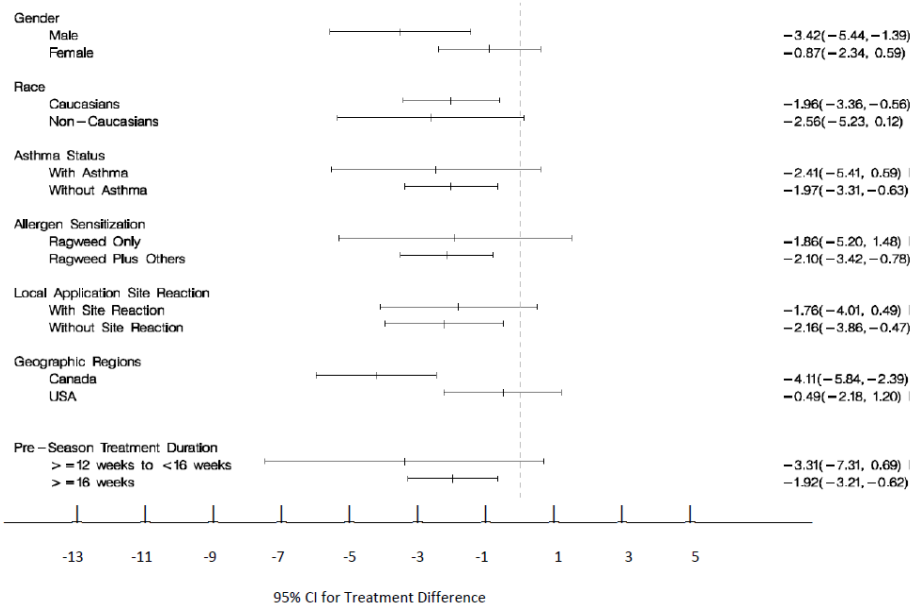
Furthermore, the applicant proposed utilizing a point estimate involving an improvement of greater than 15% based on the relative % difference, using the total combined score (TCS) of the Ragwitek® treated individuals over the placebo comparator. The applicant met these criteria for the primary endpoint during the peak pollen season. Furthermore, based on analysis of the study data, in most cases these criteria were also met for the secondary endpoints, including the DMS during the peak pollen season as well as the TCS and DMS during the entire pollen season. In the case of the DSS scores for both the peak and the entire pollen season, the applicant met the criteria for the relative % difference; however, the clinically meaningful margin of -10% based on the upper bound of the 95% CI was not explicitly met. However, the data illustrated a positive trend in the reduction of symptoms.

6.1.10.3 Subpopulation Analyses

Several subpopulations were of interest to the review team: ragweed pollen sensitivity, geographic location, and asthma status. Additionally, based on current regulations, there should be analyses based on gender, age, and race. In this study, nearly 85% of the enrolled subjects were Caucasian/white; thus, subgroup analysis of the primary endpoint based on specific races is not expected to be informative. Additionally, since this study randomized only subjects from 18-50 years of age, no subset analysis was performed stratifying by age. However, comparisons of the treatment response when considering male vs female outcomes were performed by the reviewing statistician. These results provide consistent positive trends that demonstrate Ragwitek® reduces total combined symptom and rescue medication scores when compared to placebo; however, slight differences between the two different genders can be noted.

From Figure 6.1.10.3.1 below, it can be seen that there is an observable positive treatment effect for both male and female subjects, but the effect appears to be slightly greater among males. Other comparisons of groups, including sensitivity to ragweed, asthma status, and geographic location are presented and illustrate positive trends in the effect of the Ragwitek® treatment in reducing symptoms.

Figure 6.1.10.3.1. Subpopulation Analysis by Gender, Race, Ragweed Sensitivity, and Region for the TCS during RPS, including Mean and 95% Confidence Interval for the 12 Amb a 1-U Treatment Group



Source: Original BLA 125478/000 Clinical Study Report P05233 page 133 results confirmed by reviewing statistician

Reviewer Comment: *The overall results of the efficacy data when examining a variety of subsets based on demographic and baseline characteristics suggest that there is a reduction in the total combined symptom (TCS) score, which utilizes both daily symptom scores and the daily use of rescue medication when comparing individuals who were randomized and received Ragwitek® study treatment and individuals who received a nearly identical placebo product. Two groups in which the responses are not as robust are females and those individuals located in the US; however, it should be noted that the study was not powered to detect significant differences or examine subgroup analysis, so results should be interpreted cautiously. Similar trends illustrating a positive effect of the treatment within the various subgroups were observed when examining the key secondary analyses.*

6.1.10.4 Dropouts and/or Discontinuations

For the average scores of TCS in each of the four study periods (preseason, RPS, peak season, and post-season), there was no imputation of missing diary data. The average score for each subject and study period was based on the available data within the period. However, for rhinoconjunctivitis DMS, if rescue medication use was missing on any single day of the diary card, it was assumed to be “no use” and a score of zero was assigned in such cases as a convention.

For each of the primary and key secondary endpoints of TCS, DSS, and DMS, 14% (27/187) of subjects in the Ragwitek® group and 12% (24/188) of subjects in the placebo group had no data during the peak RPS. The dropouts in each of the treatment

arms were within the expected dropout/missing values suggested during the IND phase of the study (15%).

Reviewer comment: *The proposed treatment of exclusions and missing values was considered acceptable. Several post-hoc analyses were performed using a variety of imputation methods yielding similar results to the original analysis. In addition, comparisons of missing value rates were made and were deemed comparable for both treatment groups for primary endpoints as well as key secondary endpoints for both the peak and entire pollen season.*

6.1.10.5 Exploratory and Post Hoc Analyses

The applicant provided a variety of exploratory and post hoc analyses. These analyses included but were not limited to comparisons of combined score, rescue medication score, symptom scores for IgG4, IgE, as well as examination of secondary endpoint analyses over the peak and entire pollen season. A variety of these analyses were confirmed by the reviewing statistician. The analysis of the IgG4 and IgE scores appeared to be positively affected by the use of the active treatment when compared to placebo treated individuals; however, there was a large amount of variability. Additionally, analyses of selected endpoints, time frames, and analysis sets revealed trends in which the active treatment reduced the use of rescue medication, and reduced the severity based on symptom scores of a variety of nasal and oral endpoints. This finding was observed for the full pollen season as well as the peak ragweed pollen season and for different analysis sets that were available

Reviewer Comment: *The overall results of the efficacy data provided in this study suggest that there is a reduction in the TCS, which combines the daily symptoms scores and use of rescue medication when comparing individuals who were randomized and received 12 Amb a 1-U Ragwitek® study treatment ando individuals who received a nearly identical placebo product. Furthermore, similar positive trends are noted when examining the individual DSS and DMS scores for both the peak and entire ragweed season.*

6.1.11 Safety Analyses

Safety data were collected for the entire study period. Subjects were able to note safety events on the daily diary cards, and also received periodic follow-up from study personnel. Overall, there were slightly more adverse events in the treatment group compared to the placebo group; however, there were no serious adverse events noted in either the treatment or placebo group. A summary of the adverse events can be seen in the applicant's following Table 6.1.12.a, which includes the number (and percentage) of subjects experiencing adverse events, stratified by the treatment group (confirmed via (b)(4) tabulations by the reviewing statistician).

Table 6.1.11.a. Summary of Adverse Events Observed in the Treated and Placebo Groups during the Entire Study Period

Adverse Event Category	Number (%) of Subjects			
	Ragweed AIT 6 Amb a 1-U (n=188)	Ragweed AIT 12 Amb a 1-U (n=186)	Placebo (n=186)	Total (N=560)
Any Adverse Event (n,%)	152 (80.9)	159 (85.5)	144 (77.4)	455 (81.3)
TEAEs	147 (78.2)	158 (84.9)	139 (74.7)	444 (79.3)
Treated-Related AEs[a]	112 (59.6)	128 (68.8)	53 (28.5)	293 (52.3)
Severe/Life-threatening TEAEs	21 (11.2)	33 (17.7)	24 (12.9)	78 (13.9)
Serious AEs[b]	2 (1.1)	3 (1.6)	4 (2.2)	9 (1.6)
Serious Treatment-Related TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs Leading to Study Discontinuation	15 (8.0)	19 (10.2)	3 (1.6)	37 (6.6)
Treatment-Related TEAEs Leading to Study Discontinuation	14 (7.4)	17 (9.1)	2 (1.1)	33 (5.9)

Source: Original BLA 125478/000 Clinical Study Report P05233 page 142 (confirmed by reviewing statistician)

A summary of the types of serious adverse events observed during the study can be seen in the following table that was confirmed by the reviewing statistician via (b)(4). Table 6.1.11.b shows that 147 (78%) patients had SAEs in the Placebo group and 158 (85%) patients had SAEs within the Ragwitek® 12 Amb a 1-U group, while 139 (75%) of the subjects in the 6 Amb a 1-U group had SAEs. Additionally, other less serious adverse events are included within the table, showing similar trends in adverse events occurring in both the active treated and placebo treatment groups.

Table 6.1.11.b) Summary of Reported AEs during the Treatment Period

	Number (%) of Subjects			
	Ragweed AIT 6 Amb a 1-U (n=188)	Ragweed AIT 12 Amb a 1-U (n=186)	Placebo (n=186)	Total (N=560)
Subjects Reporting Any Adverse Event	147 (78.2)	158 (84.9)	139 (74.7)	444 (79.3)
Ear and Labyrinth Disorders				
Ear Pruritus	30 (16.0)	30 (16.1)	4 (2.2)	64 (11.4)
Eye Disorders				
Eye Pruritus	9 (4.8)	9 (4.8)	1 (0.5)	19 (3.4)
Gastrointestinal Disorders				
Diarrhoea	6 (3.2)	4 (2.2)	4 (2.2)	14 (2.5)
Dyspepsia	9 (4.8)	5 (2.7)	1 (0.5)	15 (2.7)
Lip Swelling	6 (3.2)	14 (7.5)	3 (1.6)	23 (4.1)
Nausea	6 (3.2)	13 (7.0)	2 (1.1)	21 (3.8)
Oral Pruritus	36 (19.1)	36 (19.4)	6 (3.2)	78 (13.9)
Paraesthesia Oral	14 (7.4)	20 (10.8)	4 (2.2)	38 (6.8)
Swollen Tongue	22 (11.7)	36 (19.4)	6 (3.2)	64 (11.4)
Tongue Oedema	4 (2.1)	8 (4.3)	1 (0.5)	13 (2.3)
Tongue Pruritus	32 (17.0)	27 (14.5)	3 (1.6)	62 (11.1)
Vomiting	4 (2.1)	5 (2.7)	2 (1.1)	11 (2.0)
General Disorders and Administration Site Conditions				
Chest Discomfort	5 (2.7)	7 (3.8)	1 (0.5)	13 (2.3)
Infections and Infestations				
Bronchitis	6 (3.2)	4 (2.2)	4 (2.2)	14 (2.5)
Nasopharyngitis	31 (16.5)	27 (14.5)	33 (17.7)	91 (16.3)
Sinusitis	9 (4.8)	12 (6.5)	11 (5.9)	32 (5.7)
Upper respiratory Tract Infection	22 (11.7)	19 (10.2)	28 (15.1)	69 (12.3)
Musculoskeletal and Connective Tissue Disorders				
Back Pain	7 (3.7)	8 (4.3)	5 (2.7)	20 (3.6)
Neck Pain	2 (1.1)	6 (3.2)	3 (1.6)	11 (2.0)
Nervous System Disorders				
Headache	14 (7.4)	20 (10.8)	16 (8.6)	50 (8.9)
Respiratory, Thoracic and Mediastinal Disorders				
Asthma	6 (3.2)	4 (2.2)	4 (2.2)	14 (2.5)
Cough	14 (7.4)	15 (8.1)	5 (2.7)	34 (6.1)
Dry Throat	10 (5.3)	4 (2.2)	1 (0.5)	15 (2.7)
Oropharyngeal Discomfort	4 (2.1)	7 (3.8)	1 (0.5)	12 (2.1)
Oropharyngeal Pain	10 (5.3)	13 (7.0)	9 (4.8)	32 (5.7)
Pharyngeal Oedema	8 (4.3)	9 (4.8)	3 (1.6)	20 (3.6)
Throat Irritation	48 (25.5)	55 (29.6)	10 (5.4)	113 (20.2)
Skin and Subcutaneous Tissue Disorders				
Pruritus	13 (6.9)	10 (5.4)	2 (1.1)	25 (4.5)

Source: Original BLA 125478/000 Clinical Study Report P05233 page 144 (confirmed by reviewing statistician)

Reviewer's comment: *Overall, the proposed treatment group (Ragwitek® 12 Amb a 1-U) had slightly more adverse events than the placebo. However, as an active treatment designed to elicit a response via the product instead of the pollens during the pollen season, this finding is not surprising. Additional and more detailed comments can be found in the medical officer's and epidemiologist's reviews.*

6.1.11.1 Methods

The safety data analysis consisted of examining observed Adverse Events provided by the applicant. Tabulations were utilized to compare the effect of treatment versus placebo on the observation of adverse events. No pre-specified hypothesis tests were to be performed for either organ classes or specific adverse events. For further details and additional discussion, the statistician defers to the medical officer.

6.1.11.3 Deaths

No deaths were observed in this trial

6.1.11.4 Nonfatal Serious Adverse Events

No important findings were noted in the 9 subjects with observed non-fatal serious adverse events. The numbers of SAE's were fairly balanced across the treatment groups, with 3 in the 12 Amb a 1-U group, 2 in the 6 Amb a 1-U group, and 4 subjects in the placebo treated group, representing less than 5% of study subjects. One SAE was observed during the screening phase; however, this was not related to the treatment. All serious adverse events were self-limiting and were resolved upon discontinuation of study treatment. For further details and additional discussion, please refer to the medical officer's review.

6.1.11.5 Adverse Events of Special Interest (AESI)

The statistician defers to the medical officer.

6.1.11.6 Clinical Test Results

Clinical test results including IgG, IgE, and other tests performed throughout the study were expected and not considered outside of normal ranges. For further details and additional discussion, the reviewing statistician defers to the medical officer.

6.1.11.7 Dropouts and/or Discontinuations

A total of 37 subjects prematurely withdrew from the study: 3 (1.6%) from the placebo group, 15 (8%) from the 6 Amb a 1-U study group, and 19 (10.2%) from the 12 Amb a 1-U study group. The majority of these individuals indicated that it was treatment related AEs that lead to study discontinuation. Since this product exposes subjects to a product in which they are sensitive, ragweed pollen, the observation of adverse events causing study withdrawal may be consistent with other SCIT products. Additional details related to the dropouts and discontinuations can be seen in the medical officer's and epidemiologist's reviews.

Summary and conclusion: *Protocol P05233 met its objectives with respect to the primary efficacy endpoint, as well as several secondary endpoints. Additional subgroup analyses as well as sensitivity analyses provide supportive evidence that this product reduces the combined rescue medication and symptom scores, rescue medication use, and symptom scores when compared to placebo during the ragweed pollen season. The safety profile of Ragwitek® in this study appears to be acceptable, with 3 serious adverse events that were all self-limiting and resolved. No deaths occurred.*

6.2 Trial #2: Study P05234

Merck's trial P05234 was submitted to CBER under US-IND to be "*a multi-center, double-blind, randomized, placebo controlled, parallel-group study evaluating the efficacy and safety of Short Ragweed, (Ambrosia artemisiifolia) sublingual tablet (SCH 039641) in adult subjects with a history of ragweed pollen induced rhinoconjunctivitis with or without asthma.*"

This double-blind, randomized, multicenter, parallel-group, placebo-controlled Phase-2/3 study design was used to evaluate the efficacy and safety of treatment with ragweed AIT sublingual tablets in adult subjects (18 to 50 years of age) with a history of ragweed pollen-induced rhinoconjunctivitis with or without asthma and an IgE mediated response to short ragweed. The subjects were treated once daily with either ragweed sublingual tablet (1.5, 6, or 12 Amb a 1-U of *Ambrosia artemisiifolia* extract) or placebo, approximately 16 weeks prior to and during the entire Ragweed Season (RS) and following the RS with an overall exposure duration to investigational medicinal product (IMP) of approximately 52 weeks.

6.2.1 Objectives (Primary, Secondary, etc.)

The objectives of this study were to evaluate the efficacy and safety of sublingual tablets of ragweed pollen allergen extract (SCH 39641) compared with placebo for reduction of rhinoconjunctivitis symptoms and rescue medication usage.

Primary Objective:

To evaluate the efficacy of ragweed sublingual tablet (MK-3641, Ragwitek®) versus placebo in the treatment of ragweed pollen-induced rhinoconjunctivitis based on the combined sum (CS) of rhinoconjunctivitis daily symptom scores (DSS) and rhinoconjunctivitis daily medication scores (DMS) averaged over the entire ragweed pollen season (RPS).

Key Secondary Objectives:

To assess overall safety and to compare the following between the Ragwitek® and placebo groups:

- The average combined (sum of) rhinoconjunctivitis DSS and rhinoconjunctivitis DMS for the entire RS.
- The average rhinoconjunctivitis DSS for the entire and peak RPS.
- The average rhinoconjunctivitis DMS for the entire and peak RPS.
- The average weekly rhinoconjunctivitis quality of life total score for the entire RPS.

6.2.2 Design Overview

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study in subjects 18 to 50 years of age, of either sex and of any race, with a history of ragweed pollen-induced rhinoconjunctivitis with or without asthma. The subjects were treated once daily with either ragweed sublingual tablet (1.5, 6, or 12 Amb a 1-U) or placebo, approximately 16 weeks prior to and during the entire RS and following the RS with an overall exposure duration to investigational medicinal product (IMP) of approximately 52 weeks. A placebo was included as an ineffective agent against which

to compare the response to ragweed AIT (1.5, 6, or 12 Amb a 1-U of *Ambrosia artemisiifolia* extract). Additionally, the 1.5 Amb a 1 U was also included and was expected to be a "no-effect" dose.

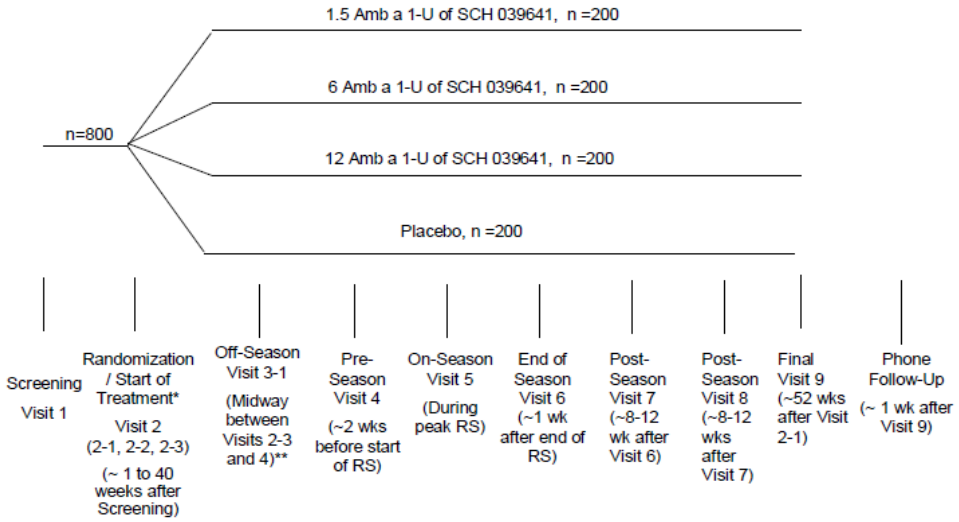
Eligible subjects were to visit the study site for at least 11 total visits: Screening, Post-screening, Pre-season, On-season, End-of-season, and Off-season Visits, and at Unscheduled Visits as appropriate. Additional Off-season Visits were scheduled depending on the timing of the Randomization Visit in relation to the anticipated start of the Ragweed Pollen Season (RPS). Qualified subjects were to be randomized into the treatment period.

In the treatment period, the subjects were treated once daily with either Ragwitek® (Short Ragweed allergy immunotherapy tablet [ragweed AIT]) or placebo for approximately 16 weeks prior to the RPS and during the RPS.

At the Randomization Visit, subjects were supplied with self-injectable epinephrine together with instructions on how and when to use it. Open-label rescue medications for the rhinoconjunctivitis and asthma symptoms were to be provided. Subjects were to visit the study site for at least 11 visits: Screening, Randomization, On-site dosing of IMP, Off-season, Pre-season, On-season, and End-of-season Visits, Post-Season (2 visits), and Final Visit as well as Unscheduled Visits as appropriate.

The first three consecutive daily doses of IMP were administered at the study site (entitled Visit 2-1, 2-2, and 2-3 by the applicant), and the subjects were monitored at the site for 30 minutes following dosing. Subsequent administration of IMP was done once daily at home at approximately the same time each day. A telephone contact between the investigator/designee and the subject occurred once daily for the first 4 days of at-home administration of IMP to monitor adverse events (AEs) and once approximately 1 week after the End-of-season Visit. A summary of the study visits and data collection points for this study are illustrated in the following study design diagram.

Figure 6.2.2.a. Study Design Diagram



Source: Original BLA 125478/000 Clinical Study Report P05234 page 44

This study was conducted in conformity with Good Clinical Practice. A data safety monitoring committee (DSMC) was established prior to the start of the treatment period. The purpose of the DSMC was to evaluate adverse event data and to provide recommendations regarding the conduct of the study to ensure the safety of the subjects.

6.2.3 Population

The treatment population consisted of male or female patients aged 18 to 50 years (inclusive) in the United States, Canada, Hungary, Russia, and the Ukraine with documented ragweed pollen-related allergic rhinoconjunctivitis, based on a clinical history of significant allergic rhinoconjunctivitis to ragweed (with or without asthma) diagnosed by a physician and who had received treatment for their disease for the previous ragweed pollen season, had a positive skin prick test (SPT) to Ragweed, and were positive for short ragweed-specific IgE at the screening visit.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Ragweed AIT (1.5, 6, and 12 Amb a 1-U) and placebo were supplied to the study site by the applicant. The active treatment (ragweed AIT [SCH 39641]) was a ragweed (*Ambrosia artemisiifolia*) pollen allergen extract formulated as a rapidly dissolving tablet administered sublingually once daily. The placebo treatment was identical to the active treatment except that no allergen extract was included in the placebo rapidly dissolving tablet. Both the active treatment and placebo were to be administered sublingually (under the tongue) every day at the same time during the entire treatment period.

6.2.5 Sites and Centers

This study was to include 114 centers. Of these centers, 72 centers were located in the United States of America, 12 centers in Canada, 20 centers in Hungary, 8 centers in

Ukraine, and 2 centers in Russia, with all centers having expected exposure to ragweed pollen.

6.2.6 Surveillance/Monitoring

A detailed synopsis of the surveillance and monitoring of the study can be found in the medical officer's and epidemiologist's reviews. However, a data safety monitoring committee (DSMC) was set up to ensure adequate safety monitoring of the study with pre-specified plans to examine and stop the study in case of unexpected safety issues.

6.2.7 Endpoints and Criteria for Study Success

There are several primary and secondary endpoints in this study that were utilized to assess how well the Ragwitek® product reduced symptoms related to ragweed allergies, as well as reduced the need to take medications to treat or prevent symptoms associated with ragweed allergies. The primary criterion for success was the combined symptom score (CS), which consisted of the patient's daily symptom scores (DSS) and daily rescue medication scores (DMS) averaged over the peak RS.

The primary efficacy endpoint of CS averaged over the peak RS was evaluated using an analysis of variance (ANOVA) model with baseline asthmatic condition (Yes/No) and pollen region as covariates, and treatment group as fixed effect. Based on the ANOVA model, comparison of each active dose versus placebo was conducted using a stepwise procedure, starting from the comparison of the high dose of SCH 39641 versus placebo, followed by the lower dose in a sequential manner. The inference on the low dose comparison against placebo was carried out only if the previous comparison was statistically significant ($p<0.05$), thus ensuring control of the type I error.

Primary efficacy variable:
The primary efficacy endpoint was the combined (sum of) rhinoconjunctivitis DSS and DMS averaged over the peak RS.

The combined score for each subject was calculated as the sum of rhinoconjunctivitis DSS and DMS during the peak RS, divided by the duration of the peak RS. Endpoints that are average scores for a specific period (e.g., during peak RS or during the entire RS, etc.) were defined based on the available number of days with data (non-missing values) in that period. This endpoint is also commonly referred to as the combined symptom score (CS) and is calculated as follows:

$$TCS = DSS + DMS.$$

Both the DSS and DMS are described in Section 6, including tables that specifically provide the scoring mechanisms and methods.

Secondary efficacy variables:
The key secondary endpoints consisted of

5. The combined (sum of) rhinoconjunctivitis DSS and DMS during the entire RS, divided by the duration of the entire RS.
6. The average rhinoconjunctivitis DSS during the peak RS, calculated for each subject as the sum of the rhinoconjunctivitis DSS during the peak RS, divided by the duration of the peak RS.
7. The average rhinoconjunctivitis DSS during the entire RS.
8. The average rhinoconjunctivitis DMS during the peak RS, calculated for each subject as the sum of the rhinoconjunctivitis DMS during the peak RS, divided by the duration of the peak RS.

In addition to examining the various scores, TCS, DSS, DMS, during the entire ragweed pollen season, these scores were also computed and compared for the worst pollen period while the patient was on treatment. Additionally, the following tertiary endpoints were examined:

- The proportion of patients who used rescue medication during the pollen period and worst pollen period while on treatment.
- The proportion of days rescue medication was used during the pollen period and worst pollen period while on treatment.
- Change in the Work Productivity and Activity Impairment-Allergy Specific Questionnaire (WPAI-AS) 7 individual outcomes from randomization to on-season and end-of-season visits.
- Proportion of Symptom-Controlled Days (PSCD) as defined by a DSS score of "0."
- Overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score.
- Global assessment and evaluation of the efficacy of the treatment by the patient.
- Asthma status and severity.
- Immunological markers (IgE specific for ragweed pollen allergen) and Skin Prick Test (SPT) results.

Safety variables:

- Adverse events (AEs).
  - Laboratory assessments.
  - Physical examinations.
  - Vital signs.

Statistician Comment: *The study design and methods of data collection and evaluation are standard for the indication studied. Subjective symptom reporting and assessment of the nasal and non-nasal symptoms are standard efficacy measurements in rhinoconjunctivitis trials for the ragweed product being studied in this BLA as well as for other products examining the effect of SLIT in reduction of pollen inducing symptoms.*

6.2.8 Statistical Considerations & Statistical Analysis Plan

Analysis sets:

For the purpose of this study, three analysis sets were defined, namely, the Safety Set, the Full Analysis Set (FAS), and the Per Protocol Analysis Set (PPS), which were pre-specified and defined as follows:

- The Safety Set includes all patients who received at least one dose of the investigational product.
- The FAS includes all patients who received at least one dose of investigational product and had at least one TCS while on treatment during the ragweed pollen season (RPS). The FAS was regarded as the primary population for the efficacy analyses.
- The PPS includes all patients from the FAS who had valid TCS during the RPS while on treatment and who completed the study according to the protocol and had no major protocol deviations.

Primary efficacy endpoints:

The primary efficacy endpoint of average TCS during the peak RS was evaluated using an analysis of variance (ANOVA) model with baseline asthmatic condition (yes/no), pollen region, and treatment group as fixed effects. Pollen region was defined based on pollen station, and included several sites within an acceptable distance from the pollen counters.

For each dose comparison against placebo, a 2-sided 95% confidence interval (CI) of the difference in adjusted means between the two treatment groups was presented. Also, the difference in adjusted means between the two treatment groups relative to the adjusted mean of the placebo group was presented as a percentage (i.e., 100*[ragweed AIT-placebo]/placebo) with a corresponding 2-sided 95% CI.

Secondary Efficacy Endpoints:

The key secondary endpoints were evaluated using the same ANOVA model defined for the primary efficacy endpoint as described above.
The following additional secondary endpoints were evaluated using the same ANOVA model defined for the primary efficacy analysis: DMS, Minimal Symptom Days, VAS, and asthma DSS over the entire RS; RQLQ, VAS, and asthma DSS during peak RS; and WPAI-AS (each individual domains) change from randomization to Visits 5 (on-season) and 6 (end-of-season). The reviewing statistician also performed sensitivity analyses on select secondary endpoints using both the peak pollen season as well as the entire pollen season.

Safety Analysis:

The number of subjects reporting any adverse events, the incidence of specific adverse events, and discontinuations due to adverse events were tabulated by treatment group. Laboratory and vital sign data were listed and summarized, and values outside the reference ranges were flagged.

Missing Data:

For the primary analysis, there was no imputation of missing data. The combined average score was based on the available data. However, the primary analysis was supplemented by sensitivity analyses using various imputation techniques to ensure the robustness of the conclusions made via the primary analysis methods.

Determination of the sample size:

For Study P05234, approximately 800 subjects would be randomized in an equal ratio to one of three treatments: 1.5, 6, and 12 Amb a 1-U of the ragweed sublingual tablet, and placebo.

Based on the original protocol primary endpoint of TCS average over the entire RS, with approximately 200 subjects per group, the study would be able to detect a difference of -1.63 in the primary endpoint between an active dose group and the placebo group with 92% power at a 5% level of significance (2-sided test). The calculation was based on the original assumptions on the estimates of the standard deviation (SD=4.77) and treatment effect (-1.63) derived from ALK-Abello study GT-08 (grass sublingual tablet).

Based on the current protocol, the primary endpoint of interest, the TCS during the peak RS, with approximately 200 subjects per group, the study would be able to detect a difference of -1.80 in the primary endpoint between an active dose group and the placebo group with 90% power at a 5% level of significance (2-sided test). The assumptions used in the power calculations were derived from the data across two US studies: P05238 and P05239 (grass sublingual tablet).

Table 6.2.8.1 Estimates and Differences, Standard Deviation, and Power

	Differences of Effect (%) from Placebo to be Detected	Estimates of		Power
		Mean Placebo Effect	Standard Deviation	
Primary Endpoint				
Average TCS Over the Peak RS[a]	-1.80 (25)	7.10	5.51	90%
Key Secondary Endpoints				
Average TCS Over the Entire RS[a]	-1.45 (23)	6.40	4.38	90%
Average DSS Over the Peak RS[a]	-1.26 (24)	5.20	3.53	95%
Average DSS Over the Entire RS[a]	1.01 (21)	4.80	3.12	90%

Source: Original BLA 125478/000 Clinical Study Report P05234 page 73

Reviewer comment: *The applicant initially proposed utilizing a point estimate in which an improvement of greater than 20% based on the combined score of the Ragwitek® treated individuals over the placebo comparator was to be considered the primary endpoint. This was agreeable to CBER; however, it was suggested that the study also meet a clinically meaningful margin of -10% for the upper bound of the 95% CI. This study sample size calculation was revised based on additional information gleaned through the grass studies, which was agreeable to the Agency.*

6.2.9 Study Population and Disposition

The study population and baseline demographics of the enrolled patients are similar for all treatment groups.

In this study, 784 patients were randomized to treatment; however, one subject although randomized to the 1.5 Amb a 1-U treatment group did not receive any treatment. A total of 783 randomized subjects received treatment and were included in the safety and efficacy analyses. These subjects were treated with either 12 Amb a 1-U ragweed AIT (n=194), 6 Amb a 1-U ragweed AIT (n=195), 1.5 Amb a 1-U ragweed AIT (n=196), or placebo (n=198). Of the 783 subjects who received treatment, 551 subjects were in North America (133 subjects in Canada; 419 subjects in the USA), and 231 subjects were in Hungary/Ukraine/Russia.

A total of 606 (77.3%) subjects overall completed the protocol-specified, double-blind treatment period. The median pre-seasonal duration of treatment was approximately 17 weeks. Demographic and Baseline characteristics were well balanced between the treatment groups. Overall, the median age was 38 years, 49% of subjects were male, and approximately 88% were white. Median duration of ragweed allergy at baseline was approximately 15 years. All subjects but one tested positive by serum specific IgE measurements to *Ambrosia artemisiifolia*, and all subjects tested positive for short ragweed pollen (*Ambrosia artemisiifolia*) by skin prick testing at screening. The majority of subjects (78.1%) also tested positive for one or more other allergens (i.e., house dust mites, trees, cat/dog, and mold). Seventeen percent of subjects had a diagnosis of asthma.

6.2.9.1 Populations Enrolled/Analyzed

The following table illustrates the population distribution in study P05234.

Table 6.2.9.1.1. Summary of Patient Population

	Ragwitek AIT 1.5 Amb a 1-U **N (%)**	**Ragwitek AIT 6 Amb a 1-U** **N (%)**	**Ragwitek AIT 12 Amb a 1-U** **N (%)**	**Placebo** **N (%)**	**Total** **N (%)**
Patients Randomized	197 (100%)	195 (100%)	194 (100%)	198 (100%)	784 (100%)
Patients in Safety Set	196 (99.5%)	195 (100%)	194 (100%)	198 (100%)	784 (100%)
Patients in Full Analysis Set	196 (99.5%)	195 (100%)	194 (100%)	198 (100%)	784 (100%)
Protocol Evaluable Data Set	171 (86.8%)	172 (88.2%)	158 (81.4%)	174 (87.9%)	657 (83.8%)

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

6.2.9.1.1 Demographics

The demographics of the individuals included in this study can be seen in the following table. Since the optimal dose for the product is 12 Amb a 1-U, the primary focus of the data and results observed within study P05234 will be based on the 12 Amb a 1-U and the placebo comparator. Within the table, the number of individuals and percent of individuals are noted for each treatment group, based on the demographic variables of gender, age, and race. This table illustrates that the baseline characteristics were similar for both treatment groups for all baseline characteristics.

Table 6.2.9.1.1 Baseline Demographics of the Patient Population

Baseline Demographic	**Ragwitek AIT 12 Amb a 1-U N=194**	**Placebo N=198**
Gender [n (%)]		
Female	91 (47%)	96 (49%)
Male	103 (53%)	102 (51%)
Age (years)		
Mean (SD)	36.5 (8.8)	36.7 (8.6)
Range	18-50	18-50
Race [n (%)]		
White/Caucasian	173 (89%)	168 (85%)
Black or African American	13 (7%)	22 (11%)
Asian	2 (1%)	6 (3%)
American Indian/Alaska	1 (1%)	0 (0%)
Other	4 (2%)	2 (1%)

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

6.2.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

The medical/behavioral characteristics of the individuals included in this study can be seen in the following table. Within the table, the mean and standard deviation of various relevant medical/behavioral characteristics are noted for each treatment group based on the BMI, height, and weight. This table illustrates that these characteristics were similar for both treatment groups.

Table 6.2.9.1.2 Baseline Medical/Behavioral Characteristics of the Patient Population

Baseline Demographic	**Ragwitek AIT 12 Amb a 1-U N=194**	**Placebo N=198**
BMI (kg/m²)		
Mean (SD)	28 (5.9)	28 (6.3)
Range	17.7-49.5	17.5-54.1
Asthma Status [n (%)]		
Asthmatic	37 (19%)	32 (16%)
Non-Asthmatic	157 (81%)	166 (84%)
Sensitization [n (%)]		
Ragweed	40 (21%)	46 (23%)
Other Allergens	154 (79%)	152 (77%)

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

6.2.9.1.3 Subject Disposition

The following table illustrates the randomization, allocation, and withdrawal of patients for this study. This table notes which treatment arm subjects were randomized to and subsequently lists the reason for dropout, including the number of subjects and percentage of subjects that withdrew prior to study completion. It is of interest to note that the discontinuation due to adverse events is slightly higher in the active treatment group (5-8%) compared to the placebo group (3%); however, other reasons for dropout were fairly similar between the placebo and active treatment groups (the 1.5 Amb a 1-U, 6 Amb a 1-U, as well as the 12 Amb a 1-U doses). Considering this is an allergen extract administered via SLIT in subjects that are sensitive to the allergen, this finding is reasonable and expected.

Table 6.2.9.1.3.2. Patient Disposition after Randomization

Disposition of Subjects	Number (%) of Subjects				
	Ragweed AIT 1.5 Amb a 1-U	Ragweed AIT 6 Amb a 1-U	Ragweed AIT 12 Amb a 1-U	Placebo	Total
Randomized	197	195	194	198	784
Treated	196 (99.5)	195 (100)	194 (100)	198 (100)	783 (99.9)
Included in the Analyses of TCS, DSS, and DMS during the Peak RS	169 (85.8)	167 (85.6)	152 (78.4)	169 (85.4)	657 (83.8)
Included in the Analyses of TCS, DSS, and DMS during the Entire RS	171 (86.8)	172 (88.2)	158 (81.4)	174 (87.9)	675 (86.1)
Discontinued Treatment	40 (20.3)	43 (22.1)	57 (29.4)	38 (19.2)	178 (22.7)
Adverse Event	10 (5.1)	16 (8.2)	16 (8.2)	6 (3.0)	48 (6.1)
Lost to follow-up	9 (4.6)	5 (2.6)	10 (5.2)	3 (1.5)	27 (3.4)
Subject did not wish to continue for reasons unrelated to assigned study treatment	13 (6.6)	17 (8.7)	24 (12.4)	20 (10.1)	74 (9.4)
Noncompliance with protocol	7 (3.6)	4 (2.1)	7 (3.6)	9 (4.5)	27 (3.4)
Did not meet protocol eligibility	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Administrative	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Completed Treatment	157 (79.7)	152 (77.9)	137 (70.6)	160 (80.8)	606 (77.3)

Source: Original BLA 125478/000 Clinical Study Report P05234 page 84

6.2.10 Efficacy Analyses

In this study, the applicant examined the efficacy response to multiple dosages and sought to determine the optimal dose. The criterion for selecting the optimal dose for efficacy was to be based on a hierarchical stepwise model in which comparisons were to be made examining the highest dose compared to placebo. Upon meeting the pre-specified criteria for efficacy for each dosage level, the next lower dosage would be examined and compared to the placebo dosage. This stepwise procedure would control the type I error.

The applicant proposed and implemented efficacy analysis based on the various efficacy endpoints including TCS, DSS, DMS, and other allergenic symptom scores and responses within this study. Although the applicant did examine the 1.5 Amb a 1-U, the 6 Amb a 1-U, and 12 Amb a 1-U dosages in this study, it was determined that the 12 Amb a 1-U dosage was the optimal dose based on the results of safety and efficacy analysis. Based on the results provided by the applicant and confirmed by the statistical reviewer, the optimal dose was determined to be 12 Amb a 1-U; thus, in most cases these results will be presented and discussed in the remainder of this section, Section 6.2., of this review.

Primary Efficacy Analysis

The primary efficacy variable to address the treatment effect for this study was the Total Combined Score (TCS) based upon the combined (sum of) rhinoconjunctivitis daily symptom score (DSS) and daily medication score (DMS) averaged over the peak Ragweed Pollen Season (RPS).

For the treatment period, the primary efficacy endpoint of the combined (sum of) rhinoconjunctivitis DSS and DMS averaged over the peak RPS was to be evaluated using a linear model with asthma status, study site, and treatment group as fixed effects. This model was to allow for heterogeneous variance estimates for the treatment groups, with appropriate adjustments made. For the primary endpoint, subjects with at least one post-baseline diary record with DSS and DMS within the defined pollen season were to be included. The combined average score was to be based on all available data during the RPS for each subject.

A 2-sided 95% confidence interval for the difference in the adjusted means (adjusted for asthma status and study site) between the two treatment groups was to be presented. Also the difference in adjusted means between the two treatment groups relative to the adjusted mean of the placebo group was to be presented as a percentage, with corresponding confidence interval.

Secondary Efficacy Analysis

The secondary efficacy variable to address the treatment effect for this study was the DSS and DMS over the peak RPS, as well as these endpoints and TCS for the entire RPS.

The DSS is composed of six rhinoconjunctivitis symptoms recorded daily, including runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes; the symptoms were measured on a scale of 0 (no symptoms) to 3 (severe symptoms), and a higher score indicated a higher level of symptoms. The DMS is composed of a sum of the scores associated with rescue medication use per day, where a lower medication score indicated less use of rescue medication. The DSS and DMS data were collected during the RPS in which the duration of the RPS was defined as the total number of days for which a subject had data during the RPS.

Safety Analysis

The safety endpoints (treatment-emergent, treatment-related AEs; local AEs; discontinuations due to AEs) were to be based on the All-Treated set, and were to be summarized by treatment group and asthma status for the frequency distribution (N and percentage).

6.2.10.1 Analyses of Primary Endpoint(s)

The primary efficacy endpoint was the Total Combined Score (TCS) during the ragweed pollen season (RPS) while on treatment. The primary analysis was performed for the Full Analysis Set (FAS), which included all patients who received at least one dose of the investigational product.

The TCS was analyzed using a linear model with asthma status, study site, and treatment group as fixed effects and also adjusting for heterogeneous variance between treatment groups. The TCS score was based on all available data during the RPS for each subject within the FAS.

A 2-sided 95% confidence interval for the difference in adjusted means between the two treatment groups was provided. Also, the difference in adjusted means between the two treatment groups relative to the adjusted mean of the placebo group was presented as a percentage, with corresponding confidence interval.

The linear model results for the primary efficacy analysis of the TCS during the pollen period for the FAS are summarized below. The point estimate is the LS Mean difference between 12 Amb a 1-U and placebo, and the relative LS Mean difference is equal to (LS Mean difference/LS Mean for the Placebo group) x 100.

For the tables provided in this review, the calculations were performed utilizing SAS ---(b)(4)-----, with the specific model noted within the footnotes. If additional methods were used to compute the 95% CI to verify and confirm the robustness of results, the methods are noted in the table footnotes.

As an additional method to ensure robustness of results, the reviewing statistician utilized the delta method to estimate the 95% CI for the difference between the treatment and placebo group for the primary efficacy endpoint. Additionally, the reviewing statistician also utilized different variance/covariance structures within the model to ensure robustness of the results of the statistical tests and conclusions drawn from them.

These results of statistical analysis of the primary endpoint, which can be seen in the below table, confirmed the applicant's results and provided an additional analysis supporting the applicant's conjecture that this product reduces the combined symptom and rescue medication score when compared to placebo.

Table 6.2.10.1.a. Primary Efficacy Analysis: ANCOVA of the TCS during the Peak Ragweed Pollen Period – FAS Comparing the 12 Amb a 1-U Dosage to Placebo

Treatment	n	LS Mean	LS Mean difference vs Placebo Point Est	LS Mean difference vs Placebo 95% CI	Relative LS Mean difference (%) Point Est	Relative LS Mean difference (%) 95% CI	Relative LS Mean difference (%) 95% CI (using the delta method)
Ragwitek®	152	6.41	-2.04	(-3.03, -0.79)	-24.2%	(-36.5%, -11.3%)	(-35.8%, -11.9%)
Placebo	169	8.46					

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, asthma status, and treatment group using SAS: ---(b)(4)---- procedure. As an additional analysis method, the delta method was used to calculate the confidence intervals.

The difference in LS means of the daily TCS during the entire ragweed pollen period between the 12 Amb a 1-U group and the Placebo group was statistically significant. The treatment effect was estimated as the difference in LS means of -2.02, corresponding to a relative LS Mean difference of -24.2% from placebo. The 95% CI expressed as

percentages was [-36.5%, -11.3%]. Furthermore, utilizing the delta method, the 95% CI expressed as percentages was [-35.8%, -11.9%], which satisfies CBER's suggested criterion of meeting a -10% threshold for reduction of combined symptom scores. In addition, it meets the applicant's pre-specified treatment difference of 15%, thus supporting the applicant's conjecture that Ragwitek® reduces the combined symptoms and rescue medication score when compared to placebo.

6.2.10.2 Analyses of Secondary Endpoints

In addition to the primary endpoint of interest, the total combined symptom and rescue medication score (TCS) during the entire RPS, several secondary endpoints were of interest. These include but are not limited to the daily symptom scores, as well as use of rescue medication during the pre-specified ragweed pollen season and the TCS during the peak pollen season.

Table 6.2.11.2.a. illustrates the difference between the placebo and treatment groups for the peak ragweed pollen season. Within this table, the DSS, and DMS sample size in each treatment arm, point estimate of the LS Mean per treatment arm as well as LS Mean difference, 95% CI of the LS Mean, and relative LS Mean Difference are presented.

Table 6.2.10.2.a Secondary Efficacy Analysis: ANCOVA of the DSS and DMS during the Peak Ragweed Pollen Season (RPS) – FAS

Treatment	n	LS Mean	LS Mean difference vs Placebo Pt Est	LS Mean difference vs Placebo 95% CI	Relative LS Mean difference vs Placebo (%) Pt Est	Relative LS Mean difference vs Placebo (%) 95% CI
DSS						
Ragwitek®	152	4.43	-0.94	(-1.67, -0.21)	-17.5%	(-29.2%, -4.5%)
Placebo	169	5.37				
DMS						
Ragwitek®	152	1.99	-1.10	(-1.89, -0.32)	-35.7%	(-55.8%, -14.6%)
Placebo	169	3.09				

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, asthma status using SAS ---(b)(4)------ procedure.

Table 6.2.10.2.b. illustrates the difference between the placebo and treatment groups for the entire ragweed pollen season. Within this table, the TCS, DSS, and DMS sample size in each treatment arm, point estimate of the LS Mean per treatment arm as well as LS Mean difference, 95% CI of the LS Mean, and relative LS Mean Difference are presented. This is a secondary analysis in which the study was not powered to detect differences between treatment groups, nor were alpha adjustments made for these multiple hypothesis tests. However, the trends observed within the table suggest that the treatment reduces the symptoms, use of rescue medication, and the combination of both when compared to individuals randomized to the placebo treated group.

Table 6.2.10.2.b. Secondary Efficacy Analysis: ANCOVA of the DSS and DMS during the Entire Ragweed Pollen Season (RPS) – FAS

Treatment	n	LS Mean	LS Mean difference vs Placebo Point Est	LS Mean difference vs Placebo (95% CI)	Relative LS Mean difference vs Placebo (%) Pt Est	Relative LS Mean difference vs Placebo (%) 95% CI
TCS						
Ragwitek®	158	5.18	-1.92	(-2.95, -0.88)	-27.0%	(-38.8%, -14.1%)
Placebo	174	7.09				
DSS						
Ragwitek®	158	3.62	-0.96	(-1.57, -0.35)	-21.0%	(-31.6%, -8.8%)
Placebo	174	4.58				
DMS						
Ragwitek®	158	1.56	-0.95	(-1.57, -0.33)	-38.0%	(-57.6%, -16.4%)
Placebo	174	2.51				

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

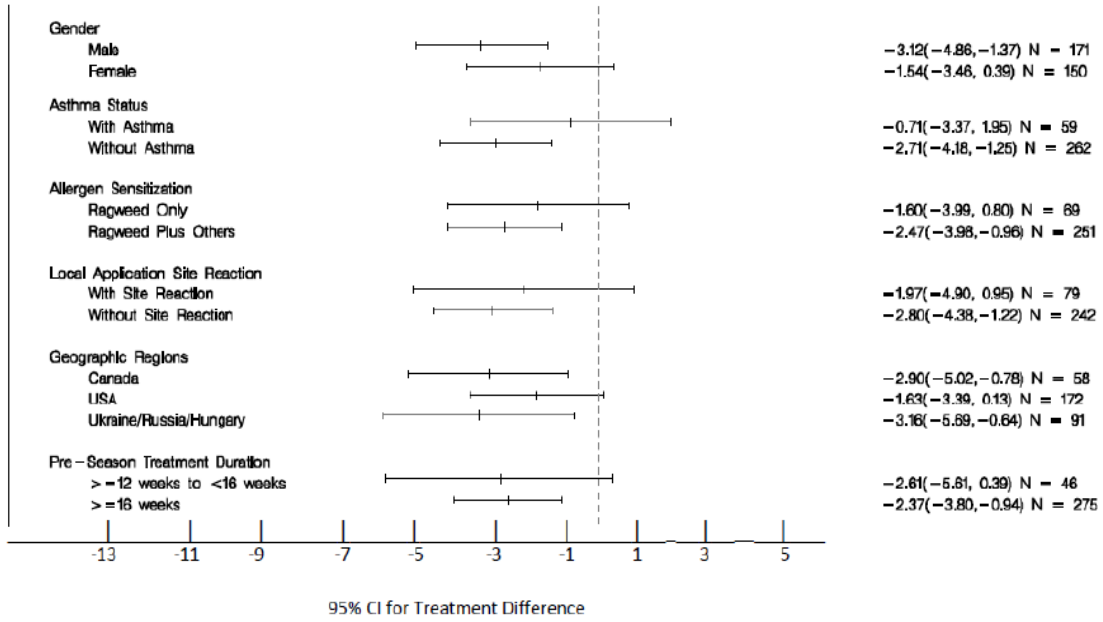
Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, asthma status using SAS--(b)(4)----- procedure.

Reviewer Comment: *The applicant proposed to meet a clinically meaningful margin of -10% for the upper bound of the 95% CI when comparing the difference between the treatment and placebo treated individuals for the primary endpoint of TCS. Furthermore, the applicant proposed utilizing a point estimate in which an improvement of greater than 15% based on the relative % difference in the total combined score (TCS) of the Ragwitek® treated individuals over the placebo comparator. The applicant met these criteria for the primary endpoint during the peak pollen season. Furthermore, based on analysis of the study data, in most cases these criteria were also met for the secondary endpoints, including the DMS during the peak pollen season as well as the TCS and DMS during the entire pollen season. In the case of the DSS scores for both the peak and the entire pollen season, the applicant met the criteria for the relative % difference; however, the clinically meaningful margin of -10% based on the upper bound of the 95% CI was not technically met. Nevertheless, the data illustrated a positive trend in the reduction of symptoms.*

6.2.10.3 Subpopulation Analyses

Several subpopulations were of interest to the review team: ragweed pollen sensitivity, geographic location, and asthma status. Additionally, based on current regulations, there should be analyses based on gender, age, and race. In this study, nearly 85% of the enrolled subjects were Caucasian/white; thus, subgroup analysis of the primary endpoint based on specific races would not be expected to be informative. Additionally, since this study randomized only subjects from 18-50 years of age, no subset analysis was performed stratifying by age. However, comparisons of the treatment response when considering male vs female outcomes were performed by the reviewing statistician. These results provide consistent positive trends that demonstrate Ragwitek® reduces total combined symptom and rescue medication scores when compared to placebo; however, differences in the two different genders can be noted.

Figure 6.2.10.3.1. Subpopulation Analysis for Gender, Race, Ragweed Sensitivity, and Region for the TCS during RPS including Mean and 95% Confidence Interval for the 12 Amb a 1-U Treatment group



Source: Modification of Original BLA 125478/000 Clinical Study Report P05234 page 137 results (to make scale easier to read) confirmed by reviewing statistician

From Figure 6.2.10.3.1, it can be seen that there is an observable positive treatment effect for both male and female subjects, but the effect appears to be slightly greater among males. Additionally, when considering the results of the different countries, all countries have a positive treatment effect in reducing the TCS score; however, individuals in Canada as well as Ukraine/Hungary/Russia appear to have slightly greater reduction in TCS scores compared to the USA. Other comparisons of groups, including sensitivity to ragweed, asthma status, and geographic location are presented and illustrate positive trends in the effect of the Ragwitek® treatment in reducing symptoms.

Reviewer Comment: *The overall results of the efficacy data when examining a variety of subsets based on demographic and baseline characteristics suggest that there is a reduction in the total combined symptom (TCS) score, which utilizes both daily symptom scores and the daily use of rescue medication when comparing individuals who were randomized and received Ragwitek® study treatment to individuals who received a nearly identical placebo product. Three groups in which the responses are not as robust are females, those subjects with asthma, and individuals located in the US. However, it should be noted that the study was not powered to detect significant differences or examine subgroup analysis; thus, caution should be used when interpreting results. Similar trends illustrating a positive effect of the treatment within the various subgroups were observed when examining the key secondary endpoints.*

6.2.10.4 Dropouts and/or Discontinuations

For the average scores of TCS in each of the four study periods (preseason, RPS, peak season, and post-season), there was no imputation of missing diary data.

The average score for each subject and study period was based on the available data within the period. However, for rhinoconjunctivitis DMS, if rescue medication use was missing on any single day of the diary card, it was assumed to be "no use" and a score of zero was assigned in such cases as a convention.

For each of the primary and key secondary endpoints of TCS, DSS, and DMS, 18.6% (36/194) of subjects in the Ragwitek® group and 12.1% (29/198) of subjects in the placebo group had no data during the RPS. The dropouts in each of the treatment arms were within the expected dropout/missing values anticipated during the IND phase of the study (15-20%).

A more detailed summary of the dropouts and missing values in the study can be observed in the following table.

Table 6.2.10.4.1. Discontinuation and Dropouts in the Study

	Number (%) of Subjects				
Disposition of Subjects	**Ragweed AIT 1.5 Amb a 1-U**	**Ragweed AIT 6 Amb a 1-U**	**Ragweed AIT 12 Amb a 1-U**	**Placebo**	**Total**
Randomized	197	195	194	198	784
Treated	196 (99.5)	195 (100)	194 (100)	198 (100)	783 (99.9)
Included in the Analyses of TCS, DSS, and DMS during the Peak RS	169 (85.8)	167 (85.6)	152 (78.4)	169 (85.4)	657 (83.8)
Included in the Analyses of TCS, DSS, and DMS during the Entire RS	171 (86.8)	172 (88.2)	158 (81.4)	174 (87.9)	675 (86.1)
Discontinued Treatment	40 (20.3)	43 (22.1)	57 (29.4)	38 (19.2)	178 (22.7)
Adverse Event	10 (5.1)	16 (8.2)	16 (8.2)	6 (3.0)	48 (6.1)
Lost to follow-up	9 (4.6)	5 (2.6)	10 (5.2)	3 (1.5)	27 (3.4)
Subject did not wish to continue for reasons unrelated to assigned study treatment	13 (6.6)	17 (8.7)	24 (12.4)	20 (10.1)	74 (9.4)
Noncompliance with protocol	7 (3.6)	4 (2.1)	7 (3.6)	9 (4.5)	27 (3.4)
Did not meet protocol eligibility	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Administrative	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Completed Treatment	157 (79.7)	152 (77.9)	137 (70.6)	160 (80.8)	606 (77.3)

Source: Original BLA 125478/000 Clinical Study Report P05234 page 84

Sensitivity Analysis based on Missing Values

To determine how robust the result is for the primary endpoint when dealing with missing values and other definitions of the pollen season, three different sensitivity analyses were implemented. These analyses included:

1. LOCF (Last Observation Carried Forward) method – Impute any missing daily values of TCS by the last observed non-missing daily value of TCS carried forward until next non-missing daily TCS value is found.
2. Worst Case Scenario – Impute missing values of TCS on a given day by the opposite treatment group's mean value for TCS in RPS. Thus, a subject in the active group with a missing value in TCS on a given day will have that missing value replaced by the mean TCS value for the placebo group and vice versa.

Results of the TCS during the peak RS using the LOCF analysis revealed lower adjusted mean TCS values, 6.41 for the 12, Amb a 1-U group, compared to 8.44 for the placebo group. Results of the TCS during the peak RS using the worst case analysis revealed lower adjusted mean TCS values, 6.67 for the 12Amb a 1-U group compared to 8.16 for the placebo group. Similar results for both the LOCF and Worst Case Scenario were computed for the entire RS, suggesting that this product reduces the TCS when compared to placebo, and in the case of the LOCF, meets the criterion of the lower bound of the 95% CI less than -10%. While the Worst Case Scenario does not meet this criterion explicitly, the results suggest this product does reduce the symptoms.

Table 6.2.10.4.1. Sensitivity Analysis of Primary Variable (TCS) during peak RPS

TCS	**12 Amb a 1-U (n=152)**	**Placebo (n=169)**	**LSMeans Difference**	**95% CI of LSMeans Difference**	**% Relative Difference**	**95% CI Relative Difference**
LOCF						
LSMeans	6.41	8.44	-2.03	(-3.30, -077)	-24.1%	(-36.6%, -11.1%)
Worst Case						
LSMeans	6.67	8.16	-1.53	(-2.69, -0.36)	-18.6%	(-30.9%, -5.8%)

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

Reviewer comment: *The proposed treatment of exclusions and missing values was considered acceptable by the reviewer. Several post-hoc analyses were performed by the reviewer using a variety of imputation methods, yielding similar results to the original analysis. In addition, comparisons of missing value rates were made and were deemed comparable by the reviewer, for both treatment groups for primary endpoints as well as key secondary endpoints*.

6.2.10.5 Exploratory and Post Hoc Analyses

The applicant provided a variety of exploratory and post hoc analyses. These analyses included but were not limited to comparisons of combined scores, rescue medication scores, symptom scores for IgG4, IgE, as well as examination of secondary endpoint analyses over the peak and entire pollen season. The analysis of the IgG4 and IgE scores appeared to be positively affected by the use of the active treatment when compared to placebo treated individuals; however, there was a large amount of variability. Additionally, analyses of selected endpoints, time frames, and analysis sets revealed trends in which the active treatment reduced the use of rescue medication, and reduced the severity based on symptom scores of a variety of nasal and oral endpoints.

This finding was observed for the full pollen season as well as the peak ragweed pollen season and for different analysis sets that were available.

6.2.11 Safety Analyses

Safety data were collected for the entire study period. Subjects were able to note safety events on the daily diary cards, and also received periodic follow-up from study personnel. Overall, there were slightly more adverse events in the treatment groups compared to the placebo group. Additionally, there were slightly more serious adverse events noted in the various treatment groups with 5 (2.5%) subjects in the 1.5 Amb a 1-U treatment group, 4 (2%) subjects in the 6 Amb a 1-U treatment group, and 4 (2%) subjects in the treatment group of interest, 12 Amb a 1-U, while there was 1 (0.5%) subject with an SAE in the placebo treated group. A summary of the adverse events can be seen in the applicant's following Table 6.2.11.a, which includes the number (and percentage) of subjects experiencing adverse events, stratified by the treatment group (confirmed via (b)(4) tabulations by the reviewing statistician).

Table 6.2.11.a. Summary of Adverse Events Observed in the Treated and Placebo Groups during the Entire Study Period

Adverse Event Category	Number (%) of Subjects				
	Ragweed AIT 1.5 Amb a 1-U (n=196)	Ragweed AIT 6 Amb a 1-U (n=195)	Ragweed AIT 12 Amb a 1-U (n=194)	Placebo (n=198)	Total (N=783)
Any Adverse Event	151 (77.0)	154 (79.0)	152 (78.4)	131 (66.2)	588 (75.1)
TEAEs	148 (75.5)	149 (76.4)	149 (76.8)	125 (63.1)	571 (72.9)
Treatment-Related Adverse Events[a]	79 (40.3)	101 (51.8)	105 (54.1)	45 (22.7)	330 (42.1)
Severe/Life-threatening Adverse Events	27 (13.8)	27 (13.8)	30 (15.5)	25 (12.6)	109 (13.9)
Serious Adverse Events[b]	5 (2.6)	4 (2.1)	4 (2.1)	1 (0.5)	14 (1.8)
Serious TEAEs	4 (2.0)	3 (1.5)	2 (1.0)	1 (0.5)	10 (1.3)
Serious Treatment-Related TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs Leading to Study Discontinuation	10 (5.1)	16 (8.2)	16 (8.2)	6 (3.0)	48 (6.1)
Treatment-Related TEAEs Leading to Study Discontinuation	4 (2.0)	12 (6.2)	14 (7.2)	4 (2.0)	34 (4.3)

Source: Original BLA 125478/000 Clinical Study Report P05234 page 149 (confirmed by reviewing statistician)

A more detailed summary of the types of adverse events observed during the study treatment period can be seen in the following table that was confirmed by the reviewing statistician via JMP. Table 6.2.11.b.1-2 shows that 125 (63%) patients had AEs in the Placebo group and 149 (77%) patients had AEs within the Ragwitek® 12 Amb a 1-U group. Additionally, other adverse events noted in the 1.5 and 6 Amb a 1-U treated group are included within the table, showing similar trends in adverse events occurring in the active treated and placebo treatment groups.

Table 6.2.11.b.1 Summary of Adverse Events

	Number (%) of Subjects				
	Ragweed AIT 1.5 Amb a 1-U (n=196)	Ragweed AIT 6 Amb a 1-U (n=195)	Ragweed AIT 12 Amb a 1-U (n=194)	Placebo (n=198)	Total (N=783)
Subjects Reporting Any Adverse Event	148 (75.5)	148 (76.4)	149 (76.8)	125 (63.1)	571 (75.6)
Ear and Labyrinth Disorders	20 (10.2)	29 (14.9)	29 (14.9)	4 (2.0)	82 (10.5)
Ear Pruritus	14 (7.1)	27 (13.8)	25 (12.9)	2 (1.0)	68 (8.7)
Eye Disorders	11 (5.6)	22 (11.3)	11 (5.7)	17 (8.6)	61 (7.8)
Conjunctivitis	2 (1.0)	4 (2.1)	1 (0.5)	1 (0.5)	8 (1.0)
Eye Pruritus	7 (3.6)	7 (3.6)	6 (3.1)	4 (2.0)	24 (3.1)
Gastrointestinal Disorders	60 (30.6)	91 (46.7)	87 (44.8)	27 (13.6)	265 (33.8)
Diarrhoea	1 (0.5)	7 (3.6)	5 (2.6)	4 (2.0)	17 (2.2)
Dyspepsia	3 (1.5)	6 (3.1)	7 (3.6)	0 (0.0)	16 (2.0)
Hypoaesthesia Oral	2 (1.0)	6 (3.1)	4 (2.1)	0 (0.0)	12 (1.5)
Lip Oedema	3 (1.5)	4 (2.1)	3 (1.5)	0 (0.0)	10 (1.3)
Lip Swelling	1 (0.5)	3 (1.5)	4 (2.1)	0 (0.0)	8 (1.0)
Nausea	2 (1.0)	7 (3.6)	3 (1.5)	5 (2.5)	17 (2.2)
Oral Pruritus	11 (5.6)	29 (14.9)	16 (8.2)	2 (1.0)	58 (7.4)
Paraesthesia Oral	10 (5.1)	15 (7.7)	9 (4.6)	5 (2.5)	39 (5.0)
Stomatitis	0 (0.0)	4 (2.1)	1 (0.5)	0 (0.0)	5 (0.6)
Swollen Tongue	11 (5.6)	12 (6.2)	15 (7.7)	1 (0.5)	39 (5.0)
Tongue Disorder	1 (0.5)	3 (1.5)	4 (2.1)	2 (1.0)	10 (1.3)
Tongue Oedema	8 (4.1)	15 (7.7)	12 (6.2)	0 (0.0)	35 (4.5)
Tongue Pruritus	13 (6.6)	19 (9.7)	18 (9.3)	3 (1.5)	53 (6.8)
Vomiting	1 (0.5)	8 (4.1)	2 (1.0)	1 (0.5)	12 (1.5)
General Disorders and Administration Site Conditions	12 (6.1)	22 (11.3)	13 (6.7)	9 (4.5)	56 (7.2)
Chest Discomfort	4 (2.0)	3 (1.5)	2 (1.0)	0 (0.0)	9 (1.1)
Pyrexia	0 (0.0)	5 (2.6)	3 (1.5)	2 (1.0)	10 (1.3)
Immune System Disorders	6 (3.1)	4 (2.1)	4 (2.1)	0 (0.0)	14 (1.8)
Allergy to Animal	4 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.5)
Infections and Infestations	70 (35.7)	72 (36.9)	69 (35.6)	77 (38.9)	288 (36.8)
Bronchitis	5 (2.6)	7 (3.6)	8 (4.1)	12 (6.1)	32 (4.1)
Gastroenteritis Viral	2 (1.0)	3 (1.5)	2 (1.0)	5 (2.5)	12 (1.5)
Influenza	4 (2.0)	2 (1.0)	3 (1.5)	3 (1.5)	12 (1.5)
Nasopharyngitis	31 (15.8)	28 (14.4)	33 (17.0)	35 (17.7)	127 (16.2)
Pharyngitis Streptococcal	4 (2.0)	1 (0.5)	6 (3.1)	3 (1.5)	14 (1.8)
Sinusitis	12 (6.1)	9 (4.6)	8 (4.1)	7 (3.5)	36 (4..6)
Upper Respiratory Tract Infection	9 (4.6)	18 (9.2)	9 (4.6)	9 (4.5)	45 (5.7)
Urinary Tract Infection	3 (1.5)	2 (1.0)	1 (0.5)	5 (2.5)	11 (1.4)
Viral Infection	1 (0.5)	0 (0.0)	1 (0.5)	4 (2.0)	6 (0.8)
Injury, Poisoning Procedural Complications	19 (9.7)	22 (11.3)	17 (8.8)	17 (8.6)	75 (9.6)
Procedural Pain	6 (3.1)	3 (1.5)	1 (0.5)	2 (1.0)	12 (1.5)
Musculoskeletal and Connective Tissue Disorders	18 (9.2)	14 (7.2)	12 (6.2)	17 (8.6)	61 (7.8)
Arthralgia	6 (3.1)	5 (2.6)	0 (0.0)	2 (1.0)	13 (1.7)
Back Pain	2 (1.0)	4 (2.1)	4 (2.1)	6 (3.0)	16 (2.0)
Myalgia	0 (0.0)	4 (2.1)	2 (1.0)	2 (1.0)	8 (1.0)
Neck Pain	0 (0.0)	0 (0.0)	4 (2.1)	2 (1.0)	6 (0.8)
Nervous System Disorders	27 (13.8)	24 (12.3)	24 (12.4)	29 (14.6)	104 (13.3)
Dizziness	3 (1.5)	2 (1.0)	2 (1.0)	4 (2.0)	11 (1.4)
Headache	15 (7.7)	12 (6.2)	18 (9.3)	20 (10.1)	65 (8.3)
Migraine	4 (2.0)	3 (1.5)	1 (0.5)	1 (0.5)	9 (1.1)
Sinus Headache	4 (2.0)	2 (1.0)	3 (1.5)	2 (1.0)	11 (1.4)

Source: Original BLA 125478/000 Clinical Study Report P05234 page 151 (confirmed by reviewing statistician)

Table 6.2.11.b.2 Summary of Adverse Events (cont.)

	Number (%) of Subjects				
	Ragweed AIT 1.5 Amb a 1-U (n=196)	Ragweed AIT 6 Amb a 1-U (n=195)	Ragweed AIT 12 Amb a 1-U (n=194)	Placebo (n=198)	Total (N=783)
Pregnancy, Puerperium and Perinatal Conditions	4 (2.0)	2 (1.0)	1 (0.5)	0 (0.0)	7 (0.9)
Pregnancy	4 (2.0)	2 (1.0)	1 (0.5)	0 (0.0)	7 (0.9)
Psychiatric Disorders	3 (1.5)	3 (1.5)	7 (3.6)	6 (3.0)	19 (2.4)
Insomnia	1 (0.5)	1 (0.5)	4 (2.1)	2 (1.0)	8 (1.0)
Respiratory, Thoracic and Mediastinal Disorders	74 (37.8)	72 (36.9)	78 (40.2)	42 (21.2)	266 (34.0)
Cough	11 (5.6)	10 (5.1)	12 (6.2)	6 (3.0)	39 (5.0)
Dyspnoea	1 (0.5)	0 (0.0)	5 (2.6)	3 (1.5)	9 (1.1)
Nasal Congestion	4 (2.0)	8 (4.1)	8 (4.1)	3 (1.5)	23 (2.9)
Nasal Discomfort	1 (0.5)	0 (0.0)	3 (1.5)	4 (2.0)	8 (1.0)
Nasal Obstruction	4 (2.0)	1 (0.5)	1 (0.5)	6 (3.0)	12 (1.5)
Oropharyngeal Pain	14 (7.1)	5 (2.6)	9 (4.6)	4 (2.0)	32 (4.1)
Pharyngeal Oedema	1 (0.5)	1 (0.5)	4 (2.1)	0 (0.0)	6 (0.8)
Rhinitis Allergic	2 (1.0)	3 (1.5)	3 (1.5)	6 (3.0)	14 (1.8)
Rhinorrhoea	5 (2.6)	6 (3.1)	5 (2.6)	8 (4.0)	24 (3.1)
Sinus Congestion	4 (2.0)	1 (0.5)	1 (0.5)	0 (0.0)	6 (0.8)
Sneezing	10 (5.1)	6 (3.1)	8 (4.1)	4 (2.0)	28 (3.6)
Throat Irritation	28 (14.3)	42 (21.5)	41 (21.1)	11 (5.6)	122 (15.6)
Throat Tightness	4 (2.0)	2 (1.0)	6 (3.1)	1 (0.5)	13 (1.7)
Skin and Subcutaneous Tissue Disorders	16 (8.2)	31 (15.9)	20 (10.3)	22 (11.1)	89 (11.4)
Dermatitis Contact	0 (0.0)	4 (2.1)	2 (1.0)	3 (1.5)	9 (1.1)
Pruritus	4 (2.0)	9 (4.6)	4 (2.1)	5 (2.5)	22 (2.8)
Pruritus Generalized	3 (1.5)	7 (3.6)	2 (1.0)	0 (0.0)	12 (1.5)
Rash	3 (1.5)	5 (2.6)	2 (1.0)	2 (1.0)	12 (1.5)
Urticaria	1 (0.5)	4 (2.1)	4 (2.1)	5 (2.5)	14 (1.8)

Source: Original BLA 125478/000 Clinical Study Report P05234 page 152 (confirmed by reviewing statistician)

A summary of all treatment-related AEs reported during the treatment period (i.e., AEs considered possibly or probably related by the investigator) is provided in the following table. A summary of treatment-related Treatment Emergent Adverse Events (TEAEs) reported during the treatment period with an incidence of 2% or higher is provided in the following table. TEAEs are adverse events that were reported by the subject after the first administration of study product, thus excludes any adverse events noted during the screening, randomization or pre-treatment phase. The majority of these treatment-related TEAEs are related to ear, gastrointestinal, and respiratory origins. Considering this product is intended to decrease sensitivity to Ragweed Pollen which induces rhinoconjunctivitis symptom in the eyes, nose, throat, and tongue, these AEs are not unexpected.

Table 6.2.11.c. Summary of Serious Adverse Events Considered to be Treatment Related.

	Number (%) of Subjects				
	Ragweed AIT 1.5 Amb a 1-U (n=196)	Ragweed AIT 6 Amb a 1-U (n=195)	Ragweed AIT 12 Amb a 1-U (n=194)	Placebo (n=198)	Total (N=783)
Subjects Reporting Any Adverse Event	55 (28.1)	78 (40.0)	86 (44.3)	17 (8.6)	236 (30.1)
Ear and Labyrinth Disorders	14 (7.1)	26 (13.3)	24 (12.4)	2 (1.0)	66 (8.4)
Ear Pruritus	14 (7.1)	26 (13.3)	24 (12.4)	2 (1.0)	66 (8.4)
Gastrointestinal Disorders	38 (19.4)	62 (31.8)	55 (28.4)	11 (5.6)	166 (21.2)
Oral Pruritus	10 (5.1)	28 (14.4)	16 (8.2)	2 (1.0)	56 (7.2)
Paraesthesia Oral	10 (5.1)	15 (7.7)	9 (4.6)	5 (2.5)	39 (5.0)
Swollen Tongue	11 (5.6)	11 (5.6)	13 (6.7)	1 (0.5)	36 (4.6)
Tongue Oedema	8 (4.1)	15 (7.7)	12 (6.2)	0 (0.0)	35 (4.5)
Tongue Pruritus	13 (6.6)	19 (9.7)	18 (9.3)	3 (1.5)	53 (6.8)
Respiratory, Thoracic and Mediastinal Disorders	24 (12.2)	41 (21.0)	41 (21.1)	7 (3.5)	113 (14.4)
Throat Irritation	24 (12.2)	41 (21.0)	41 (21.1)	7 (3.5)	113 (14.4)
Skin and Subcutaneous Tissue Disorders	3 (1.5)	7 (3.6)	4 (2.1)	4 (2.0)	18 (2.3)
Pruritus	3 (1.5)	7 (3.6)	4 (2.1)	4 (2.0)	18 (2.3)

Source: Original BLA 125478/000 Clinical Study Report P05234 page 153 (confirmed by reviewing statistician)

Reviewer's comment*: Overall, the proposed treatment group (Ragwitek® 12 Amb a 1-U) had slightly more adverse events than the placebo; however, as an active treatment designed to elicit a response via the product instead of the pollens during the pollen season, this finding is not surprising. Additional and more detailed comments can be found in the medical officer's and epidemiologist's reviews.*

6.2.11.1 Methods

The safety data analysis consisted of examining observed Adverse Events provided by the applicant. Tabulations were utilized to compare the effect of treatment versus placebo on the observation of adverse events. No pre-specified hypothesis tests were to be performed for either organ classes or specific adverse events. For further details and additional discussion, the statistician defers to the medical officer.

6.2.11.3 Deaths

No deaths were observed in this trial

6.2.11.4 Nonfatal Serious Adverse Events

No important findings were noted in the 14 subjects with observed non-fatal serious adverse events. The number of SAEs were fairly balanced between the treatment groups with: 4 (2.1%) in the 12 Amb a 1-U group, 4 (2.1%) in the 6 Amb a 1-U group, 5 (2.6%) in the 1.5 Amb a 1-U group, and 1 (0.5%) subject in the placebo treated group, representing less than 5% of study subjects. All serious adverse events were self-limiting and were resolved upon discontinuation of study treatment. For further details and additional discussion, please refer to the medical officer's review.

6.2.11.5 Adverse Events of Special Interest (AESI)

The statistician defers to the medical officer.

6.2.11.6 Clinical Test Results

Clinical test results including IgG, IgE, and other tests performed throughout the study had results that were expected and not considered outside of normal ranges. For further details and additional discussion, the reviewing statistician defers to the medical officer.

6.2.11.7 Dropouts and/or Discontinuations

A total of 48 subjects discontinued the trial as a result of TEAEs: 16 subjects in the12 Amb a 1-U group, 16 subjects in the 6 Amb a 1-U group, 10 subjects in the1.5 Amb a 1-U group, and 6 in the placebo group. There were statistically significantly higher proportions of subjects discontinuing the trial due to TEAEs in the 12 Amb a 1-U groups (8.2% for 12 Amb a 1-U dose) compared to those in the placebo group (difference of 3.0%; p= 0.026). Similarly, although not planned for licensing, the 6 Amb a 1-U treatment group had a similar drop out pattern as the 12 Amb a 1-U dosage. The difference between the 1.5 Amb a-1-U group and placebo was not statistically significant (5.1% versus 3.0%, respectively; p = 0.298).

The majority of the AEs leading to withdrawal were assessed by the investigator as mild or moderate in severity and possibly or probably related to study drug.

There were eight severe treatment-related adverse events that resulted in study discontinuation: 3 in the 12 Amb a 1-U group and 5 in the 6 Amb a 1-U group, with no severe events leading to discontinuation in the 1.5 Amb a 1-U and placebo groups. Several individuals discontinuing study treatment indicated that it was treatment related AEs that led to study discontinuation. Since this product exposes subjects to a product in which they are sensitive, ragweed pollen, the observation of adverse events causing study withdrawal may be consistent with other SCIT products. Additional details related to the dropouts and discontinuations can be seen in the medical officer's and epidemiologist's reviews.

Summary and conclusion: *Protocol P05234 met its objectives with respect to the primary efficacy endpoint, as well as several secondary endpoints. Additional subgroup analyses as well as sensitivity analyses provide supportive evidence that this product reduces the combined rescue medication and symptom scores, rescue medication use, and symptom scores when compared to placebo during the ragweed pollen season. The safety profile of Ragwitek® in this study appears to be acceptable, and all serious adverse events reported during the study treatment period were self-limiting and resolved. No deaths occurred.*

7. INTEGRATED OVERVIEW OF EFFICACY

The following section summarizes the totality of evidence from all studies submitted by the applicant to this BLA. Based on the results presented by the applicant and confirmed by the reviewing statistician, it appears that this product reduces daily symptom scores, reduces the use of daily rescue medication, and reduces the combined symptom score that incorporates both the daily allergic symptoms as well as the use of rescue medication.

7.1 Indication #1

Based on the applicant provided Label and Package Insert, the following is the proposed indication for this product:

"*Ragwitek® is indicated as immunotherapy for the treatment of diagnosed ragweed pollen induced allergic rhinitis, with or without conjunctivitis, in adults 18 to 65 years of age and older*."

7.1.1 Methods of Integration

Overall, approximately ~1750 subjects 18 to 65 years of age participated in the clinical development program of MK-3641, which consisted of a total of five (5) clinical trials in the MK-3641/Ragwitek® Clinical Development program. The effectiveness and safety of MK- MK-3641/Ragwitek® was evaluated in the following clinical trials from Phase I to Phase III:

- One 28-day Phase 1 safety trial in adults with ragweed-induced rhinoconjunctivitis without asthma (RT-01);
- One 28-day Phase 2 safety trial in adults 50 years and older with ragweed-induced rhinoconjunctivitis with or without asthma (P06081);
- Two 52-week, Phase 2/3 dose-finding efficacy and safety trial in adults with ragweed-induced rhinoconjunctivitis with or without asthma (P05233, P05234); and
- One 28-day Phase 3 safety trial in adults with ragweed-induced rhinoconjunctivitis with or without asthma (P05751).

The clinical trials were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such trials, including the archiving of essential documents. All trials were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed.

Both of these studies were performed over one allergy season. A summary of the two efficacy studies, including the purpose of the study and number of patients exposed to various doses of the Merck Ragwitek® product, is provided in the table below.

Table 7.1.1.a. Efficacy Studies provided within the BLA for Merck's Ragwitek®

Study Number, Phase, and Description	Treatment Groups/ Duration of Active Treatment	No. of Subjects/ Age Range	Countries Involved
Adult Studies			
P05233 (Phase 2/3, Efficacy and Safety) To evaluate the single season efficacy and safety of MK-3641 in adult subjects with a history of ragweed pollen-induced rhinoconjunctivitis with or without asthma.	MK-3641(6 Amb a 1-U), MK-3641 (12 Amb a 1-U), or Placebo Duration of treatment was approximately 52 weeks (including approximately 16 weeks prior to and during the RS)	560 (565) [a] total (6 Amb a 1-U) = 188 (12 Amb a 1-U) = 186 Placebo = 186 /18 to 50 years	US and Canada
P05234 (Phase 2/3, Efficacy and Safety) To evaluate the single season efficacy and safety of MK-3641 in adult subjects with a history of ragweed pollen-induced rhinoconjunctivitis with or without asthma.	MK-3641 (1.5 Amb a 1-U), MK-3641 (6 Amb a 1-U), MK-3641 (12 Amb a 1-U), or Placebo Duration of treatment was approximately 52 weeks (including approximately 16 weeks prior to and during the RS)	784 (783) [b] total (1.5 Amb a 1-U) = 197 (6 Amb a 1-U) = 195 (12 Amb a 1-U) = 194 Placebo = 198 /18 to 50 years	US, Canada, Hungary, Russia, and Ukraine

Source: Original BLA 125478/000 Clinical Overview page 18

From the above table and previously examined studies in this review, it can be seen that the majority of the studies of this product consisted of natural exposure field investigations after 2-4 months of treatment over one ragweed pollen season.

The primary measure of efficacy, as per CBER Standards, is the (TCS) total combined score, which incorporates both the rescue medication score and the rhinoconjunctivitis symptom score during the pollen season. It is important to note that since many of these studies were performed internationally and not under US-IND, the pre-specified primary efficacy endpoints varied among studies.

Integration of results was to incorporate both the primary endpoints as well as secondary endpoints of the various studies in order to utilize and compare the TCS as the primary efficacy endpoint. Furthermore, the clinically meaningful difference was to be set utilizing the US standard, based on the May 2011 Advisory Committee agreed upon criterion of -10% as the clinically meaningful upper bound for the % difference between treatment and placebo responses in the TCS endpoint.

In both studies, the primary efficacy endpoint (i.e., the symptom score or symptom/rescue medication score) was analyzed using a linear model, specifically an ANCOVA with treatment as main effect, pooled study center/geographic location as stratification factor, and several covariates (including asthma status) which could potentially impact the TCS, DDS, or DMS score.

7.1.2 Demographics and Baseline Characteristics

Across studies, no notable differences in demographic characteristics were observed between the active and placebo treatment groups. Specific details related to demographic and baseline characteristics can be seen in the following table, which examines the number and percentage of individuals in the Full Analysis set, stratified by treatment group, age, gender, race/ethnicity, asthma status, and sensitivity to ragweed pollens.

Table 7.1.2.a. Summary of Demographic and Baseline Characteristics

Baseline Demographic	**Ragwitek AIT 12 Amb a 1-U N=381**	**Placebo N=386**	**Total N=767**
Gender [n (%)]			
Female	200 (52%)	189 (49%)	389 (51%)
Male	181 (48%)	197 (51%)	278 (49%)
Age (years)			
Mean (SD)	35.3 (9.1)	36.3 (8.8)	35.8 (8.9)
Range	18-51	18-50	18-51
Race [n (%)]			
White/Caucasian	326 (86%)	307 (80%)	633 (83%)
Black or African American	34 (9%)	49 (13%)	83 (11%)
Asian	12 (3%)	25 (6%)	37 (5%)
American Indian/Alaska	2 (1%)	0 (0%)	2 (0%)
Other	6 (2%)	5 (1%)	11 (1%)
Asthma Status			
Asthmatic	79 (21%)	75 (19%)	154 (20%)
Non-Asthmatic	302 (79%)	311 (81%)	613 (80%)
Sensitization			
Ragweed	68 (18%)	74 (19%)	142 (19%)
Other Allergens	313 (82%)	312 (81%)	625 (81%)

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

The racial profile of subjects was predominantly white/Caucasian (80-90%) in all studies performed by the applicant and 80-86% in the pooled analysis. In various studies, the distribution of gender did slightly differ, as can be seen in the tables provided in Section 6.1.9.1 and Section 6.2.9.1.; however, when pooling the studies from the randomized treatment groups, no imbalances were noted. Furthermore, when examining the pooled studies, no differences were noted with respect to the racial profile, asthma status, and ragweed vs multiple pollen sensitization.

7.1.3 Analysis of Primary Endpoint(s)

Considering the results of the primary and secondary analyses (depending on the study examined), it can be seen that when comparing the study treatment at a dose of Ragwitek® to placebo, the study treatment group had a lower point estimate of TCS than placebo.

The primary efficacy endpoint (dependent variable), TCS score, was analyzed using a linear model, specifically an ANCOVA with treatment as main effect, pooled study center as stratification factor for the multicenter studies, and baseline asthma status which could potentially impact the clinical score. The table below summarizes the difference in LS Means (and 95% CI) of the treated group versus placebo as well as the relative LS Mean difference (and 95% CI) utilizing the TCS endpoint for all of the field studies that collected efficacy data provided in this submission. The results demonstrate that the

treatment (particularly the dosage proposed of 12 Amb a 1-U Ragwitek®) reduces the TCS score when compared to placebo, based on both the point estimate of the difference as well as the 95% CI considering the LS Mean values.

Table 7.1.3.a. Summary of treatment difference and 95% CI of the TCS for the combined studies

Endpoint	N	Adjusted Mean	Treatment Difference (95% CI)[a]	% Relative to Placebo (95% CI)[b]	p-Value
TCS Peak					
12 Amb a 1-U	311	6.69	-2.02 (-2.87, -1.17)	-23.23 (-32.28, -14.60)	<0.0001
6 Amb a 1-U	317	7.01	-1.70 (-2.55, -0.86)	-19.54 (-28.57, -9.25)	<0.0001
Placebo	333	8.71	—	—	—

Source: Original BLA 125478/000 Clinical Overview page 91

Across both efficacy trials, a consistent trend in favor of Ragwitek® was observed, with some variation in overall magnitude of effect as expected in seasonal allergic rhinitis trials.

Both trials had statistically significant findings and met CBER's clinically meaningful criterion for efficacy, stated in the May 2011 Allergenic Advisory Committee meeting and Merck's agreed upon criterion for effect of -10% for the upper bound of the relative % difference between treatment and placebo based on the 95% CI. From the above table, the pooled efficacy % difference is -23% and the 95% CI is (-32.3%, -14.6%). Thus, based on the pooled data, it appears this product provides a clinically meaningful reduction in the TCS during the peak ragweed season.

7.1.4 Analysis of Secondary Endpoint(s)

Similar to the primary pooled efficacy data, the secondary endpoint data also suggested an overall reduction of rhinoconjuctivitis symptoms and rescue medication use for both the peak and entire ragweed pollen season.

For an overall assessment of efficacy, data from the two Phase 3 efficacy trials were pooled. The following figure presents the results for the efficacy (key and select secondary) endpoints during the peak and entire RPS for the 12 Amb a 1-U dose. The pooled analysis utilized individual level data and thus differs from other integrated efficacy analysis approaches, such as meta-analysis which utilizes trial-level results.

Table 7.1.4.a. summarizes the difference in LS Means (and 95% CI) of the treated group versus placebo as well as the Relative LS Mean difference (and 95% CI) utilizing the DSS, DMS, and TCS endpoints for the field studies for the peak and entire pollen season. The results demonstrate that the treatment, particularly the dosage proposed of 12 Amb a 1-U of the Ragwitek® product reduces the DMS score when compared to placebo, based on both the point estimate of the difference as well as the 95% CI considering the LS Mean values. Although not meeting the clinically meaningful lower bound of -10% for the 95% CI of the DDS, the analysis suggests a positive trend in the reduction of symptom scores compared to placebo.

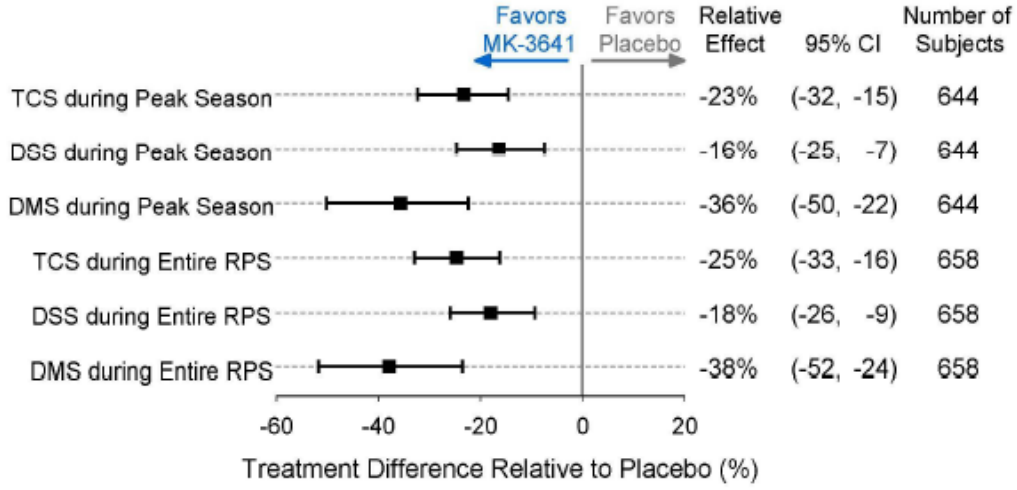
Table 7.1.4.a. Analysis of the Daily Symptom Score (DSS), Daily Medication Score (DMS) for Peak Pollen Season and TCS, DSS, DMS for the Entire Pollen Season: Summary of Pooled Efficacy Studies based on the Two Phase II/III Studies Submitted by Merck-FAS

Endpoint	N	Adjusted Mean	Treatment Difference (95% CI)[a]	% Relative to Placebo (95% CI)[b]	p-Value
TCS Entire RS					
12 Amb a 1-U	318	5.49	-1.79 (-2.51, -1.08)	-24.63 (-32.88, -16.18)	<0.0001
6 Amb a 1-U	324	6.05	-1.23 (-1.94, -0.52)	-16.94 (-26.29, -6.86)	0.0007
Placebo	340	7.28	—	—	—
DSS Peak					
12 Amb a 1-U	311	4.67	-0.91 (-1.44, -0.38)	-16.33 (-24.96, -7.44)	0.0007
6 Amb a 1-U	317	4.87	-0.71 (-1.24, -0.19)	-12.76 (-21.63, -2.69)	0.0079
Placebo	333	5.58	—	—	—
DSS Entire RS					
12 Amb a 1-U	318	3.96	-0.87 (-1.31, -0.42)	-17.96 (-25.90, -9.29)	0.0001
6 Amb a 1-U	324	4.33	-0.49 (-0.93, -0.04)	-10.09 (-19.58, -0.27)	0.0311
Placebo	340	4.82	—	—	—
DMS Peak					
12 Amb a 1-U	311	2.02	-1.11 (-1.61, -0.62)	-35.55 (-50.11, -22.41)	<0.0001
6 Amb a 1-U	317	2.14	-0.99 (-1.48, -0.50)	-31.64 (-45.63, -15.45)	<0.0001
Placebo	333	3.13	—	—	—
DMS Entire RS					
12 Amb a 1-U	318	1.53	-0.93 (-1.34, -0.52)	-37.80 (-51.76, -23.51)	<0.0001
6 Amb a 1-U	324	1.71	-0.75 (-1.16, -0.34)	-30.39 (-44.22, -13.69)	0.0004
Placebo	340	2.46	—	—	—

Source: Original BLA 125478/000 Clinical Overview page 91

A forest plot of these values can be seen in Figure 7.1.4.a., which illustrates the effect of the treatment versus placebo difference for DSS, DMS, and TCS for the peak and entire pollen season. It is of note that the applicant included both the 95% CI bars as well as a line denoting a difference of "0." CBER's preferred clinically meaningful difference is based on the % relative difference of -10%, based on the upper bound of a 95% CI (which can be compared to the final column in the presented values below).

Figure 7.1.4.a. Analysis of the Daily Symptom Score (DSS), Daily Medication Score, and Total Combined Score (TCS) for the Peak and Entire Pollen Season: Summary of Pooled Efficacy Studies based on Phase II/III Studies Submitted by Merck-FAS



Source: Original BLA 125478/000 Clinical Overview page 91

The results and figures included in this section provide evidence that Ragwitek® reduces the use of daily relief medication (DMS), as well as the daily symptom score (DSS) for the LS Means, utilizing the pre-specified model for both the entire pollen season as well as the peak pollen season. Furthermore, the TCS is also improved when comparing the 12 Amb a 1-U treated individuals to the placebo treated individuals for the entire pollen season. These findings are consistent with the results found regarding the primary efficacy endpoint in which the treatment was found to reduce the TCS in individuals treated with 12 Amb a 1-U of Ragwitek®.

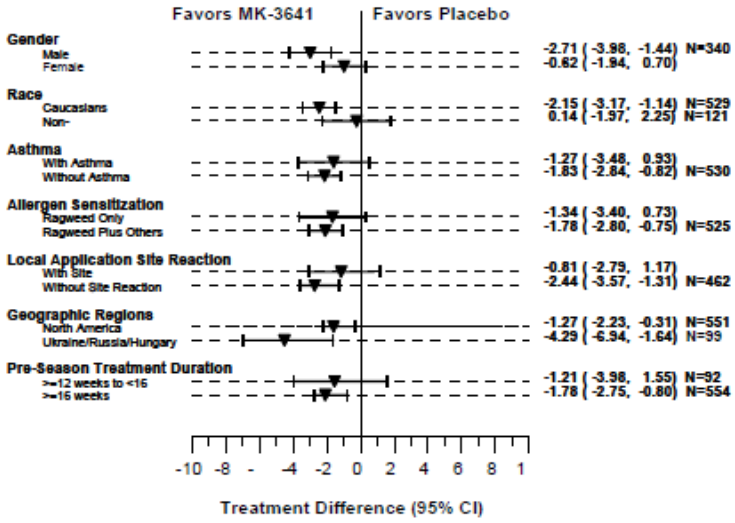
7.1.5 Other Endpoints

Analyses of exploratory and additional endpoints have little impact on the evaluation of the product, and thus will not be addressed in the Integrated Analysis of Efficacy. However, other exploratory analyses based on other endpoints, including clinical and symptom scores, different analysis sets, quality of life scores, and other subset analyses yield similar trends that demonstrate the positive effect of this treatment when compared to placebo.

7.1.6 Subpopulations

Based on the results provided by the applicant and select analyses performed by the reviewing statistician, there do not appear to be significant differences in efficacy between subjects who were mono-sensitized (defined as sensitive to the group of ragweed pollen allergen) and those who were not, and between Caucasians and non-Caucasians. In addition, there were no significant differences in efficacy between subjects with and without asthma, or between children and adults. Differences were noticeable when comparing regions (North America versus Europe), but this finding may be due to differences in pollen season as well as different standards of care. Results of the subset analyses are presented in Figure 7.1.7.a. for the pooled data for both adult Phase II/III efficacy studies.

Figure 7.1.6.a. Point Estimate and 95% CI for the Difference in the Total Combined Symptom and Rescue Medication Score (TCS) in Select Subgroups during the Ragweed Pollen Season-ITT Analysis Population in Adult Studies



Source: Original BLA 125478/000 Summary of Clinical Efficacy page 97

Overall, subgroup analyses of the pooled studies provide supportive evidence that the Ragwitek® product reduces the TCS for a variety of subgroups, including age, gender, race, asthma status, and geographic location.

7.1.7 Additional Efficacy Issues/Analyses

There are no additional efficacy issues or analyses that provide additional insight into the effect of this product. The statistical reviewer did perform additional subset analyses on the applicant-provided data to determine if there may have been a specific group that had efficacy results that did not yield similar conclusions regarding the positive effect of this treatment. These subsets included (but are not limited to) baseline skin prick test values, asthma status, dichotomization based on use of rescue medication, and geographic region. Since this study was not powered to examine these subsets nor were any alpha adjustments made, these subgroup-specific results are not presented here; however, the trends consistently supported that this treatment improves the combined symptom score and daily medication score. Furthermore, the reviewing statistician also performed sensitivity analyses of the primary and key secondary endpoints for both the individual studies and pooled studies, utilizing a variety of variance/covariance structures, examining several different methods for estimation of 95% CI, various analysis sets, as well as subgroups. In addition to the reduction of allergy symptoms, this product in general appears to reduce the use of rescue medication.

7.1.8 Efficacy Conclusions

The overall results of the efficacy data suggest that there is a reduction in symptoms and use of rescue medication when comparing individuals who were randomized and

received Ragwitek® study treatment to individuals who received a nearly identical placebo product.

The applicant's proposed indication is:

"Ragwitek® is indicated as immunotherapy for diagnosed ragweed pollen induced allergic rhinitis, with or without conjunctivitis, in adults 18-65 years of age."

Reviewer Comment:
Based on the applicant's data and analyses, which were confirmed by the reviewing statistician, this indication appears to be supported. However, it is important to note that no efficacy study included patients older than 51 years of age.

Overall, the statistical reviewer agrees with the applicant's statement that Ragwitek® is effective for immunotherapy for the reduction of rhinoconjuctivis symptoms and use of rescue medication due to ragweed pollen allergy.

8. INTEGRATED OVERVIEW OF SAFETY

The safety methods incorporated a variety of active and passive adverse event reporting mechanisms, depending on the study. Subjects were provided daily diary cards in which adverse event symptoms could be noted. Additionally, regular clinic visits were scheduled for the various studies in which subjects were to be asked questions to assess if any symptoms that could be considered adverse events had occurred. All subjects were to be administered the initial dose of Ragwitek® within a physician's office and observed for a minimum of 30 minutes to 1 hour, depending on the study for the first 3 days of administration. During this time frame in the physician's office, all individuals were observed and queried for potential symptoms and adverse events. Additional details related to safety assessment methods can be seen in the medical officer's and epidemiologist's review.

8.1 Safety Assessment Methods

The safety datasets provided in this submission include the efficacy datasets described in Section 1, Table 1. Within Table 1, information about each of the safety studies is provided, including the protocol, time of study, study title, study design and objectives, study population, treatment doses and schedule, number of patients exposed, and treatment duration.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The overall exposure and demographics of the safety database based on the treatment groups were provided by the applicant and confirmed by the reviewing statistician via JMP. The results of the tabulations of the pooled exposure to treatment or placebo can be seen within tables provided within this section of this review.

The following table summarizes the extent of exposure to any treatment (including placebo and dosages of Ragwitek® submitted but not selected as the optimal dosage for consideration within this BLA) in all studies provided within this BLA.

Table 8.2.1.a. Exposure to Treatment or Placebo of All Subjects

Study no. (Study centers)	Study Objective	Design	Dose (Amb a 1-U)	No. of Subjects Randomized and Exposed	Age Range (years)	Planned Duration of Treatment
P007 (RT-01)[†] (US)	Ph 1 Safety	Dose escalation, double blind, randomized, placebo controlled	3, 6, 12, 24, 50, placebo[a]	Total=53 Active=40	18-50	28 days
P06081 (US)	Ph 2 Safety	Double blind, randomized, placebo controlled	6, 12, placebo[b]	Total=203 Active=136	≥50	28 days
P05233 (US and Canada)	Ph 2/3 Safety/ efficacy Primary endpoint: TCS over the peak ragweed season	Double blind, randomized, placebo controlled	6, 12, placebo[c]	Total=565 Active=377	18-50	52 weeks
P05234 (US, Canada, Hungary, Ukraine, Russia)	Ph 2/3 Safety/ efficacy Primary endpoint: TCS over the peak ragweed season	Double blind, randomized, placebo controlled	1.5, 6, 12, placebo[d]	Total=783 Active=585	18-50	52 weeks
P05751 (US Canada)	Phase 3 Safety	Double blind, randomized, placebo controlled	12, placebo[e]	Total = 913 Active = 609	≥18	28 days

Source: Original BLA 125478/000 Summary of Clinical Safety page 18

Further details about the exposure for each treatment dosage can be seen in the following table.

Table 8.2.1.b. Exposure to Specific Treatment Dosage or Placebo of All Subjects including Duration of Exposure

Study	Total Subjects	Total Active	1.5 Amb a 1-U	3 Amb a 1-U	6 Amb a 1-U	12 Amb a 1-U	24 Amb a 1-U	50 Amb a 1-U
RT-01	53	40	0	9	9	9	9	4
P06081	203	136	0	0	69	67	0	0
P05751	913	609	0	0	0	609	0	0
P05233	565	377	0	0	190	187	0	0
P05234	783	585	196	0	195	194	0	0
Total	2517	1747	196	9	463	1066	9	4
Treated for 1 month			190	8	429	918	7	2
Treated for 6 month			165	0	301	301	0	0
Treated for 52 weeks			152	0	271	269	0	0

Source: Original BLA 125478/000 Summary of Clinical Safety page 21

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The following table provides insight into the demographics of individuals in the studies provided within this submission. The table includes the sample size (n) and percentage of individuals for the Safety Analysis set based on age, gender, asthma status, geographic region, and allergen sensitization stratified by treatment group. Overall, the demographics appear to be similar between the treatment groups when pooling all the studies that collected safety data; however, as can be seen in the below table, it is of note that there are slightly more females in these studies than males (51.3% and 55.8% for the active and placebo treated groups in the studies).

Table 8.2.2.a. Demographic and Baseline Characteristics of Subjects Randomized to Treatment or Placebo for All Subjects in Phase I/II/III Studies

	1.5 Amb a 1-U N=197	6 Amb a 1-U N=454	12 Amb a 1-U N=1058	Placebo N=757
Sex (n,%)				
Female	110 (55.8%)	233 (51.3%)	587 (55.5%)	406 (53.6%)
Male	87 (44.2%)	221 (48.7)	471 (44.5%)	351 (46.4%)
Race (n,%)				
White	176 (89.3%)	379 (83.5%)	877 (82.9%)	590 (77.9%)
Non-White	21 (10.7%)	75 (16.5%)	181 (17.1%)	167 (22.1%)
American Indian or Alaskan Native	0 (0%)	2 (0.4%)	5 (0.5%)	2 (0.3%)
Asian	4 (2.0%)	20 (4.4%)	20 (1.9%)	34 (4.5%)
Black or African American	14 (7.1%)	47 (10.4%)	132 (12.5%)	116 (15.3%)
Multiracial	3 (1.5%)	5 (1.1%)	22 (2.1%)	14 (1.8%)
Native Hawaiian or Other Pacific Islander	0 (0%)	1 (0.2%)	2 (0.2%)	1 (0.1%)
Age (yrs.)				
Mean (SD)	34.2 (9.5)	38.1 (11.6)	38.1 (12.1)	39.4 (11.8)
Median	34.0	37.0	38.5	41.0
Range	18 – 50	20 – 73	18 – 85	18 – 67
Age (n,%)				
< 50	192 (97.5%)	373 (82.2%)	842 (79.6%)	590 (77.9%)
>=50	5 (2.5%)	81 (17.8)	216 (20.4%)	167 (22.1%)
Asthma Status (n,%)				
No	163 (82.7%)	377 (83.0%)	864 (81.7%)	621 (82.0%)
Yes	34 (17.3%)	77 (17.0%)	194 (18.3%)	136 (18.0%)
Geographic Region				
Canada	35 (17.8%)	112 (24.7%)	206 (19.5%)	172 (22.7%)
Ukraine/Russia/Hungary	56 (28.4%)	60 (13.2%)	55 (5.2%)	60 (7.9%)
USA	106 (53.8%)	282 (62.1%)	797 (75.3%)	525 (69.4%)
Allergen Sensitization				
N	197	385	381	386
Ragweed/weed Only	42 (21.3%)	68 (17.7%)	68 (17.8%)	74 (19.2%)
Ragweed/weed Plus Others	155 (78.7%)	315 (81.8%)	313 (82.2%)	310 (80.3%)

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

Based on the above table, it appears there is balance across the treatment groups for the majority of baseline characteristics.

8.3 Caveats Introduced by Pooling of Data across Studies/Clinical Trials

These studies were performed in a variety of similar locations in the US, Canada, and select countries in Europe under similar, if not nearly identical, INDs. Thus, pooling studies and utilizing a model which incorporates the studies may be appropriate and interpreting results and making generalizations may be acceptable. Considering that the results and trends were consistent regardless of the specific study examined, the pooling of results may be less of a concern than if conclusions were not globally consistent and did not depend on the individual study.

8.4 Safety Results

A summary of the adverse events can be seen in the table below. Based on the tabulated values, trends of adverse events can be seen to be slightly higher in the treatment group versus the placebo treated patients (50%, 57%, and 56% for the 1.5, 6, and 12 Amb a 1-U

doses, respectively, compared to 38% for the placebo treated group). The table below provides a brief description of the adverse event, the count, and % of observed subjects with the Adverse Event, stratified by treatment group.

Table 8.4.1.a Overview of Adverse Events-Safety Analysis Set-All Doses from All Studies-within 28 Days of Treatment

Category	1.5 Amb a 1-U (N=196) n(%)	6 Amb a 1-U (N=454) n(%)	12 Amb a 1-U (N=1057) n(%)	Placebo (N=757) n(%)
At Least One AE	97(49.5)	261(57.5)	597(56.5)	285(37.6)
Treatment Related AE	70(35.7)	230(50.7)	482(45.6)	155(20.5)
Serious AE	0	1(0.2)	2(0.2)	4(0.5)
Treatment Related Serious AE	0	0	0	1(0.1)
Discontinued Due to AE[a]	4(2.0)	24(5.3)	55(5.2)	7(0.9)
Discontinued Due to Treatment Related AE	3(1.5)	19(4.2)	46(4.4)	6(0.8)
Discontinued Due to Serious AE	0	1(0.2)	2(0.2)	2(0.3)
Discontinued Due to Treatment Related Serious AE	0	0	0	1(0.1)
Death	0	0	0	0

Source: Original BLA 125478/000 Summary of Clinical Safety page 43

Considering treatment emergent adverse events listed in the table above, the treated group had a greater likelihood of TEAEs with 45% for the 12 Amb a 1-U treated subjects versus 20% in the placebo treated group. Within those experiencing treatment related AEs, those in the 12 Amb a 1-U treated group discontinued the study 5% of the time, while only 1% of individuals in the placebo treated group discontinued due to perceived treatment related adverse events.

These safety data including reporting of AEs can be supplemented with the 52-week safety data collected within the two efficacy studies.

Table 8.4.1.b Overview of Adverse Events-Safety Analysis Set-All Doses from Studies that Collected AE Data throughout 52 Weeks Post Treatment

Category	Number (%) of Subjects				
	1.5 Amb a 1-U n=196	6 Amb a 1-U n=385	12 Amb a 1-U n=381	Total Ragweed AIT n=962	Placebo n=386
Any TEAEs	148 (75.5)	296 (76.9)	307 (80.6)	751 (78.1)	264 (68.4)
Any Treatment-Related Adverse Events	79 (40.3)	213 (55.3)	233 (61.2)	525 (54.6)	98 (25.4)
Any Serious TEAEs	4 (2.0)	5 (1.3)	3 (0.8)	12 (1.2)	4 (1.0)
Any Serious Treatment-Related Adverse Events	0	0	0	0	0
Any TEAEs Leading to Study Discontinuation	10 (5.1)	31 (8.1)	35 (9.2)	76 (7.9)	9 (2.3)
Any Treatment-Related TEAEs Leading to Study Discontinuation	4 (2.0)	26 (6.8)	31 (8.1)	61 (6.3)	6 (1.6)

Source: Original BLA 125478/000 Summary of Clinical Safety page 44

The types of adverse events observed during this study can be seen in the following tables, which include events common (>2% of subjects experiencing the adverse event) in Adult subjects and can be seen for both the 28 day safety data as well as for the longer term 52-week duration.

Table 8.4.2.a Summary of Adverse Events-All reported AEs within 28 Days of Treatment

	1.5 Amb a 1-U N=196		6 Amb a 1-U N=454		12 Amb a 1-U N=1057		Placebo N=757	
	n	%	N	%	n	%	n	%
SUBJECTS REPORTING ANY ADVERSE EVENT	97	(49.5)	261	(57.5)	597	(56.5)	285	(37.6)
EAR AND LABYRINTH DISORDERS								
EAR PRURITUS	14	(7.1)	60	(13.2)	113	(10.7)	8	(1.1)
EYE DISORDERS								
EYE PRURITUS	4	(2.0)	11	(2.4)	27	(2.6)	13	(1.7)
GASTROINTESTINAL DISORDERS								
DYSPEPSIA	0		9	(2.0)	9	(0.9)	3	(0.4)
HYPOAESTHESIA ORAL	2	(1.0)	9	(2.0)	20	(1.9)	3	(0.4)
LIP SWELLING	0		7	(1.5)	32	(3.0)	3	(0.4)
OEDEMA MOUTH	7	(3.6)	33	(7.3)	64	(6.1)	4	(0.5)
ORAL MUCOSAL ERYTHEMA	0		9	(2.0)	5	(0.5)	3	(0.4)
ORAL PRURITUS	10	(5.1)	88	(19.4)	116	(11.0)	15	(2.0)
PARAESTHESIA ORAL	12	(6.1)	35	(7.7)	106	(10.0)	30	(4.0)
SWOLLEN TONGUE	7	(3.6)	13	(2.9)	32	(3.0)	4	(0.5)
TONGUE PRURITUS	9	(4.6)	27	(5.9)	55	(5.2)	4	(0.5)
INFECTIONS AND INFESTATIONS								
NASOPHARYNGITIS	7	(3.6)	11	(2.4)	36	(3.4)	31	(4.1)
UPPER RESPIRATORY TRACT INFECTION	0		5	(1.1)	19	(1.8)	16	(2.1)
NERVOUS SYSTEM DISORDERS								
HEADACHE	7	(3.6)	11	(2.4)	54	(5.1)	27	(3.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS								
COUGH	2	(1.0)	11	(2.4)	24	(2.3)	8	(1.1)
DRY THROAT	0		9	(2.0)	8	(0.8)	4	(0.5)
OROPHARYNGEAL PAIN	5	(2.6)	8	(1.8)	29	(2.7)	13	(1.7)
PHARYNGEAL OEDEMA	1	(0.5)	10	(2.2)	20	(1.9)	3	(0.4)
SNEEZING	3	(1.5)	7	(1.5)	25	(2.4)	12	(1.6)
THROAT IRRITATION	24	(12.2)	95	(20.9)	180	(17.0)	29	(3.8)
THROAT TIGHTNESS	4	(2.0)	4	(0.9)	14	(1.3)	4	(0.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS								
PRURITUS	2	(1.0)	17	(3.7)	20	(1.9)	12	(1.6)

Source: Original BLA 125478/000 Summary of Clinical Safety page 53

The most common adverse events for the 28-day safety pooled population are presented in the previous table. From this table it can be seen that the percentage of subjects who experienced adverse events is similar when comparing the 6 and 12 Amb a 1-U doses. The most common AEs which occurred in any dose of the Ragwitek® treated subjects include the local allergic reactions, such as throat irritations, oral pruritus, paraesthesia, oral and ear pruritus. Similar types but fewer actual allergic reactions were observed in the placebo treated individuals.

In addition to the common adverse events, the following table illustrates the treatment related AEs.

Table 8.4.2.b. Summary of Adverse Events-All Reported Treatment Related AEs within the First 28 Days of Treatment

	1.5 Amb a 1-U N=196		6 Amb a 1-U N=454		12 Amb a 1-U N=1057		Placebo N=757	
	n	%	n	%	n	%	n	%
SUBJECTS REPORTING ANY ADVERSE EVENT	70	(35.7)	230	(50.7)	482	(45.6)	155	(20.5)
EAR AND LABYRINTH DISORDERS								
EAR PRURITUS	14	(7.1)	59	(13.0)	110	(10.4)	8	(1.1)
EYE DISORDERS								
EYE PRURITUS	4	(2.0)	10	(2.2)	22	(2.1)	13	(1.7)
GASTROINTESTINAL DISORDERS								
HYPOAESTHESIA ORAL	2	(1.0)	9	(2.0)	20	(1.9)	3	(0.4)
LIP SWELLING	0		7	(1.5)	32	(3.0)	3	(0.4)
OEDEMA MOUTH	7	(3.6)	32	(7.0)	64	(6.1)	4	(0.5)
ORAL MUCOSAL ERYTHEMA	0		9	(2.0)	5	(0.5)	2	(0.3)
ORAL PRURITUS	10	(5.1)	87	(19.2)	115	(10.9)	15	(2.0)
PARAESTHESIA ORAL	12	(6.1)	35	(7.7)	106	(10.0)	30	(4.0)
SWOLLEN TONGUE	7	(3.6)	13	(2.9)	31	(2.9)	4	(0.5)
TONGUE PRURITUS	9	(4.6)	27	(5.9)	54	(5.1)	4	(0.5)
NERVOUS SYSTEM DISORDERS								
HEADACHE	2	(1.0)	3	(0.7)	24	(2.3)	11	(1.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS								
PHARYNGEAL OEDEMA	0		9	(2.0)	20	(1.9)	3	(0.4)
THROAT IRRITATION	23	(11.7)	94	(20.7)	175	(16.6)	25	(3.3)
THROAT TIGHTNESS	4	(2.0)	4	(0.9)	14	(1.3)	4	(0.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS								
PRURITUS	1	(0.5)	15	(3.3)	19	(1.8)	10	(1.3)

Source: Original BLA 125478/000 Summary of Clinical Safety page 54

The highest percentage of subjects experienced treatment related AEs on Day 1, with most of the remaining treatment related adverse events typically occurring within the first 1-2 weeks of treatment (e.g., 460 out of 478 subjects (96%) developed treatment related AEs during the first 14 days of treatment for 12 Amb a 1-U dose).

In addition to the 28-Day safety data provided by all 5 studies, the two efficacy studies also provided additional safety data for the 52-week duration of the study. The Adverse Events experienced during this additional time frame can be observed in the following table.

Table 8.4.2.c. Summary of Adverse Events-All Reported AEs **after** 28 Days of Treatment

Category	1.5 Amba a 1-U (N=190)	6 Amb a 1-U (N=355)	12 Amb a 1-U (N=345)	Placebo (N=372)
	n(%)	n(%)	n(%)	n(%)
At Least One AE	110(57.9)	202(56.9)	220(63.8)	232(62.4)
Treatment Related AE	21(11.1)	52(14.6)	74(21.4)	32(8.6)
Serious AE	4(2.1)	5(1.4)	3(0.9)	3(0.8)
Treatment Related Serious AE	0	0	0	0
Discontinued Due to AE[a]	6(3.2)	9(2.5)	6(1.7)	6(1.6)
Discontinued Due to Treatment Related AE	1(0.5)	7(2.0)	4(1.2)	3(0.8)
Discontinued Due to Serious AE	2(1.1)	1(0.3)	0	1(0.3)
Discontinued Due to Treatment Related Serious AE	0	0	0	0
Death	0	0	0	0
Severe/Life-threatening AE	26(13.7)	39(11.0)	45(13.0)	41(11.0)

Source: Original BLA 125478/000 Summary of Clinical Safety page 53

8.4.1 Deaths

In the 5 Ragwitek® clinical trials provided by the applicant, there were no deaths reported.

8.4.2 Nonfatal Serious Adverse Events

There was one report of a treatment-related, life-threatening AE across the 5 clinical studies. This event occurred on Day 1 of study medication in a subject randomized to placebo and was assessed as "treatment-related" by the blinded investigator at the time of the event. Additional details related to this subject can be seen in the Medical Officer's and Epidemiologist's reviews.

8.4.3 Study Dropouts/Discontinuations

Within all studies submitted by the applicant, approximately 4% of treated subjects in the 6 Amb a 1-U treated group, approximately 4% of treated subjects in the 12 Amb a 1-U treated group, and approximately 1% of placebo treated subjects discontinued treatment. The reason for discontinuation varied, but the predominant reason for dropping out was local side effects, including GI disorders and respiratory disorders, including swelling and irritation in the mouth/tongue and oral region. There were 2 individuals who dropped out due to anaphylaxis, one in the 12 Amb a 1-U treatment group and 1 in the placebo treatment group.

Table 8.4.3.1) Discontinuation of Study Subjects due to AEs-First 28 Days

Number of Subjects	**6 Amb a 1-U (N=454)**	**12 Amb a 1-U (N=1057)**	**Placebo (N=757)**
Any Reason	**19 (4%)**	**46 (4%)**	**6 (1%)**
GI Disorder	12 (3%)	34 (3%)	1 (0%)
Respiratory	19 (4%)	24 (2%)	4 (1%)
Skin Disorder	4 (1%)	6 (1%)	2 (0%)
Analphylaxis	0 (0%)	1 (0%)	1 (0%)

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

A more detailed discussion related to dropouts and discontinuations is deferred to the medical officer and epidemiologist.

8.4.4 Common Adverse Events

The majority of adverse events that were observed and noted within the various studies were related to allergies (i.e., rhinoconjunctivitis symptoms) for both active treated and placebo treated patients. A summary of the common adverse events can be seen in the following table.

Table 8.4.4.1) Most Commonly Reported Treatment Related AEs in the 12 Amb a 1-U Dosage vs Placebo

	First 28 Days Ragwitek® (N=1057)	**First 28 Days Placebo (N=757)**	**Week 1-52 Ragwitek® (N=381)**	**Week 1-52 Placebo (N=386)**
Any	45.6%	20.5%	61.2%	25.4%
Oral pruritus	10.9%	2.0%	17.3%	2.6%
Oral paresthesia	10.0%	4.0%	8.4%	2.8%
Throat irritation	16.6%	3.3%	24.9%	4.4%
Ear pruritus	10.4%	1.1%	13.9%	1.6%
Mouth edema	6.1%	0.5%	9.2%	0.5%

Source: Table created by reviewing statistician utilizing data provided in:
----------(b)(4)----------

Overall, approximately 45% and 20% of subjects in the treatment and placebo groups, respectively, experienced adverse events in the first 28 days, while 61% and 25% of subjects in the treatment and placebo groups, respectively, experienced adverse events from week 1 to week 52. The majority of these adverse events were local reactions that involved the throat, nasal, and oral regions as well as the GI tract, which is to be expected when considering ragweed allergic individuals with symptoms noted at baseline. Further discussion and details related to common adverse events is deferred to the medical officer and epidemiologist.

8.4.5 Clinical Test Results

Clinical test results varied between and within the studies. However, endpoints including IgG, IgE, and other tests performed had results that were expected and not considered outside of normal ranges. Additional Details can be seen in the medical officer's review.

8.4.6 Systemic Adverse Events

There were few episodes of anaphylaxis or anaphylactic shock observed in any subjects within the submitted studies, with all issues resolving with epinephrine administration. Rarely (less than 1% of individuals) were uticaria and systemic rashes observed. Additional details related to systemic adverse events can be found in the medical officer's review.

8.4.7 Local Reactogenicity

There were local reactions noted in both the treated and placebo treated individuals, up to 20% and up to 3%, respectively, depending on the study. The majority of these adverse reactions were either gastro-intestinal or were irritation located in the administration site: the throat. The majority of these events were mild or moderate and all were self-limiting.

Additional details related to systemic adverse events can be found in the medical officer's review.

8.4.8 Adverse Events of Special Interest

Several adverse events of special interest were noted in the submitted studies. These involved symptoms related to anaphylaxis, some of which required administration of epinephrine. All issues were self-limiting and as per the applicant resolved by study completion.

8.5 Additional Safety Evaluations

Although this product had adverse events noted, these AEs were to be expected since this product is composed of the allergen the individuals are allergic to. All issues associated with these adverse events were self-limiting and resolved by study completion.

8.6 Safety Conclusions

Based on the observed safety data including AEs, this product frequently causes local AEs in the oral region, that are known to be associated with SLIT (since it is administered by mouth) in adult subjects. The data reviewed support the general conclusion that the incidence of severe or serious AEs associated with SLIT was not typically life-threatening and self-limiting. The single life-threatening episode was resolved by administering epinephrine to the individual, who was subsequently sent to a hospital but was not admitted because the issue had resolved. Additional details can be seen in the medical officer's and epidemiologist's reviews.

9. ADDITIONAL STATISTICAL ISSUES

No additional statistical issues were noted during the examination and re-analysis of the efficacy and safety data provided by the applicant.

9.1 Special Populations

No special populations were examined in any studies submitted within this BLA.

9.1.1 Human Reproduction and Pregnancy Data

There are no data regarding human reproduction or pregnancy provided within this submission.

9.1.2 Use During Lactation

There are no data regarding the use of this product in lactating individuals provided within this submission.

9.1.3 Pediatric Use and PREA Considerations

There are no data regarding the use of this product in pediatric individuals provided within this submission.

9.1.4 Immunocompromised Patients

There are no data regarding individuals with compromised immunity provided within this submission, particularly since immunocompromised subjects were excluded from the studies.

9.1.5 Geriatric Use

There are no data regarding geriatric use in individuals older than 65 years of age provided within any studies submitted by the applicant.

9.2 Aspect(s) of the Statistical Evaluation Not Previously Covered

The reviewer has no additional comments.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The data from the studies provided in this submission appear to support the applicant's conjecture that the Ragwitek® 12 Amb a 1-U product is safe and effective in the treatment of allergic rhinoconjunctivitis caused by ragweed pollen, using CBER's pre-specified criterion for efficacy based on the Combined Symptom score that incorporates both rescue medication and symptom scores. Furthermore, similar positive trends are observed for the individual endpoints of Total Symptom Scores as well as the Total Rescue Medication Scores for both the peak and the entire ragweed pollen season.

10.2 Conclusions and Recommendations

Based on the data submitted and reviewed, Ragwitek® 12 Amb a 1-U per dose, appears to be safe and effective for immunotherapy of allergic rhinoconjunctivitis due to sensitivity to any combination of the short ragweed (*Ambrosia artemisiifolia*) pollen included in the product for adults 18-65 years of age. Furthermore, the product appears to be safe and effective for adults 18-65 years of age, based on the statistical analyses performed and examined by the reviewing statistician.