BLA Clinical Review Memorandum

Application Type	Biologics License Application- Efficacy Supplement
STN	125478/293
CBER Received Date	6/17/2020
Non-PDUFA Goal Date	4/17/2021
Division / Office	DVRPA/ OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Anubha Tripathi, MD
Review Completion Date / Stamped Date	4/14/2021
Supervisory Concurrence	Kathleen Hise, MD Maria Allende, MD
Applicant	ALK-Abello A/S
Proper (Established) Name	Short Ragweed Pollen Allergen Extract (*Ambrosia artemisiifolia*)
(Proposed) Trade Name	Ragwitek
Pharmacologic Class	Allergenic Extract
Formulation, including Adjuvants, etc.	Extract
Dosage Form, Route of Administration	Tablet, Sublingual
Dosing Regimen	One tablet daily [each tablet contains: 12 *Ambrosia artemisiifolia* major allergen 1 Units (Amb a 1-U)] to be initiated at least 12 weeks before the expected onset of ragweed pollen season and continued throughout the season
Indication(s) and Intended Population(s)	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 persons 5 through 65 years of age. [Licensed indication (April 17, 2014): 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 in adults 18 through 65]
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIT	Allergen Immunotherapy
Amb a 1 U	Units of Amb a 1, the major component allergen of *Ambrosia artemisiifolia* (Short Ragweed)
ANOVA	Analysis of Variance
APAC	Allergenic Products Advisory Committee
AR	Allergic Rhinitis
ARC	Allergic Rhinitis with or without Conjunctivitis
BIMO	Bioresearch Monitoring Branch
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research (U.S. FDA)
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research (U.S. FDA)
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls (DBPAP/ OVRR/ CBER)
CRF	Case Report Form
CSR	Clinical Study Report
DB	Division of Biostatistics (OBE/ CBER)
DBPC	Double-Blind Placebo-Controlled
DE	Division of Epidemiology (OBE/ CBER)
DMC	Data Monitoring Committee
DMS	Daily Medication Score
DSS	Daily Symptom Score
E-Diary	Electronic Diary
EoE	Eosinophilic Esophagitis
FAS	Full Analysis Set
GCP	Good Clinical Practice
DVRPA	Division of Vaccines and Related Product Applications (OVRR/ CBER)
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
FEV1	Forced Expiratory Volume in 1 second
GI	Gastrointestinal
HLT	High-Level Term (terms per MedDRA)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgE	Immunoglobulin E
IM	Intramuscular
IP	Investigational Product
IR	Information Request
ITT	Intention to Treat
LABA	Long-acting Beta-agonist
LOCF	Last non-missing Observation Carried Forward
LS	Least Square

MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MG	Medication Guide
OBE	Office of Biostatistics and Epidemiology (CBER)
OVRR	Office of Vaccines Research and Review (CBER)
PDUFA	Prescription Drug User Fee Act
PEF	Peak Expiratory Flow
PeRC	Pediatric Review Committee
PI	Prescribing Information
PMC	Post-Marketing Commitment
PMR	Post-Marketing Requirement
PO	per oral (by mouth)
PP	Per Protocol
PREA	Pediatric Research Equity Act
PSP	Pediatric Study Plan
PT	Preferred Term (terms per MedDRA)
PVP	Pharmacovigilance Plan
QoL	Quality of Life
RS	Ragweed Season
SABA	Short-acting Beta-agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
sIgE	Specific Immunoglobulin E
sIgG4	Specific Immunoglobulin G subtype 4
SCIT	Subcutaneous Immunotherapy
SLIT	Sublingual Immunotherapy
SMQ	Standardized MedDRA Query
SOC	System Organ Class (terms per MedDRA)
SPT	Skin Prick Test
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCS	Total Combined Score
VEB	Vaccine Evaluation Branch (DB/ OBE/ CBER)
WAO	World Allergy Organization
WRO	Written Response Only

1. Executive Summary

On July 17, 2020, ALK-Abello A/S (the Applicant) submitted a biologics license application (BLA) supplement (STN 125478/ Amendment 293) to support licensure of Short Ragweed (*Ambrosia artemisiifolia*) pollen allergen extract (licensed product name: Ragwitek®) for use in children and adolescents 5 through 17 years of age. The proprietary name for this product, Ragwitek, will be used in this document. The original BLA for Ragwitek (STN 125478/ Amendment 0) was approved for licensure on April 17, 2014, 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 in adults 18 through 65 years of age. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), the Applicant was required to conduct studies to evaluate Ragwitek in children and adolescents 5 through 17 years of age (studies in this age group had not been completed at the time of the approval of this

product in adults). The proposed indication is, “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 approved for use in persons 5 through 65 years of age.” The product is sourced from short ragweed [*Ambrosia artemisiifolia* (Amb a)] pollen and consists of extracted, purified, (b) (4) ragweed pollen allergen extract (dose of 12 Amb a 1-U).

This BLA supplement includes efficacy and safety data from one phase 3 clinical study, Study P008. Study P008 was a phase 3, randomized, double-blind, placebo-controlled, multi-site clinical trial that evaluated the efficacy and safety of Ragwitek in 1,022 children and adolescents 5 through 17 years of age with a history of ragweed-induced rhinoconjunctivitis with or without asthma. Participants were randomized in a 1:1 ratio to receive Ragwitek or placebo once daily for approximately 20 to 28 weeks. To be eligible for inclusion, all participants had to have a Forced Expiratory Volume in 1 second (FEV1) ≥80% of predicted value at the Screening and Randomization Visits. Randomization was stratified by age group [5 through 11 years of age: n=410 (approximately 40%); 12 through 17 years of age: n=612 (approximately 60%)] and by presence or absence of a history of asthma. Three cohorts were recruited over 3 consecutive ragweed seasons to complete the enrollment goal. Each cohort underwent the following three periods: a screening period (up to one year prior to randomization), a pre-seasonal treatment period (approximately 12 to 20 weeks), and a co-seasonal treatment period (approximately 8 weeks). The first dose of Ragwitek was administered under medical supervision in a healthcare setting equipped to treat systemic allergic reactions, and subsequent doses were self-administered at home.

Efficacy was evaluated by self-reporting of rhinoconjunctivitis daily symptom scores (DSS) and daily medication scores (DMS), which were recorded in electronic diaries (e-diaries) by the participant or the participant’s parent/ guardian. The sum of the DSS and DMS equated to the Total Combined Score (TCS) (see Section 6.1.2 for details on the DSS and DMS). Each of these scores were enumerated over the peak and entire ragweed pollen seasons (RS) during which the trial was conducted. The primary efficacy endpoint was the comparison of the average TCS between the treatment and placebo groups in the FAS population over the peak RS. The pre-specified criteria for success were a treatment difference relative to placebo of at least -15% and an upper bound of the 95% confidence interval for this treatment difference no higher than -10%. Treatment with Ragwitek resulted in a lower average TCS over the peak RS relative to placebo of -38.3% [95% confidence interval (-46.0, -29.7)] which met the pre-specified criteria for success. The results of the primary analysis (FAS population) were corroborated by sensitivity analyses in the FAS population, a sensitivity analysis in the PP population, and subgroup analyses in the FAS population. Lower average scores were similarly demonstrated for each of the key secondary endpoints (treatment difference relative to placebo): average TCS during the entire RS, average rhinoconjunctivitis DSS during the peak RS, and average rhinoconjunctivitis DMS during the peak RS.

Safety data from Study P008 revealed that the majority (81.9%) of participants in the Ragwitek group reported at least 1 adverse event (AE) over the course of the study and that the proportion of participants with AEs was comparable between the 2 age groups. The most frequently reported adverse events in the Ragwitek group were throat irritation, oral pruritus, and ear pruritus. Discontinuation from the study due to an AE occurred in

3.9% of participants in the Ragwitek group and 1.0% in the placebo group. In the Ragwitek group, the most reported AE resulting in discontinuation was throat irritation, which occurred in 3 participants (0.6%), followed by pharyngeal edema (0.4%, n= 2), swollen tongue (0.4%, n=2), tongue ulceration (0.4%, n=2), lip swelling (0.4%, n=2), glossodynia (0.4%, n=2), and dysphagia (0.4%, n=2). The incidence of serious AEs (SAEs) overall was low (<2%) and similar in the Ragwitek and placebo groups.

Adverse events of special interest (AESIs) were pre-specified solicited and unsolicited local adverse reactions, systemic allergic reactions including anaphylaxis, events treated with epinephrine, severe edema of the mouth and/or throat, severe drug-related asthma exacerbations, eosinophilic esophagitis (EoE), abnormal liver function values, and overdose without adverse effect. The rates of local adverse events that are known to occur with sublingual immunotherapy (SLIT) (pre-specified solicited and unsolicited local adverse events) (45.8% in total) were higher in the Ragwitek group (64.5%, n= 331) compared to the placebo group (26.9%, n=137), with a similar distribution of rates for pre-specified solicited local adverse reactions. Pre-specified solicited local adverse reactions were of mild intensity, with onset within the first 10 days of treatment and of short duration (median of 30 minutes). Rates of systemic allergic reactions were low [Ragwitek group: 0.6% (n=3); placebo group: 0.2% (n=1)]; no cases of severe systemic allergic reactions (anaphylaxis) occurred during treatment. Two events were treated with epinephrine (one participant in the placebo group was treated with systemic epinephrine for urticaria and one participant in the Ragwitek group was treated with inhaled racemic epinephrine for laryngitis). There were no cases of severe local edema of the mouth and/or throat, severe drug-related asthma exacerbations, eosinophilic esophagitis, or abnormal liver function values. The most frequently reported AESI in both treatment groups was overdose (defined as taking more than 1 tablet per day of study treatment) without adverse effect (approximately 1% in both groups; Ragwitek group, n=6; placebo group, n=5). There was one overdose that occurred in the Ragwitek group (participant took 1 extra dose of Ragwitek), which resulted in oral pruritus of mild intensity which self-resolved; most cases of overdose were unintentional and were of two doses taken on the same day due to a result of memory lapse with regard to having already taken the daily dose.

Overall, the AE profile appeared similar in participants with and without asthma and those who did and did not use ICS. Of the participants with asthma, about one-third had inhaled corticosteroid (ICS) use at baseline; a higher proportion of participants using ICS at baseline in the Ragwitek group reported AEs compared with those in the placebo group.

The clinical data from Study P008 support the safety and effectiveness of Ragwitek in children and adolescents 5 through 17 years of age.

The pediatric study plan for Ragwitek initially included two studies: Study P008 was to evaluate both efficacy and safety in this pediatric population, and Study P009 was to supplement the safety database from Study P008 in this pediatric population (see Section 2.5 for details of the proposed pediatric study plan). After review of the data from Study P008, in which no new safety signals were identified that would require additional evaluation in this age group, CBER determined that the Applicant could be released from conduct of Study P009.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

A total of 80 study sites in 6 countries randomized at least 1 participant (listed by number of sites and percentage of participants randomized per country): United States (43 sites, 20.4%), Canada (6 sites, 24%), Croatia (7 sites, 7.7%), Hungary (8 sites, 14.1%), Serbia (10 sites, 15.7%), and Ukraine (6 sites, 18%). Review of demographic data (gender, age, race) for participants in Study P008 revealed a balanced distribution between the two study arms (Section 6.1.10, Table 9). The study population was 63% male which is consistent with the greater prevalence of allergic rhinitis among males in childhood. Approximately 60% of participants were adolescents 12 through 17 years of age and 40% were children 5 through 11 years of age. The study population was predominantly Caucasian (93%). The population size of non-Caucasian participants was small; therefore, subgroup analyses by race were not performed since interpretation of any treatment differences in the non-Caucasian populations is limited by small population size.

1.2 Patient Experience Data

Patient experience data were not submitted as part of this application.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Allergic rhinitis with or without conjunctivitis (ARC) is a worldwide disease affecting over 500 million people, including up to 60 million Americans, annually. ARC is among the most common chronic conditions affecting both children and adults. ARC can potentially impact asthma and is often associated with rhinosinusitis. ARC can have a major impact on quality of life (QoL); issues of QoL include disturbed sleep; daytime somnolence and fatigue; irritability; depression; impairment of physical and social functioning; and attention, learning, and memory deficits. Thirty-five percent to 50% of adults reported that nasal allergies have at least a moderate effect on their daily life. Sleep disturbances associated with rhinitis include difficulty falling asleep, staying asleep, and awakening refreshed. [1] The burden of allergic rhinitis in Europe is also substantial. In a 2004 study, approximately 23% of adults (19% in Spain, 29% in Belgium) were found to have clinically confirmed allergic rhinitis. [2]

ARC falls within a spectrum of chronic diseases driven by allergen-induced IgE-mediated and cell-mediated immune responses. ARC presents as a constellation of nasal and non-nasal symptoms including sneezing, anterior and posterior rhinorrhea, congestion, and ocular itching and congestion. Common environmental triggers include perennial allergens, such as house dust mites and cat dander, and seasonal allergens, such as grass and ragweed pollens. Polysensitization is common among individuals with allergic rhinitis; reported rates of prevalence of polysensitization in populations seeking medical care for allergic rhinitis range between 31% to 74%.[3] Allergic rhinitis commonly coexists with asthma, which typically develops after allergic rhinitis. It has been estimated that about 20 to 40% of individuals with allergic rhinitis also have asthma. Conversely, about 30 to 80% of individuals with asthma have allergic rhinitis. [4]

Ragweed pollen allergen is a major cause of seasonal ARC in the United States. Three of the 50 species of the genus *Ambrosia* (commonly known as ragweed) in the US predominate: short ragweed (*Ambrosia artemisiifolia*), giant ragweed (*Ambrosia trifida*),

and western ragweed (*Ambrosia psilostachya*). The most abundant of the three species that predominate is short ragweed, which thrives in disturbed soil such as roadsides, vacant lots, and tilled soil, and is the chief cause of late summer and fall ARC in the eastern half of the United States (growing most profusely in the Mississippi and Ohio river drainages, the lower Missouri river valley, and Ontario in Canada). Giant ragweed follows much the same pattern of occurrence but tends to grow in river bottoms. Western ragweed extends westward across the Rocky Mountains into areas where lack of sufficient rainfall limits short ragweed growth. There is a high degree of cross-reactivity among the ragweed species. [5] [6] [7] Ragweed is present in several areas in Europe, particularly the Rhone/Burgundy areas of France, northern Italy, Hungary, Croatia, the Czech Republic, the Ukraine, Austria, Bulgaria, Poland, and Slovakia. [5] [8] It is estimated that currently 33 million people in Europe are sensitized to various species of ragweed. [5] [9]

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

The treatment for ARC, allergen avoidance (e.g. staying indoors during ragweed pollen season), is usually hard to achieve and sustain. Therefore, clinical management typically relies on combined pharmacologic therapy regimens of steroids (intranasal) and antihistamines (oral, intranasal, and ocular) which provide temporary relief from allergic symptoms, but which may not be effective in all patients and are not disease-modifying. In addition, nasal rinsing with saline using over-the-counter kits is commonly recommended for symptom management.

Table 1 summarizes the efficacy of pharmacologic agents used to treat ARC. [11] A short discussion of each agent follows the table. [10] [11]

Table 1. Differential Response to Allergic Rhinitis Symptoms by Different Drug Classes as per ARIA (Allergic Rhinitis and its Impact on Asthma) Guidelines

Drug Class	Route of Administration	Most Effective	Moderately Effective	Least Effective
Antihistamines	p.o.	Sn, Rh, It	Op	Co
Antihistamines	i.n.	Rn	Sn, Co, It	Op
Corticosteroids	p.o./i.n.	Sn, Rh	Co, It	Op
Mast Cell Stabilizers	i.n.	-	-	Sn, Rh, It, Co, Op
Decongestants	i.n.	-	Co	Sn, Rh, It, Op
Decongestants	p.o.	-	-	Co, Sn, Rh, It, Op
Anticholinergics	i.n.	Rh	-	Sn, It, Op, Co
Antileukotrienes	p.o.	-	Co. Op	Sn, Rh, It

Abbreviations: p.o.= per os (by mouth), i.n.= intranasal, Sn= sneezing, Rh= rhinorrhea, It= nasal itching, Op= ophthalmic symptoms, Co= nasal congestion

Decongestants

Decongestants are often the first line of treatment for AR. Oral (e.g. pseudoephedrine) and topical decongestants (oxymetazoline) can be purchased without a prescription, are relatively inexpensive, and are non-sedating. Pseudoephedrine and other decongestants are vasoconstrictors that reduce tissue hyperemia, edema, and nasal congestion. The decongestants also increase the drainage of sinus secretions and opening of obstructed Eustachian tubes. Oral decongestants may cause hypertension, tachycardia, agitation,

and insomnia. One advantage of oral decongestants is that they do not cause rebound congestion (rhinitis medicamentosa), which may be a consequence of the topical preparations.

Antihistamines
Both oral and topical preparations of antihistamines are available without a prescription. Topical antihistamines (e.g. azelastine) are safe and have a rapid onset of action (~15 min), but don't affect co-morbid conditions such as conjunctivitis. Oral antihistamines, (e.g. loratadine) are also effective and have an onset of action ~1 hour. In contrast to topical antihistamines, oral antihistamines may reduce conjunctival and skin symptoms. Oral antihistamines are most effective when taken regularly, rather than on-demand, and, some patients are sedated by the second-generation antihistamines.

Chromones
The chromones (e.g. cromolyn, nedocromil) block mast cell degranulation and are also known as mast cell stabilizers. They are safe but require several applications per day and are among the least effective of available agents for the treatment of AR.

Anticholinergics
Topical anticholinergics (ipratropium bromide) are relatively safe and affect only rhinorrhea. They require several applications per day and may cause dry nose, epistaxis, glaucoma or urinary retention.

Antileukotrienes
Antileukotrienes may either be receptor-antagonists (montelukast) or inhibitors of leukotriene synthesis (zileuton). They are safe and effective but are associated with AEs such as headache and gastrointestinal symptoms.

Corticosteroids
Topical corticosteroids (fluticasone, mometasone, and others) are the effective anti-inflammatory agents that suppress all nasal symptoms and can affect conjunctival symptoms and enhance the quality of life. Reduction of symptoms does require long term use, and often they are used incorrectly, which may result in treatment failure or epistaxis. Oral corticosteroids are used for rescue treatment but are not indicated for long-term therapy for AR because of the well-known adverse events associated with systemic corticosteroid therapy.

2.3 Safety and Efficacy of Pharmacologically Related Products

Unlike avoidance and symptomatic therapy, allergen-specific immunotherapy offers the potential to reduce allergic symptoms and decrease the need for symptomatic treatment by increasing an individual's tolerability to a specific allergen. It is the only known treatment that modifies the immune response and treats the cause rather than the symptoms. Allergen immunotherapy (AIT) involves the administration of gradually increasing doses of the allergen over a period of time to desensitize the patient to the allergen. In the United States, the licensed routes of administration of allergen immunotherapy for inhalant allergens are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT).

Effectiveness of SCIT extracts is based on a 1985 publication by the Panel on Review of Allergenic Extracts, an advisory committee to the U.S. FDA (Implementation of Efficacy Review, Allergenic Extracts, Federal Register 1985).[12] There is no defined dose or regimen (i.e., standard versus accelerated) for SCIT, which is tailored to an individual patient and varies from one allergist-immunologist to another. In poly-sensitized individuals, SCIT prescriptions may be one or two different mixture of multiple allergens. SCIT is contraindicated in persons with severe, unstable, or uncontrolled asthma. Despite the documented benefits of SCIT, only 5% of the US population with allergic rhinitis, asthma, or both receive SCIT due to: the level of discomfort associated with SCIT; the inconvenience of the frequency of administration of the injections; the inconvenience of delivery of SCIT, which is required to occur in a monitored healthcare setting due to the risk of systemic allergic reactions associated with SCIT; and the risks of occurrence of local and systemic allergic reactions associated with SCIT. The most common adverse reactions occurring in over 26 to 82% of all patients who receive SCIT are local adverse reactions at the injection site (e.g., erythema, itching, swelling, tenderness, pain). Systemic adverse reactions, occurring in ≤ 7% of patients, include generalized skin erythema, urticaria, pruritus, angioedema, rhinitis, wheezing, laryngeal edema, and hypotension.

Though the mechanism of SLIT is complex and not fully characterized, administration and absorption of allergens through the oral and gingival mucosa through the sublingual route can decrease the allergic response through desensitization to the allergen, at least temporarily and potentially permanently (i.e., tolerance).

A Cochrane review suggested that SLIT is a viable alternative to SCIT with a significantly lower risk profile and little difference in overall efficacy.[13] Notably, the lower incidence of severe or serious adverse events associated with SLIT allows SLIT to be self-administered at home while safe use of SCIT requires administration in a clinic that is capable of treating systemic allergic reactions. However, as with SCIT products, SLIT is contraindicated in persons with severe, unstable, or uncontrolled asthma. Unlike SCIT products, SLIT products are used according to defined dosing regimens.

SLIT products approved for licensure in the US to date (Table 2) are: Grastek®, Oralair®, Ragwitek®, and Odactra®. Grastek® (Timothy Grass Pollen Allergen Extract, Tablet for Sublingual Use), a sublingual immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens, was approved for use in persons 5 through 65 years of age in the US in 2014 (this product was approved under the name Grazax® in the EU). Oralair® (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract, Tablet for Sublingual Use), a sublingual immunotherapy for the treatment of confirmed grass pollen-induced allergic rhinitis with or without conjunctivitis for any of the five grass pollens contained in the product, was approved for use in the US in persons 10 through 65 years of age in 2014 and in persons 5 through 9 years of age in 2018. Odactra® (House Dust Mite Pollen Allergen Extract, Tablet for Sublingual Use), a sublingual immunotherapy for house dust mite-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts, was approved for use in adults 18 through 65 years of age in the US in 2017.

Table 2. Sublingual Allergen Immunotherapy Products Currently Approved for Licensure in the United States

Proper Name (Dose, Schedule)	**Indication**	**Approval Date/ Age Range (Trade Name)**
Timothy Grass Pollen Allergen Extract (2,800 BAU, 1 tablet daily)	Treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens in persons 5 through 65 years of age	2014/ persons 5 through 65 years of age (Grastek®)[1]
Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract (300 IR, 1 tablet daily in persons 18 through 65 years of age; 100 IR, 1 tablet daily in persons 5 through 17 years of age)	Treatment of confirmed grass pollen-induced allergic rhinitis with or without conjunctivitis for any of the five grass pollens contained in the product in persons 5 through 65 years of age	2014/ persons 10 through 65 years of age (Oralair®) 2018/ persons 5 through 9 years of age (Oralair®)
Short Ragweed Pollen Allergen Extract (12 Amb a 1-U, 1 tablet daily)	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 in persons 18 through 65 years of age	2014/ persons 18 through 65 years of age (Ragwitek®)[2]
House Dust Mite Pollen Allergen Extract (12 SQ-HDM, 1 tablet daily)	Treatment of house dust mite-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts in persons 18 through 65 years of age	2017/ persons 18 through 65 years of age (Odactra®)

Abbreviations: BAU= Bioequivalent Allergen Units, IR= Index of Reactivity, Amb a 1-U= Units of *Ambrosia artemisiifolia* major allergen 1, SQ-HDM= the dose unit for Odactra (SQ is a method of standardization of biological potency, major allergen content, and complexity of the allergen extract; HDM= house dust mite)
[1] Approved in the European Union under the trade name Grazax®
[2] Approved in Canada under the trade name Ragwitek® in 2014 and approved in 9 European countries (Austria, Czech Republic, France, Hungary, Italy, Romania, Slovakia, Slovenia, and Germany) and Russia under the trade name of Ragwizax® in 2017

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

The clinical development of Ragwitek, a sublingual immunotherapy tablet containing a pharmaceutical formulation of 12 Amb a 1-U of short ragweed pollen extract, was conducted under five clinical studies, of which two were Phase 2/3 clinical safety and

efficacy studies (Study P05233 and Study P05234, BLA STN 125478). In Study P05233, 565 adult participants 18 through 50 years of age from the US and Canada were administered Ragwitek (12 Amb a 1-U or 6 Amb a 1-U; n= 190) or placebo (n= 188) for approximately 52 weeks beginning approximately 16 weeks prior to the start of and throughout the 2010 ragweed pollen season (study completed May 2011). The primary objective was to evaluate the efficacy of Ragwitek versus placebo in the treatment of ragweed pollen-induced rhinoconjunctivitis based on the TCS during the peak ragweed pollen season. The percent change in the TCS was -26.5% (95% CI -38.7%, -14.6%) in the 12 Amb a 1-U group compared to the placebo group. In Study P05234, 784 adult participants 18 through 50 years of age from the US, Canada, Hungary, Ukraine, and Russia were administered Ragwitek [12 Amb a 1-U (n= 194), 6 Amb a 1-U (n=195), 1.5 Amb a 1-U (194)] or placebo (n=198) for approximately 52 weeks beginning approximately 16 weeks prior to the 2010 ragweed season (study completed May 2011). The primary objective was to evaluate the efficacy of Ragwitek versus placebo in the treatment of ragweed pollen-induced rhinoconjunctivitis based on the TCS during the peak ragweed pollen season. The percent change in the TCS was -24.2% (95% CI -36.5%, -11.3%) in the 12 Amb a 1-U group compared to the placebo group. In the trials that included participants greater than 50 years of age, 216 participants received 12 Amb a 1-U of Ragwitek and 167 participants received placebo. Of the participants that received Ragwitek, 194 participants were 50 through 64 years of age, 17 participants were 65 through 74 years of age, and 5 participants were 75 through 85 years of age. The data from both trials met the pre-specified statistical criteria for success; Ragwitek® was approved for use in the US in 2014 for the treatment of ARC due to Short Ragweed Pollen Allergy in adults 18 through 65 years of age (see Ragwitek Summary Basis of Regulation and Clinical Review Memorandum for details).

> *Reviewer Comment:*
> *The pre-specified statistical criteria for success for the two Phase 2/3 studies discussed above was the same as that for Study P008. Per the Clinical Review Memorandum (STN 125478/0): "CBER considers the point estimate of the improvement in the TCS of 15% over placebo as clinically significant, and an upper limit of the 95% CI of < -10% as statistically acceptable. Thus, CBER's pre-specified criteria for efficacy to support U.S. licensure included a point estimate difference between treatment and placebo of -15% and an upper bound of the 95% CI of that difference of ≤ -10%."*

The product was also approved in Canada under the trade name of Ragwitek® in 2014 and in 9 European countries (Austria, Czech Republic, France, Hungary, Italy, Romania, Slovakia, Slovenia, and Germany) and Russia in 2017 under the trade name of Ragwizax®, for the treatment of short ragweed pollen-induced AR, with or without conjunctivitis, in adults.

Post-marketing exposure is based on an estimated cumulative patient exposure of (calculated as treatment years of the ragweed SLIT tablet) approximately 14,070 treatment years worldwide. As of October 9, 2019, a total of 381 individual case safety reports from post-marketing sources have been reported to the Applicant for patients treated with the ragweed SLIT tablet. Of these, 45 reports were serious including 99 serious adverse events. A tabulation of all serious events from post-marketing sources (spontaneous, literature, other organized data collection systems) reported to the Applicant as of October 9, 2019 was provided in the appendix of the Summary of Clinical

Safety (Module 2.7.4, Appendix 7.4). This tabulation revealed the following cases of systemic allergic reactions (by preferred term): anaphylactic reaction (9 cases, spontaneously reported/ unsolicited; 3 cases, solicited), anaphylactic shock (1 case, spontaneously reported/ unsolicited), anaphylactoid reaction (1 case, spontaneously reported/ unsolicited), drug hypersensitivity (1 case, spontaneously reported/ unsolicited), and hypersensitivity (1 case, spontaneously reported/ unsolicited). It also revealed the following cases that were either diagnosed as EoE or may be a sign of development of EoE: EoE (1 case, spontaneously reported/ unsolicited), dysphagia (1 case, spontaneously reported/ unsolicited), choking (2 cases, spontaneously reported/ unsolicited).

No new safety concerns were identified during the period of review that impacted the benefit-risk profile of the ragweed SLIT-tablet, and the overall benefit-risk profile for the ragweed SLIT-tablet was evaluated to remain positive (for further details, see Summary of Clinical Safety, section 6.1).

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

This is a supplemental BLA submission containing safety and efficacy data to support U.S. licensure of Ragwitek for use in children and adolescents 5 through 17 years of age. The original BLA for Ragwitek®, was previously submitted for the adult population 18 through 65 years of age under STN 125478 and was approved for licensure in this population in 2014.

Reviewer Comment (Note to reader):

- *The timing of the correspondence on the pediatric plan for this product pre-dated the implementation of the Pediatric Study Plan (PSP) procedure under the Food and Drug Administration Safety and Innovation Act (FDASIA) 2012 amendment; therefore, there is no official Agreed iPSP document for this product in the pediatric study population. Key correspondence between FDA/ CBER and the Applicant (Merck Sharp & Dohme Corp. in collaboration with ALK-Abello A/S) on the pediatric study plan is detailed below.*
- *The Sponsor of Study P008 was Merck, Sharp, & Dohme Corporation (a subsidiary of Merck & Co., Inc.). The Applicant of the BLA is ALK-Abelló A/S (the owner of the IND and BLA). Since most documents submitted to the BLA were submitted by both entities in combination, the two entities will herein be referred to collectively as 'the Applicant.'*

<u>Pre-Submission:</u>
The following timeline includes a list of major clinical pre-submission regulatory activity associated with the submission of this sBLA (with key agreements reached/ decisions made/ information confirmed listed under the respective regulatory activity):

- June 27, 2013: The Applicant submitted a Response to an FDA Request for Information document (STN 125478/0/5) (initial Request for Information from FDA/ CBER dated May 24, 2013) in which they included the following requests for waivers and deferrals for studies assessing the safety and efficacy of Ragweed AIT for the treatment of ragweed-pollen induced allergic rhinitis with or

without conjunctivitis in segments of the pediatric population and a detailed synopsis of the pediatric study requested for deferral:
    - a waiver for pediatric studies in children less than 5 years of age on the basis that "the drug product does not represent a meaningful therapeutic benefit in this population. Seasonal allergic rhinitis typically does not develop until at least 2 years of age, and at least two seasons of pollen allergen exposure are needed before it becomes clinically relevant. As recommended in the allergen immunotherapy treatment guideline, using allergen immunotherapy to treat allergic rhinitis in children under the age of 5 years is considered a Special Consideration. Allergen immunotherapy for inhalant allergens is usually not considered in the very young because there might be difficulty in communicating with the child regarding systemic reactions."
    - a deferral for pediatric studies in children and adolescents 5 to 17 years of age until after approval of the licensure of Ragwitek in adults
- April 17, 2014: Ragwitek was licensed in persons 18 through 65 years of age (STN 125478/0). Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), ALK-Abello A/S was required to conduct study(ies) to evaluate Ragwitek in children and adolescents 5 through 17 years of age [study(ies) in this age group had not been completed at the time of the approval of this product in adults]. The pediatric study requirement for children less than 5 years was waived because necessary studies were stated as impossible or highly impracticable because the number of children younger than 5 years of age with allergic rhinitis who have been diagnostically confirmed with sensitivity to Short Ragweed pollen is too small.
- March 24, 2014: The Applicant submitted a revised pediatric study plan (STN 125478/0/24) in response to CBER requests, in which the Applicant incorporated feedback received from CBER. Prior CBER feedback on the initial pediatric plan proposal included the following requests:
    - the pivotal efficacy and safety trial must be powered to demonstrate at least -15% treatment difference relative to placebo along with the associated upper bound of the 95% confidence interval be at least -10% for the primary endpoint
    - the proportion of children between 5-11 years and 12-17 years be equally stratified
    - the number of children exposed in the overall pediatric program should be adequate to detect severe or systemic reactions which occur with a frequency of 0.2-0.3%

  In total, the Applicant estimated that approximately 1,000 ragweed allergic children between 5 and 17 years of age treated with Ragwitek would need to be included in the program to meet the CBER requests. Based on the Applicant's prior experience conducting studies in this age range, the Applicant stated that this large program would require recruitment from pediatric sites globally over several years. To meet the required efficacy and safety requirements, the Applicant proposed two trials:
    - Deferred pediatric study, protocol #P008, under PREA to evaluate both safety and efficacy of Ragwitek 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 in pediatric participants aged 5 to 17 years.
    - Projected dates: Final Protocol Submission: December 31, 2014; Study Completion Date: December 31, 2018; Final Report Submission: September 30, 2019
  - Deferred pediatric study, protocol #P009, under PREA to evaluate safety of Ragwitek 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 in pediatric participants aged 5 to 17 years.
    - Projected dates: Final Protocol Submission: June 30, 2016; Study Completion Date: September 30, 2017; Final Report Submission: September 30, 2019

  The Applicant proposed the above 2 trials to satisfy FDA's efficacy and safety requirements. With this program, the Applicant stated in summary that efficacy will be demonstrated in children and adolescents 5 to 17 years of age with a treatment difference of at least -15% (point estimate) as well as the minimal clinically important difference (MCID) of the upper limit of the 95% confidence interval at least -10% and that the overall pediatric program will include approximately 1000 participants exposed t12 Amb a 1-U for the duration of the proposed pre-and co-season treatment period and will allow for the detection of AEs that occur less commonly.
- May 15, 2015: Applicant submitted Study P008 Protocol version 1.0 (IND 12970/100). This study was completed in November 2018.
- July 3, 2019: Applicant submitted Study P008 Clinical Study Report (STN 125478/279).
- July 10, 2019: Applicant submitted Type C Meeting Request and Meeting Package (IND 12970/159) stating the purpose of the meeting as follows: "On the background of the recently obtained data from pediatric study P008, ALK wishes to discuss the pediatric development program for Ragwitek and the contribution of the two required post-marketing studies to the evaluation of efficacy and safety in children and adolescents 5 through 17 years of age. Specifically, the purpose of this type C meeting is to obtain the Agency's concurrence on:
  - acceptance to review P008 data as part of a supplemental BLA filing with the purpose of having the results reflected in the Prescribing Instructions
  - provided a positive review outcome, that based on the body of evidence obtained in the P008 trial, the indication can be extended to include the age group 5 through 17 years of age
  - provided the indication is extended to include the age group 5 through 17 years of age, the Applicant is released from the commitment to conduct the planned supplementary pediatric safety trial RT-02 (previously referred to as P009)
  - the proposed data package and the format of the standardized data for the P008 trial supporting the supplemental BLA submission."
- Sept. 18, 2019: A Type C Meeting Written Response Only (WRO) document (CRMTS#11982, dated Sept. 18, 2019) was issued by CBER to provide responses (see summary below) to the Applicant's questions.
  - CBER concurred that data from Study P008 could be submitted as a clinical efficacy supplement to the Applicant's existing BLA stating that, "a determination as to whether the clinical data from Study P008 will support

an indication to include children and adolescents 5 through 17 years of age will be made during the course of our review."
    - CBER agreed that "the efficacy results from Study P008 are adequate to support filing of a supplemental BLA for our review."
    - CBER anticipated that the Applicant "may be released from conducting Trial RT-02 provided that the assessment of Study P008 supports your proposed indication and no new safety signals that would require additional evaluation in the 5 through 17 age group are identified."
- July 17, 2020: The BLA supplement (STN 125478/293) containing safety and efficacy data for Ragwitek in children and adolescents 5 through 17 years was submitted.

Post-Submission:

- February 9, 2021: A meeting with the FDA's Pediatric Review Committee was held in which the findings of Study P008 and CBER's proposed release of the Applicant from the requirement to conduct Study P009 as initially proposed in the pediatric study plan were discussed (see Reviewer Comment below for further details). The Pediatric Review Committee determined that the Applicant has fulfilled the PMR for pediatric studies assessing the safety and efficacy of Ragweed AIT for the treatment of ragweed-pollen induced allergic rhinitis with or without conjunctivitis.

    Reviewer Comment:
    'Study P009' was re-named by the Applicant to 'Trial RT-02' as stated above; this study is referred to as 'Study P009' in this review.

    As noted above, Study P009 was originally proposed by the Applicant in response to a past CBER request (made in 2014) that approximately 1,000 ragweed allergic children and adolescents (5-17 years of age) be exposed to the ragweed SLIT-tablet in order to detect severe systemic allergic reactions (due to the frequency at which these occur in the allergic population: 0.2-0.3%). Study P009 was to supplement the safety database in this pediatric population with an additional 500 participants exposed to the investigational product.

    The final Clinical Study Report for Study P008 was submitted to STN 125478/279 on July 3, 2019. A request for a Type C Meeting was also submitted by the Applicant shortly thereafter to discuss whether data from Study P008 would be sufficient to submit as a clinical efficacy supplement to support approval of Ragwitek in children and adolescents 5 through 17 years of age such that the Applicant could be released from the requirement to conduct Study P009. CBER concurred that the data from Study P008 could be submitted in a clinical efficacy supplement and that the sufficiency of the data to support approval in children and adolescents 5 through 17 years of age would be determined during the review and indicated that determination of the release from conduct of Study P009 would be based on whether data from Study P008 supports use in children and adolescents 5 through 17 years of age and that no new safety signals are identified that would require additional evaluation in this age group.

After review of the data from Study P008, which supports use of Ragwitek in this age range and in which no new safety signals were identified that would require additional evaluation in this age group, CBER proposed to the Pediatric Review Committee (PeRC) that the Applicant be released from Study P009. Additional considerations presented to PeRC for this release were the approval of two sublingual allergen immunotherapeutic products for licensure in the pediatric population (which occurred subsequent to proposal of the pediatric study plan in 2014 for Ragwitek) based on data from sample sizes similar to the sample size of Study P008. PeRC agreed with the assessments provided by CBER with regard to the adequacy of the safety and efficacy data to support approval of Ragwitek for licensure in children and adolescents 5 through 17 years of age and with regard to release of the Applicant from the PMR Study P009.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The application was, in general, organized to accommodate the conduct of a complete clinical review.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The Applicant attested that the studies submitted in support of this application were conducted in compliance with Good Clinical Practices through provision of the following statement in the Clinical Study Report for Study P008: "This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human participants participating in biomedical research."

3.3 Financial Disclosures

For Study P008, financial disclosure information was submitted for Merck Sharp & Dohme Corporation (the Sponsor of the IND, referred to as the Sponsor) by ALK-Abelló A/S (owner of the IND and BLA, referred to as the Applicant).

Covered clinical study (name and/or number):		
Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 103		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided?	Yes ☐	No ☒ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason?	Yes ☒	No ☐ (Request explanation from applicant)

Reviewer Comment:
Both the Sponsor and the Applicant submitted Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) to the BLA. The Sponsor additionally submitted Form FDA 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators). Financial disclosure information summarized in the table below was obtained from: these forms, the document entitled, "Summary of Financial Disclosures" submitted to Module 1.3.4 of the BLA, and the document entitled, "List of Investigators and Independent Ethics Committees" submitted to Module 5, Section 16.1.3.1 of the BLA.

Note that the number of investigators listed above does not include the sub-investigators.

A description of steps taken to minimize potential bias was not provided with the original submission (STN 125478/293/0); therefore, an IR was sent to the Applicant to obtain this information. A response was received from the Applicant (STN 125478/293/14) stating that a description of the steps taken to minimize the potential bias of clinical study results was not provided as this was deemed unnecessary since the 1 investigator with disclosable financial interests/ arrangements did not randomize any participants in Study P008.
The Applicant also confirmed in the response to this IR that the due diligence process was not undertaken for any of the 103 investigators that randomized participants since none had any disclosable financial interests/arrangements (thereby obviating the need for provision of attachments with reasons). The Applicant's response to this IR satisfactorily addressed these issues.

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

4.1 Chemistry, Manufacturing, and Controls

This submission did not include new Chemistry, Manufacturing, and Controls (CMC) data. Please see the CMC review memorandum for STN 125478/0 for details.

4.2 Assay Validation

Not applicable.

4.3 Nonclinical Pharmacology/Toxicology

Not applicable.

4.4 Clinical Pharmacology

Not applicable.

4.4.1 Mechanism of Action

The precise mechanisms of action of allergen-specific sublingual immunotherapy have not been established.

> *Reviewer comment:*
> *Although the precise mechanisms of action are not known, pharmacokinetic studies have demonstrated that sublingually delivered allergen extracts are captured by mucosal dendritic cells and transported to local draining lymph nodes. [14] A recent review of animal and human data have presented molecular and cellular changes associated with allergen immunotherapy in a temporal framework. Early on, there is suppression of mast cell and basophil degranulation. This is followed by induction of regulatory T and B cells and suppression of pro-allergic Th2 cells in peripheral blood. Late effects include reduction in numbers of pro-allergic cells (i.e., mast cells, eosinophils) residing in mucosal tissues. [15]*

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistics

A complete statistical review of the clinical study submitted to the BLA was conducted by Mridul K. Chowdhury within CBER's Office of Biostatistics and Epidemiology (OBE)/ Division of Biostatistics (DB)/ Vaccine Evaluation Branch (VEB) who verified the safety data, efficacy data, and analyses submitted to the BLA. Please see the biostatistical review memorandum for a detailed discussion of these analyses.

4.6 Pharmacovigilance

A complete review of the pharmacovigilance plan (PVP) (submitted to STN 125478/293/1) was conducted by Dr. Jonathan Reich, MD within CBER's Office of Biostatistics and Epidemiology (OBE)/ Division of Epidemiology (DE)/ Pharmacovigilance Branch. Please see the pharmacovigilance review memorandum for details.

The Applicant proposed the following changes to the PVP:

1. Removal of two previously identified important safety risks from specific monitoring:
    a. acute worsening of asthma symptoms (exacerbations)
    b. serious local reactions with the potential to compromise the airway
2. Addition of a safety risk for specific monitoring: Eosinophilic esophagitis
3. Removal of the following specific "missing" populations from labeling:
    a. Pediatrics (<18 years of age)
    b. Pregnancy, Lactation
    c. Co-administration of grass and ragweed immunotherapy

The final recommendations of the review with respect to the proposed PVP were as follows (please see DE review memorandum for details):

- DE disagreed with the Applicant's proposed change of removal of "acute worsening of asthma symptoms (exacerbations)" and "serious local allergic reactions with potential to compromise airway" from the pharmacovigilance plan (PVP) and recommended that the PVP continue to include these as Important Potential Risks as these risks continue to be adverse events of special interest (AESI) to the FDA, and we continue to further characterize and evaluate these risks as we obtain additional data from post-marketing use.
- DE agreed to the Applicant's proposed change of removal of 'pediatric populations' as the submitted study P008 provides data relevant to this population.
- DE acknowledged the Applicant's proposed change of removal of 'Pregnancy, Lactation' and 'Co-administration of Ragweed AIT with Grass AIT' from the Missing Information section of the PVP based on an effort to align with the Applicant's global risk management plan (RMP) in accordance with the European Medicines Agency (EMA) guidance. DE requested that the Applicant provide any available updates on 'Pregnancy, lactation' and 'Co-administration of Ragweed AIT with Grass AIT' in their periodic safety reports.

These recommendations were communicated to the Applicant who agreed to amend the PVP as recommended by DE (STN 125478/293/9 and 10). The review concluded that the agreed upon changes to the PVP were adequate and acceptable and that DE will continue surveillance, including routine activities and review of ongoing post-marketing commitments (PMCs).

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

5.1 Review Strategy

Investigation of safety and efficacy of Ragwitek in the pediatric population was performed under STN 125478 in one clinical trial (125478/279: Clinical Study Report for Study P008) to support the use of Ragwitek in children and adolescents 5 through 17 years of age. Study P008, a phase 3, randomized, double-blind, placebo-controlled trial in children and adolescents 5 through 17 years of age, was reviewed to support efficacy and safety (see Section 6 Discussion of Individual Studies/ Clinical Trials).

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following served as the basis for the clinical review of STN 125478/293:

- 125478/293/0:

    - Module 1.2 Cover Letter
    - Module 1.3.4 Certification and Disclosure of Financial Interests and Arrangements of Clinical Investigators
    - Module 1.6 Meetings
    - Module 1.14 Labeling
    - Module 2
        - Module 2.2 Introduction
        - Module 2.5 Clinical Overview
        - Module 2.7 Clinical Summary (Summary of Clinical Efficacy, Summary of Clinical Safety, Synopses of Individual Studies)
    - Module 5 Clinical Study Reports
- 125478/293/0, 6, 11, 13, 15, 16: Labeling [Prescribing Information (PI) and Medication Guide (MG)] Review
- 125478/293/14: Applicant response to information request (IR) on Financial Disclosure
- Review Memoranda from CBER/OBE [DB (Biostatistics), DE (Pharmacovigilance)]

5.3 Table of Studies/Clinical Trials

Table 3. Summary of Pediatric Clinical Studies of Ragwitek in Participants 5 through 17 years of age

Trial ID **Study Dates** (month/ year) **Trial Design**	**Study Arms** **Treatment Duration**	**Study Endpoints**	**N**	**Study Population** (years of age)	**Countries** (# of study sites)
P008 7/2015 – 11/2018 Phase 3, R, DB, PC	Ragwitek 12 Amb a 1 Units sublingual daily: Placebo 1 tablet sublingual daily (1:1) Stratified by age group (5 through 11 years of age, 12 through 17 years of age) and by presence or absence of asthma	Efficacy *Primary*: - Average TCS, peak RS *Key Secondary:* - Average TCS, entire RS - Average DSS, peak RS - Average DMS, peak RS Safety - % prespecified local application site reactions - % reporting systemic allergic reactions including anaphylaxis - % treated with epinephrine	1,022 (Ragwitek: n= 512; placebo: n=510) 5 through 11 years of age: n=410 (40.1 %) 12 through 17 years of age: 612 (59.9 %)	5 through 17 ARC due to Short Ragweed Pollen (with or without asthma) Diagnosed by positive SPT and specific IgE to Short Ragweed	US (43), CA (6), Croatia (7), Hungary (8), Serbia (10), Ukraine (6) (80 study sites in total)

Source: Adapted from BLA 125478/293/0: Tabular Listing of All Clinical Studies, p. 4; Clinical Overview, Section 1.5, p.7-12.
Abbreviations: R= randomized; DB= double-blind; PC= placebo-controlled; RS= Ragweed Season; TCS= Total Combined Score; DSS= Daily Symptom Score; DMS= Daily Medication Score; N= Number of participants (includes all participants who were randomized and received at least one dose of treatment; ARC= Allergic rhinoconjunctivitis; SPT= skin prick test; US= United States; CA= Canada

5.4 Consultations

Not Applicable

5.4.1 Advisory Committee Meeting (if applicable)

Not Applicable

5.4.2 External Consults/Collaborations

Not Applicable

5.5 Literature Reviewed

1. Dykewicz MS, Wallace DV, Amrol DJ, Baroody FM, Bernstein JA, Craig TJ, Dinakar C, Ellis AK, Finegold I, Golden DBK, Greenhawt MJ, Hagan JB, Horner CC, Khan DA, Lang DM, Larenas-Linnemann DES, Lieberman JA, Meltzer EO, Oppenheimer JJ, Rank MA, Shaker MS, Shaw JL, Steven GC, Stukus DR, Wang J; Chief Editor(s):, Dykewicz MS, Wallace DV; Joint Task Force on Practice Parameters:, Dinakar C, Ellis AK, Golden DBK, Greenhawt MJ, Horner CC, Khan DA, Lang DM, Lieberman JA, Oppenheimer JJ, Rank MA, Shaker MS, Stukus DR, Wang J; Workgroup Contributors:, Dykewicz MS, Wallace DV, Amrol DJ, Baroody FM, Bernstein JA, Craig TJ, Finegold I, Hagan JB, Larenas-Linnemann DES, Meltzer EO, Shaw JL, Steven GC. Rhinitis 2020: A practice parameter update. J Allergy Clin Immunol. 2020 Oct;146(4):721-767.
2. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J. 2004 Nov;24(5):758-64.
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11. Mandhane SN, Shah JH, Thennati R. Allergic rhinitis: an update on disease, present treatments and future prospects. Int Immunopharmacol. 2011 Nov;11(11):1646-62.
12. Panel on Review of Allergenic Extracts, an advisory committee to the U.S. FDA. Implementation of Efficacy Review, Allergenic Extracts. 50 Fed. Reg. 3085 (1985), Wednesday, January 23, 1985, p. 2947- 3306.
13. Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev. 2010 Dec 8;(12):CD002893.
14. Frati F, Moingeon P, Marcucci F, et al. Mucosal immunization application to allergic disease: sublingual immunotherapy. Allergy Asthma Proc. 2007; 28: 35-39.
15. Akdis M and Akdis CA. Mechanisms of allergen-specific immunotherapy: Multiple suppressor factors at work in immune tolerance to allergens. J Allergy Clin Immunol 2014; 133(3):621-31.

16. Wegienka G, Johnson CC, Zoratti E, Havstad S. Racial differences in allergic sensitization: recent findings and future directions. Curr Allergy Asthma Rep. 2013 Jun;13(3):255-61.
17. Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, Bousquet J, Calderón M, Compalati E, Durham SR, van Wijk RG, Larenas-Linnemann D, Nelson H, Passalacqua G, Pfaar O, Rosário N, Ryan D, Rosenwasser L, Schmid-Grendelmeier P, Senna G, Valovirta E, Van Bever H, Vichyanond P, Wahn U, Yusuf O. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J. 2014 Mar 28;7(1):6.
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6. Discussion of Individual Studies/Clinical Trials

6.1 Study P008

Study Title:
A Phase III, Randomized, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of RAGWITEK, a Ragweed (*Ambrosia artemisiifolia*) Sublingual Immunotherapy Tablet, in Children with a History of Ragweed-Induced Rhinoconjunctivitis With or Without Asthma

6.1.1 Objectives (Primary, Secondary)

The primary objective was to evaluate the efficacy of Ragwitek sublingual immunotherapy tablet (12 Amb a 1-U) versus placebo in the treatment of children and adolescents 5 to 17 years of age with ragweed-induced rhinoconjunctivitis, with or without asthma, based on the Total Combined Score (TCS) [sum of rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS)] averaged over the peak ragweed season (RS) and to assess the overall safety of Ragwitek (12 Amb a 1-U) in children and adolescents 5 to 17 years of age with ragweed-induced rhinoconjunctivitis, with or without asthma.

The secondary objectives were to compare the following between the Ragwitek (12 Amb a 1-U) and placebo groups:

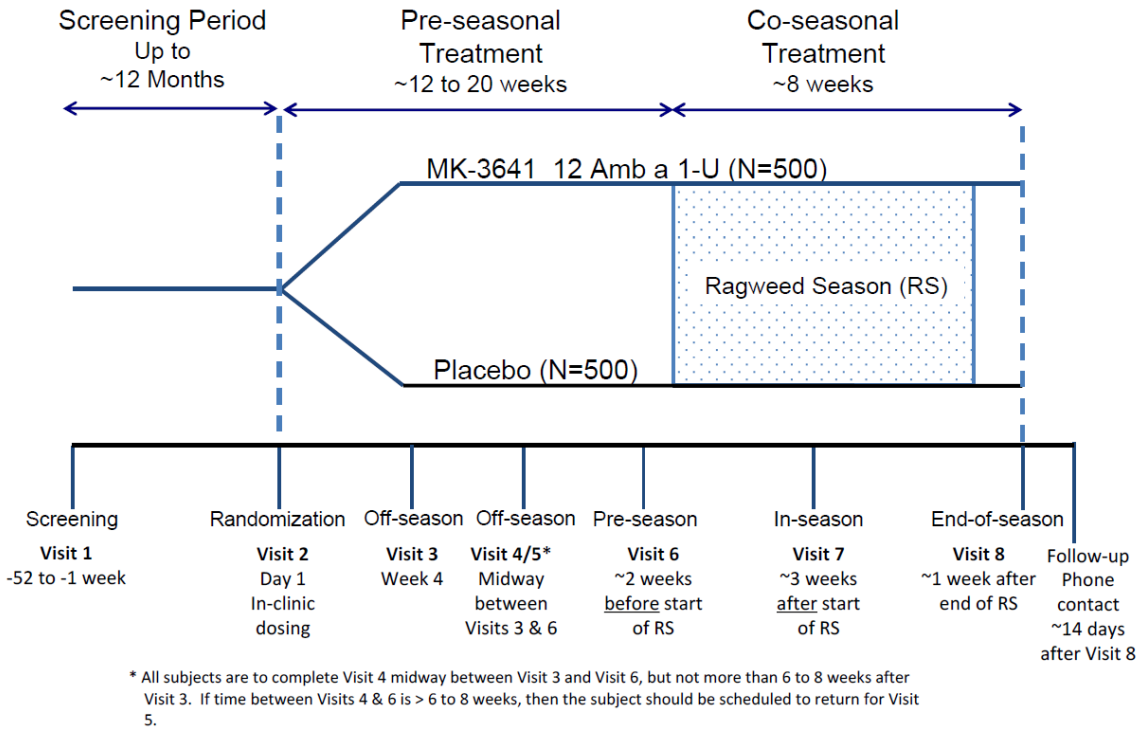
- Average TCS during the entire RS
- Average rhinoconjunctivitis DSS during the peak RS
- Average rhinoconjunctivitis DMS during the peak RS

6.1.2 Design Overview

Study P008 was a phase 3, randomized, placebo-controlled, double-blind, multi-site clinical trial that evaluated the efficacy and safety of Ragwitek, a sublingual tablet containing 12 Amb a 1 Units of ragweed pollen allergen extract, in children and adolescents 5 through 17 years of age with a history of ragweed-induced rhinoconjunctivitis with or without asthma. A total of 1,002 children were randomized in a 1:1 ratio to or placebo once daily for approximately 20 to 28 weeks. Randomization was stratified by age group (5 to 11 years or 12 to 17 years) and by history of asthma (yes or no).

To be eligible for inclusion, all participants had to have an FEV1 ≥80% of predicted value at the Screening and Randomization Visits. Three separate cohorts were recruited over consecutive ragweed seasons to complete the enrollment goal. Each cohort underwent the following three periods: a screening period (up to one year prior to randomization), a pre-seasonal treatment period (approximately 12 to 20 weeks), and co-seasonal treatment period (approximately 8 weeks). There were 8 study site visits, including the screening, randomization, off-season, pre-season, in-season, and end-of season visits. The first dose of Ragwitek was administered under supervision in the clinic and subsequent doses were self-administered at home. The study design is depicted in Figure 1.

Figure 1. Study P008: Study Design



Source: BLA 125478/293/0, Study P008 CSR, Section 9.1, Figure 9-1 p. 29.
Abbreviations: Ragwitek= investigational product name for Ragwitek, N= number of participants per treatment arm/ group, RS= ragweed season.

Efficacy was established by self-reporting of rhinoconjunctivitis daily symptom scores (DSS) and daily medication scores (DMS) and recording in e-diaries by the participant or the participant's parent/ guardian. The sum of the DSS and DMS equated to the Total Combined Score (TCS). Each of these scores were enumerated over the peak and entire ragweed pollen seasons (RS) during which the trial was conducted. The rhinoconjunctivitis DSS was comprised of 6 allergy symptoms: 4 rhinitis symptoms (runny nose, stuffy nose, sneezing, itchy nose) and 2 conjunctivitis symptoms (itchy eyes, watery eyes); each symptom was recorded on a scale from 0 to 3 resulting in a score range of 0-18. The rhinoconjunctivitis DMS was based on the class of medication used and was a composite score of individually assigned score values ranging from 0-20. The DSS and DMS scales are depicted in Table 4 and Table 5.

Table 4. Study P008: Rhinoconjunctivitis Daily Symptom Score (DSS) Scale[1]

Score	Intensity	Description
0	None	No sign/ symptoms evident
1	Mild	Sign/ symptom clearly present, but minimal awareness; easily tolerated
2	Moderate	Definite awareness of sign/ symptom, which is bothersome but tolerable
3	Severe	Sign/ symptom that is hard to tolerate, may cause interference with activities of daily living

Source: BLA 125478/293/0, Study P008 CSR, Section 4.2.3.1.1.2, p. 21.
[1] Rhinitis symptoms: rhinorrhea, nasal congestion, sneezing, nasal pruritus; Conjunctivitis symptoms: ocular pruritus, watery eyes

Table 5. Study P008: Rhinoconjunctivitis Daily Medication Score (DMS) Scale

Step	Rescue Medication[1]	Participant Dosing Instructions	Score/ Dose Unit	Maximum Daily Score
1	Loratadine syrup, 1 mg/mL	5 years old: 5 mL once daily	6 per 5 mL	6
--	Loratadine oral tablet, 5 mg or 10 mg	6 to 17 years old: 10 mL once daily	6 per 10 mL	6
--		5 years old: 5 mg tablet (1 tablet) once daily 6 to 17 years old: 10 mg tablet (1 tablet) once daily	6 per tablet	6
1b	Olopatadine hydrochloride ophthalmic solution, 0.1%	1 drop in each affected eye twice daily	1.5 per drop	6
2	Mometasone furoate monohydrate nasal spray, 50 mcg	5 to 11 years old: 1 spray in each nostril once daily	4 per spray	8
--		12 to 17 years old: 2 sprays in each nostril once daily	2 per spray	8
Maximum DMS	--	--	--	20

Source: BLA 125478/293/0, Study P008 CSR, Section 4.2.3.1.1.3, Table 2, p. 21-22.
[1] In countries where a rescue medication was not available, a similar medication was dispensed in a clinically equivalent dosage.

6.1.3 Population

Key Inclusion Criteria

- Legal representative for the participant to comprehend details of the study and to provide written informed consent for the study
- Age ≥4 to ≤17 years on the day of obtaining informed consent and age ≥5 years at the Randomization Visit
- Clinical history of significant ragweed pollen-induced ARC of ≥1 year (at least 1 season for ages 4 to 6 years) or ≥2 years (at least 2 seasons for ages 7 to 17 years),
- Physician diagnosis (with or without asthma), and treatment for the condition during the previous RS
- Positive skin prick test response (average wheal diameter ≥5 mm larger than the saline control after 15 to 20 minutes) to *Ambrosia artemisiifolia* at the Screening Visit
- Specific IgE against *Ambrosia artemisiifolia* ≥ IgE Class 2 (0.7 kU/L) at the Screening Visit
- FEV1 ≥80% of predicted value at the Screening and Randomization Visits
- Negative urine pregnancy test at the Screening and Randomization Visits for female participants of reproductive potential

Key Exclusion Criteria

- Clinical history of symptomatic seasonal ARC and/or asthma due to another allergen, which has required regular medication during, or potentially overlapping, the RS
- Clinical history of significant symptomatic perennial ARC and/or asthma due to an allergen to which the participant is regularly exposed during the RS
- Nasal condition that could confound the efficacy or safety assessments (e.g., nasal polyposis)
- Asthma requiring high daily doses of inhaled corticosteroids within the 6 months prior to the Screening Visit
- Severe, unstable, or uncontrolled asthma at any time within the last 3 months prior to the Screening or Randomization Visit
- History of anaphylaxis with cardiorespiratory symptoms with prior immunotherapy, unknown cause, or inhalant allergen
- Diagnosis of Eosinophilic Esophagitis
- History of chronic urticaria and/or chronic angioedema
- Clinical history of chronic sinusitis during the 2 years prior to the Screening or Randomization Visits
- Inability to meet medication washout requirements as pre-specified
- Greater risk of developing adverse reactions after epinephrine administration

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study treatments were either Ragwitek (investigational product) or placebo (control product), administered daily by sublingual route (Table 6). To maintain the treatment blind, the study product and placebo were matched in appearance and were packaged identically.

Table 6. Study P008: Study Treatments

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Treatment Period	Use
Ragwitek	12 Amb a 1-U	Once daily	Sublingual	Up to ~28 weeks	Experimental
Placebo	Not applicable	Once daily	Sublingual	Up to ~28 weeks	Placebo comparator

Source: BLA 125478/293/0: Study P008 CSR, Section 2, p. 3.
Abbreviations: Amb a 1-U= *Ambrosia artemisiifolia* 1 Unit

Ragwitek is a white to off-white, circular, (b) (4) , sublingual, orally-disintegrating tablet (oral lyophilisate) containing 12 Amb a 1-U of standardized short ragweed pollen allergen extract derived from extraction and purification of the natural source material, short ragweed [*Ambrosia artemisiifolia* (Amb a)] pollen. *Ambrosia artemisiifolia* is cultivated and harvested in North America for the express purpose of pollen collection. The biological potency of the ragweed SLIT tablet was determined by the content of major allergen (Amb a 1) as required by the FDA Center for Biologics Evaluation & Research (CBER) and contains 12 Amb a 1 Units of ragweed pollen extract. This unit was also used for the tablets during the development program. The dose for pediatric use is same as the marketed dose in adults (12 Amb a 1-U). Table 7 provides the quantitative composition of the drug product (Ragwitek). The placebo product contained only the inactive ingredients (excipients) of the drug product. The tablets were packaged

in aluminum blister packs composed of a blister film and a lidding foil. The lidding foil was designed to be peeled back from the blister film to allow the removal of the tablets.

Table 7. Quantitative Composition of Ragwitek

	Quality Standard	Type of Ingredient/ Function	Amount per Tablet
Ragwitek	In House	Active ingredient; Drug Substance	12 Amb a 1-U
Gelatin (Fish. (b) (4) (b) (4)	NF	Inactive ingredient; (b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	
Mannitol	(b) (4)	Inactive ingredient; (b) (4)	(b) (4)
Sodium Hydroxide	(b) (4)	Inactive ingredient; (b) (4)	
Purified Water	(b) (4)		
--	--	--	--
(b) (4)			(b) (4)
(b) (4)			(b) (4)

Source: Adapted from BLA 125478/0/0, Module 3.2.P.1 Description and Composition of the Drug Product, Table 1, p. 1.
Abbreviations: Amb a 1-U= *Ambrosia artemisiifolia* 1 Unit, NF= National Formulary, (b) (4) .
[2] Represents (b) (4) may vary slightly depending on the amount of sodium hydroxide (b) (4)

Reviewer Comment:
Composition of the drug product (Ragwitek) and the placebo was the same as the composition of the study treatments used in the clinical development of Ragwitek in the adult population (original BLA, STN 125478/0/0), and, therefore, was not included in this BLA submission (STN 125478/293).

6.1.5 Directions for Use

Treatment with Ragwitek is initiated at least 12 weeks before the expected onset of ragweed pollen season and treatment is continued throughout ragweed season.

The first dose of Ragwitek must be administered in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases including severe allergic reactions (i.e., anaphylaxis). Patients must be monitored for 30 minutes to allow for direct observation of any adverse events (AEs) that occur soon after study drug including signs and symptoms of an acute allergic reaction. If the first dose is tolerated, subsequent doses can be administered under adult supervision at home. The physician/ qualified designee will provide instructions on proper administration of the tablet, as well as discuss expected immediate application site reactions and potential severe AEs requiring medical evaluation and/or treatment,

prior to dispensing the study drug to the patient/parent/guardian for at-home administration.

The tablet should be removed from packaging when ready to use, and immediately placed in the mouth and held underneath the tongue without swallowing for at least one minute, until the tablet is completely dissolved, and hands should be washed after handling Ragwitek. To avoid swallowing allergen extract, food or beverage should not be taken with the tablet or for 5 minutes following dissolution of the tablet.

6.1.6 Sites and Centers

A total of 80 study sites in 6 countries (Canada, Croatia, Hungary, Serbia, Ukraine, and the US) randomized at least one participant. The number of sites in each of the 6 countries are as follows (number of sites is listed in parentheses): United States (43), Canada (6), Croatia (7), Hungary (8), Serbia (10), and Ukraine (6).

> *Reviewer Comment:*
> *Please note that the synopsis in the CSR for Study P008 misstates that the study was conducted at 103 sites in 6 countries. The data listed above was verified from the list of investigators and sites included with the submission and from Study P008 CSR Section 10.1 Disposition of Participants.*

6.1.7 Surveillance/Monitoring

The surveillance/ monitoring procedures for Study P008 are described in Table 8.

Table 8. Surveillance and Monitoring Procedures: Study P008

Trial Period	**Screening**	**Treatment**	**--**	**--**	**--**	**--**	**--**	**Post-Treatment**
Visit Number:	**1**	**2**	**3**	**4/5** [a]	**6**	**7**	**8**	**--**
Visit Title:	**Screening**	**Randomization**	**Off-Season**	**Off-Season**	**Pre-Season**	**In-Season**	**End-of-Season/ Discontinuation**	**Telephone/ Follow-up**
Scheduled Day/Week:	**Weeks -52 to -1** [b]	**Day 1**	**Week 4** [c]	**Midway between Visits 3 & 6**	**~2 weeks before start of**	**~3 weeks after start of**	**~1 week after end of RS**	**Post 14 days**
Scheduling Window (Days):	**-**	**-**	**+7 days**		**± 7 days**		**± 7 days**	**± 5 days**
Informed Consent [e]	X							
Informed Consent for Future Biomedical Research [f]	X							
IVRS/IWRS	X	X	X	X	X	X	X	
Inclusion/Exclusion Criteria	X	X						
Demography	X							
Medical History	X	X						
Allergic Rhinitis Baseline Profile and Family History of Atopy	X	X						
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X
Issue/Update Participant Identification Card	X	X [g]						
Issue/Instruct in the use of e-diary				X				
Review e-diary data and nstructions for use					X	X		
Activate Medication section of e-diary					X			

Trial Period	Screening	Treatment	--	--	--	--	--	Post-Treatment
Discontinue/Collect e-diaries							X	
Dispense/Review Anaphylaxis Emergency Action Plan [h]		X	X	X	X	X		
Provide Self-Injectable Epinephrine and Educational Information, Instruct in its use [i]		X						
Provide albuterol/salbutamol to participants with asthma [j]		X	X [j]	X [j]	X [j]	X [j]		
Issue/Instruct in the use of SLIT Report Card		X						
Collect/Review SLIT Report Card			X					
Issue/Instruct in the use of Comment Card		X	X	X	X	X		
Collect/Review Comment Card			X	X	X	X	X	
Vital Signs (Temperature, Blood Pressure, Pulse, Respiration Rate) [k]	X	X	X	X	X	X	X	
Body Height and Weight [k]	X	X						
Physical Examination	X						X [k]	
Oropharyngeal Examination [l]	X	X [l]	X	X	X	X	X	
Pulmonary Function Tests [m]	X	X			X	X	X	
Beta2-agonist reversibility [n]		X						
Skin Prick Test	X							
Adverse Events Monitoring		X	X	X	X	X	X	X
On-site Dosing of Study Medication		X						
Dispense Study Medication		X	X	X	X	X		
Verify Participant has Self-Injectable Epinephrine and Review Instructions for use			X	X	X	X		
Verify participants with history of asthma have albuterol/salbutamol			X	X	X	X		
Check/Collect Study Medication			X	X	X	X	X	
Dispense/Review Need for Allergy Rescue Medication					X	X		
Record Use of Allergy Rescue Medication (e-diary)					X	X	X	
Collect Rescue Medication/Self-Injectable Epinephrine							X	
Monitor compliance with Study Medication			X	X	X	X	X	
Monitor Compliance with e-dairy completion				X	X	X	X	
Serum specific IgE to a panel of allergens	X							

Trial Period	Screening	Treatment	--	--	--	--	--	Post-Treatment
Hematology, Chemistry, Urinalysis	X							
Urine Pregnancy Test – if applicable [o]	X	X	X	X	X	X	X	
Immunologic sample (IgE, IgG4) [p]		X			X		X	
Saliva (DNA) for Future Biomedical Research [q]		X						

Source: sBLA 125478/293/0; Clinical Study Report Study P008, Section 16.1.1.3, Study P008 Protocol (Amendment 2), Section 6.1, Trial Flow Chart.

Abbreviations: DNA = deoxyribonucleic acid; e-diary = electronic diary; FBR = future biomedical research; FEV1 = forced expiratory volume in 1 second; IgE = immunoglobulin E; IgG4 = immunoglobulin G4; IVRS/IWRS = Interactive Voice/Web Response System; PFT = pulmonary function test; RS = ragweed season; SLIT= sublingual immunotherapy; US = United States.

a. All participants are to complete Visit 4 midway between Visit 3 and Visit 6, but not more than 6 to 8 weeks after Visit 3. If time between Visits 4 & 6 is > 6 to 8 weeks, then participant should be scheduled to return for Visit 5 approximately midway between Visits 4 and 6; study drug is not dispensed at Visit 5 (see Section 9.2 for the visits when study drug is dispensed).
b. During the first season of screening, participants may be in screening up to approximately 9 months (-39 to -1 week). During subsequent season(s) of screening, participants may be in screening up to approximately 12 months (-52 to -1 week).
c. Visit 3 should be scheduled on Day 28 (+7 days) to allow the participant to complete the SLIT Report Card for ~28 days.
d. It is preferable that Visit 7 be scheduled approximately 3 weeks after the start of the ragweed season.
e. Informed consent/assent must be obtained before any trial-related procedures are performed.
f. Informed consent for future biomedical research samples (optional) must be obtained before the saliva for DNA sample.
g. Update Participant Identification Card with randomization number.
h. The Anaphylaxis Emergency Action Plan can be modified outside the US to meet local standards for the use (or type) of epinephrine dispensed, and for calls to 911 or alternative local emergency services.
i. Self-injectable epinephrine is provided only in those countries where it is a regulatory requirement.
j. Albuterol/salbutamol should also be dispensed to participants diagnosed with asthma during the trial as needed.
k. Vital Signs (axillary temperature, blood pressure, pulse, respiration rate) in a seated position, height, and weight should be performed prior to performing pulmonary function tests. At the End-of- season/Discontinuation visit a limited physical exam will be performed.
l. Oropharyngeal examinations will be performed before and after study drug administration at Visit 2. Targeted physical examinations may be conducted at visits that do not already include a physical exam, if deemed necessary by the investigator, due to signs/symptoms.
m. FEV1 results should be available and reviewed by investigator or designee prior to administration of first dose of study medication to ensure results meet inclusion criteria. Following randomization, PFTs are required only for participants with asthma at the subsequent visits identified in the trial flow chart, unless the investigator feels a PFT is warranted for a participant without asthma. Note: PFTs are not required for those participants ≤7 years of age who cannot perform reproducible FEV1 maneuvers despite coaching; those participants ≤7 years of age who can perform reproducible FEV1 maneuvers, including those who initially could not at the Screening Visit, must complete the PFTs.
n. Beta2-agonist reversibility (Section 12.9) will be performed at Visit 2 for all participants performing PFTs (i.e., all participants >7 years of age and all participants ≤7 years of age who can perform reproducible FEV1 maneuvers).
o. If a urine test result is positive, confirm with a serum β-hCG test.
p. Immunologic samples will only be collected at selected sites. The Visit 2 sample should be collected prior to administration of the first dose of study drug. Leftover main study serum samples will be stored for future biomedical research if the participant consents to future biomedical research.
q. Saliva (DNA) for FBR should be the last procedure performed at Visit 2. If not obtained at Visit 2, can be obtained at a subsequent visit once the informed consent for FBR is obtained.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint and Pre-Specified Criteria for Study Success

The primary efficacy endpoint was the average TCS during the peak ragweed season. The pre-specified criteria for success of this primary endpoint were a treatment difference relative to placebo of at least -15% and the upper bound of the 95% confidence interval (CI) for this difference of at least -10%.

Reviewer Comment:
The pre-specified statistical criteria for success for demonstration of efficacy for Study P008 were discussed by the Applicant and CBER and first documented by the Applicant (STN 125478/0/24, Proposal for Pediatric Study Amendment, dated March 24, 2014). These criteria were again documented in the Statistical Analysis Plan (SAP) (see Statistical Review for this supplemental BLA).

Key Secondary Efficacy Endpoints

- Average TCS during the entire RS
- Average rhinoconjunctivitis DSS during the peak RS
- Average rhinoconjunctivitis DMS during the peak RS

Tertiary Efficacy Endpoints

- Average rhinoconjunctivitis DSS during the entire RS
- Change from baseline in IgE level against *Ambrosia artemisiifolia* at Visit 6 and at Visit 8
- Change from baseline in IgG4 level against *Ambrosia artemisiifolia* at Visit 6 and at Visit 8

Exploratory Endpoints

- Average Asthma DSS during the peak RS and the entire RS (all participants)
- Average daily number of puffs of as-needed short-acting beta-agonist (SABA) used during the peak RS and the entire RS (participants with asthma only)
- Average weekly number of nights with nocturnal awakening due to asthma symptoms requiring SABA use during the peak RS and the entire RS (participants with asthma only)

Secondary Safety Endpoints

- Percentage of participants reporting pre-specified local adverse reactions
- Percentage of participants reporting anaphylaxis and/or systemic allergic reactions
- Percentage of participants treated with epinephrine

6.1.9 Statistical Considerations & Statistical Analysis Plan

In terms of power and sample size prior to the start of Study P008, the SAP stated that a total of approximately 1000 participants will be randomized in a 1:1 ratio to either Ragwitek
or placebo. Assuming a 15% dropout rate, this gives approximately 425 evaluable participants per treatment group.
With 425 participants per arm, the study will have:

- approximately 90% power (2-sided, $\alpha = 0.05$) to have the upper bound of the 95% CI for relative difference below -10%, and
- more than 90% power (2-sided, $\alpha = 0.05$) to have an estimated relative difference below -15%.

The primary efficacy analysis compared the efficacy of Ragwitek to placebo with respect to the TCS averaged over the peak RS using the Analysis of Variance (ANOVA) model, which included fixed effects of treatment, baseline asthma status (yes or no), and age group (5 to 11 years or 12 to 17 years). Two-sided 95% CI of the treatment difference in adjusted means were presented, along with the treatment difference in adjusted means relative to the adjusted mean of the placebo group as a percentage with corresponding 2-sided 95% CI derived using the bootstrap method. The secondary efficacy analyses followed an approach similar to the primary analysis.

The primary efficacy analysis was based on the observed data only. Missing data approaches were implemented for the primary efficacy endpoint sensitivity analyses

[including multiple imputation, last non-missing observation carried forward (LOCF), and model based] and immunologic endpoints (model-based). All other analyses were based on the observed data only.

Pollen count data were used to determine the ragweed season for each participant; missing pollen data were imputed by the LOCF approach. For each participant, only the pollen count observations within the pollen season were eligible to be carried forward.

A fixed sequence procedure was applied to control multiplicity, where the primary efficacy endpoint was tested first followed by key secondary efficacy endpoints analyzed in the sequential order of average TCS during the entire RS, average rhinoconjunctivitis DSS during the peak RS, and average rhinoconjunctivitis DMS during the peak RS. A lower order endpoint was tested only if all higher order endpoints were tested and claimed statistically significant.

Safety and tolerability were assessed by clinical review of relevant parameters, including AEs, laboratory tests, and vital signs using a tiered approach. Tier 1 safety endpoints were pre-specified for the study and were subject to inferential testing for statistical significance with *p*-values and 95% CI for between-group comparisons using the Miettinen and Nurminen method, with baseline asthma status and age group as stratification factors. Point estimates and 95% CIs were provided for the Tier 2 endpoints.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed
The definitions of the analysis populations are presented below.

Full Analysis Set (FAS) Population:
The full analysis set (FAS) consisted of all randomized and treated participants in which participants were analyzed according to the treatment group to which they were randomized. This was the primary population for the efficacy analyses. For efficacy analyses, participants with insufficient data during the peak RS or entire RS (e.g., participants with no e-diary data during the efficacy assessment period) were not evaluable in that period.

Per Protocol (PP) Population:
The per protocol (PP) population excluded participants from the FAS population who met pre-specified protocol violations that may substantially affect the results of the primary efficacy endpoint. A supportive efficacy analysis for the primary endpoint was conducted using the PP population.

All Subjects as Treated (ASaT) Population:
The all subjects as treated (ASaT) population consisted of all randomized and treated participants (as did the FAS population), however, participants in the ASaT population were included in the treatment group corresponding to the study intervention they actually received during the study. This was the primary population for safety analyses. Cross-treated participants were analyzed based on pre-specified data handling conventions for cross-treated participants (see the supplemental SAP for Study P008); the 1 participant randomized to placebo who incorrectly received Ragwitek for 1 day was

analyzed under the Ragwitek group for safety analyses and the other participant who was randomized to Ragwitek and incorrectly received placebo for 8 days remained in the Ragwitek group for safety analyses.

6.1.10.1.1 Demographics

Baseline demographics and characteristics for all randomized and treated participants in Study P008 are summarized by treatment group in Table 9.

Table 9. Demographic Characteristics of Randomized Participants by Treatment Arm (FAS population): Study P008

Demographic Characteristic	**Ragwitek** N= 512 **n (%)**	**Placebo** N= 510 **n (%)**	**Total** N= 1,022 **n (%)**
Gender	--	--	--
Male	324 (63.3)	319 (62.5)	643 (62.9)
Female	188 (36.7)	191 (37.5)	379 (37.1)
Age (years)	--	--	--
5 through 11	206 (40.2)	204 (40.0)	410 (40.1)
12 through 17	306 (59.8)	306 (60.0)	612 (59.9)
Race	--	--	--
American Indian or Alaska Native	1 (0.2)	0 (0.0)	1 (0.1)
Asian	4 (0.8)	6 (1.2)	10 (1.0)
Black or African American	18 (3.5)	14 (2.7)	32 (3.1)
Multiple	13 (2.5)	11 (2.2)	24 (2.3)
Native Hawaiian or Other Pacific Islander	3 (0.6)	2 (0.4)	5 (0.5)
Caucasian	473 (92.4)	477 (93.5)	950 (93.0)
Ethnicity	--	--	--
Hispanic or Latino	15 (2.9)	21 (4.1)	36 (3.5)
Not Hispanic or Latino	490 (95.7)	483 (94.7)	973 (95.2)
Not Reported	4 (0.8)	5 (1.0)	9 (0.9)
Unknown	3 (0.6)	1 (0.2)	4 (0.4)
Geographic Location	**513***	**512***	**1025***
United States	110 (21.4)	99 (19.3)	209 (20.4)
Canada	116 (22.6)	130 (25.4)	246 (24)
Croatia	49 (9.6)	30 (5.9)	79 (7.7)
Hungary	71 (13.8)	74 (14.5)	145 (14.1)
Serbia	79 (15.4)	82 (16.0)	161 (15.7)
Ukraine	88 (17.2)	97 (18.9)	185 (18)

Source: Adapted from BLA 125478/293/0, Clinical Study Report P008, Section 10.4.1, Table 10-3, p. 40 and Section 16 Appendices, Section 16.2.4, Table 16.2.4.1, p. 1-6.
Abbreviations: N= number of randomized participants in the FAS population, n (%) = number of participants, percentage of participants based on number of participants in the FAS Population
* Number of participants randomized per treatment group and in total (note that percentages for each treatment group by country are based on the number of participants randomized per treatment group)

Reviewer Comment:
Overall, the distribution of demographic characteristics in Study P008 was balanced between the Ragwitek group and the placebo group.

A total of 80 study sites in 6 countries randomized at least 1 participant (listed by number of sites and percentage of participants randomized per country): United

States (43 sites, 20.4%), Canada (6 sites, 24%), Croatia (7 sites, 7.7%), Hungary (8 sites, 14.1%), Serbia (10 sites, 15.7%), and Ukraine (6 sites, 18%). The majority of participants were male (62.9%), which is consistent with the greater prevalence of allergic rhinitis among males in childhood. Ninety-three percent of the study participants were Caucasian in this study (in comparison, demographics for the adult population in which Ragwitek was studied were 86% Caucasian, 9% African American, and 3% Asian). Incidence of AR in specific racial groups is not readily available in the published literature on this topic, but literature does suggest that AR/ ARC occurs in persons of all races, with varied prevalence among different populations and cultures (possibly due to various factors including genetic differences, geographic factors, environmental differences, or other population-based factors).[16] Therefore, the cause for the racial demographic imbalance in this study is not clear although it may possibly be due to enrollment of participants at study sites outside of the US that may be less diverse than the US in terms of ethnicity. While clinical presentation of AR/ ARC is not known to differ among races, interpretation of any treatment differences with Ragwitek in the non-Caucasian populations in Study P008 was limited by the small number of non-Caucasian participants.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Summary statistics of baseline disease characteristics are presented in Table 10.

All randomized and treated participants reported a primary diagnosis of ARC (72.9%) or AR (27.1%). Participants were highly sensitized to short ragweed with large average wheal sizes and high average serum specific IgE values (the skin prick test and the serum specific IgE test for short ragweed pollen allergen were measured at baseline for all randomized participants). The majority of subjects (Ragwitek group: 79%, placebo group: 76%) were polysensitized to ragweed pollen allergen and other allergens (see Table 10 for data on other allergens to which study participants were allergic).

Besides ARC and AR, the most frequently reported medical history conditions (>10% participants overall) included asthma (45.9%), atopic dermatitis (16.7%), eczema (13.2%), and food allergy (12.0%). The reported conditions were comparably balanced across intervention groups.

Overall, 63.8% of participants reported using prior medications. The most frequently reported prior medications (≥10% participants overall) included albuterol (20.0%), cetirizine hydrochloride (17.1%), mometasone furoate (15.9%), fluticasone propionate (11.4%), loratadine (11.0%), and desloratadine (10.4%). There were no clinically meaningful differences between intervention groups in the types of prior medications taken. Most participants (75.2%) used concomitant medications. The most frequently reported concomitant medications (≥10% participants overall) included ibuprofen (18.8%), cetirizine hydrochloride (17.3%), mometasone furoate (15.9%), albuterol (15.3%), loratadine (14.8%), acetaminophen (11.8%), and desloratadine (11.5%). There were no clinically meaningful differences between intervention groups in the types of concomitant medications taken.

Table 10. Baseline Characteristics of Randomized Participants by Treatment Arm (FAS population): Study P008

Baseline Characteristic	Ragwitek N= 512 n (%)	Placebo N= 510 n (%)	Total N= 1,022 n (%)
Asthma	--	--	--
Yes	219 (42.8)	217 (42.5)	436 (42.7)
No	293 (57.2)	293 (57.5)	586 (57.3)
History of Atopic Dermatitis	145 (28.3)	164 (32.2)	309 (30.2)
Symptoms in the past year	77 (15.0)	80(15.7)	157 (15.4)
History of Nasal Polyps	2 (0.4)	1 (0.2)	3 (0.3)
History of Sinusitis	28 (5.5)	35 (6.9)	63 (6.2)
Acute sinusitis	28 (5.5)	33 (6.5)	61 (6.0)
Chronic sinusitis	0 (0)	2 (0.4)	2 (0.2)
Sensitization Type	--	--	--
Ragweed Pollen Only	107 (20.9)	121 (23.7)	228 (22.3)
Ragweed Pollen + Others	405 (79.1)	389 (76.3)	794 (77.7)
Primary Diagnosis	--	--	--
ARC	367 (71.7)	378 (74.1)	745 (72.9)
AR	145 (28.3)	132 (25.9)	277 (27.1)
Seasonal AR	512 (100.0)	509 (99.8)	1021 (99.9)
Seasons	--	--	--
Spring	257 (50.2)	230 (45.1)	487 (47.7)
Summer	385 (75.2)	397 (77.8)	782 (76.5)
Fall	509 (99.4)	504 (98.8)	1013 (99.1)
Winter	17 (3.3)	18 (3.5)	35 (3.4)
Allergens	--	--	--
Tree	236 (46.1)	209 (41.0)	445 (43.5)
Grass	303 (59.2)	292 (57.3)	595 (58.2)
Weed	511 (99.8)	510 (100.0)	1021 (99.9)
Mold	31 (6.1)	40 (7.8)	71 (6.9)
Perennial AR	102 (19.9)	119 (23.3)	221 (21.6)
Allergens	--	--	--
Cat	121 (23.6)	136 (26.7)	257 (25.1)
Cockroach	8 (1.6)	2 (0.4)	10 (1.0)
Dog	55 (10.7)	66 (12.9)	121 (11.8)
Dust Mite	99 (19.3)	125 (24.5)	224 (21.9)
Other	39 (7.6)	46 (9.0)	85 (8.3)
AC	--	--	--
Seasonal AC	383 (74.8)	383 (75.1)	766 (75.0)
Seasons	--	--	--
Spring	173 (33.8)	177 (34.7)	350 (34.2)
Summer	273 (53.3)	297 (58.2)	570 (55.8)
Fall	369 (72.1)	360 (70.6)	729 (71.3)
Winter	11 (2.1)	7 (1.4)	18 (1.8)
Perennial AC	56 (10.9)	74 (14.5)	130 (12.7)
Ragweed-specific IgE (kU/mL)	--	--	--
Median	14.7	17.3	16.0
Range	0.7- 476.9	0.7- 209.6	0.7- 476.9
Ragweed SPT (mm)	--	--	--
Median	9.8	9.8	9.8
Range	5.0- 29.5	4.3- 29.5	4.3-29.5

Source: Adapted from BLA 125478/293/0, Study P008 CSR, Section 10.4.1, Table 10-3, p. 40- 43 and Section 14.1.4, Table 14.1-7, p. 97.
Abbreviations: AR= Allergic Rhinitis, ARC= Allergic Rhinitis with Conjunctivitis, AC= Allergic Conjunctivitis, IgE= Immunoglobulin E, kU/ mL= kilounit per milliliter, SPT= skin prick test, mm= millimeter.

Reviewer Comment:
Overall, the distribution of baseline characteristics in Study P008 was balanced between the Ragwitek group and the placebo group.

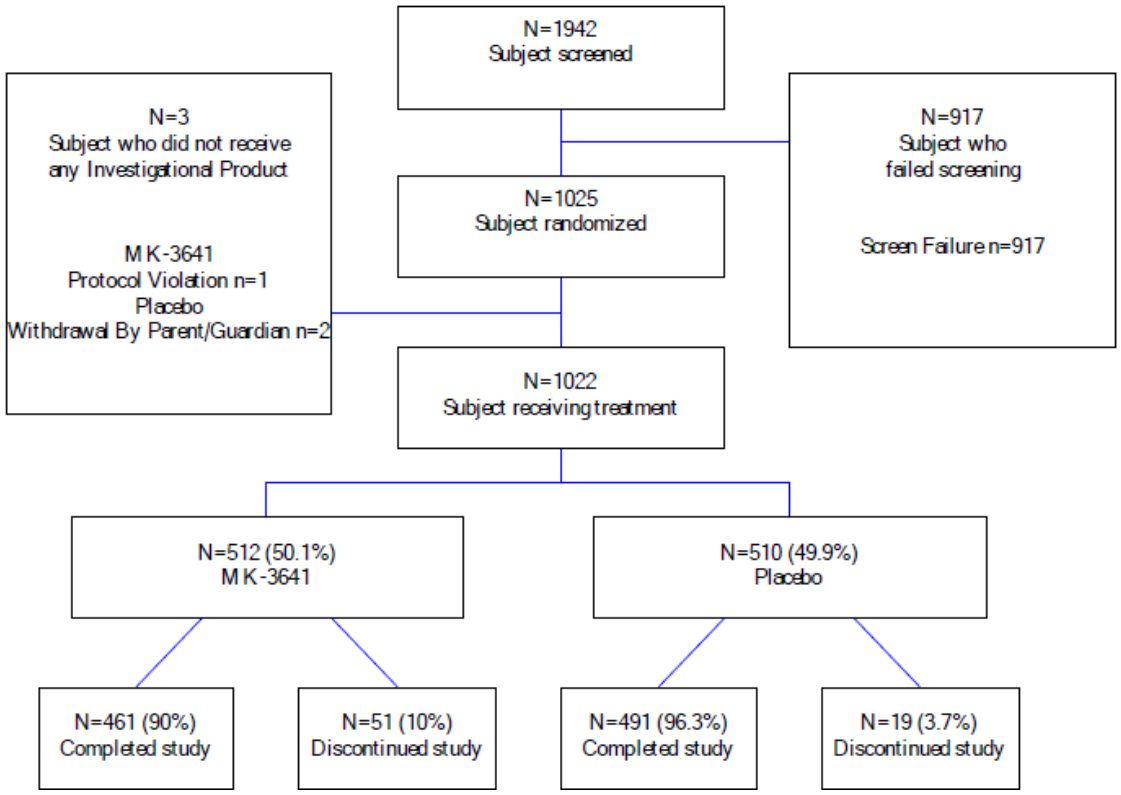
The majority of participants (77.7%) in both treatment groups were polysensitized (Ragweed + Others). Polysensitization to other weed pollens (which pollinate with the same seasonal variation as ragweed pollen) and perennial allergens (which cause allergy symptoms year-round) can affect the TCS (composed of the DSS and DMS) since allergy to these inhalant allergens could cause ongoing concurrent ARC symptoms despite treatment with Ragwitek. Approximately 22% of participants in total had perennial AR due to perennial allergens and approximately 12% had perennial AC due to perennial allergens. Presence of polysensitization [in comparison to monosensitization (Ragweed only)] affected the level of reduction of TCS during peak RS by Ragwitek compared to placebo, in that, the treatment difference relative to placebo for the primary endpoint (average TCS in the peak RS) was -60% in the subgroup that was mono-sensitized to ragweed (Ragweed only) and -29% in the subgroup that was polysensitized (Ragweed and Other Allergens)(see Section 6.1.11.3, Table 17); however, since the treatment groups appear to be well-balanced with respect to number of polysensitized participants, the treatment difference between mono-sensitized participants and polysensitized participants was accounted for in the primary efficacy endpoint estimate (treatment difference relative to placebo of -38%).

6.1.10.1.3 Subject Disposition

A total of 1942 participants were screened, 1025 were randomized, and 1022 received at least 1 dose of study intervention. The majority of non-randomized participants were screen failures of the inclusion criteria of positive skin prick test response and specific serum IgE against *Ambrosia artemisiifolia.* Of all randomized participants, 93.2% received at least 1 dose of study intervention and completed the study.

Participant disposition for the randomized population for Study P008 is displayed in Figure 2.

Figure 2. Participant Disposition Flowchart



Source: BLA 125478/293/0; Study P008 CSR, Section 10.1, p. 37.
Abbreviations: RAGWITEK= Investigational Product Name for Ragwitek®

The primary reasons for study discontinuation were AEs and withdrawal by participant or parent/guardian. The percentage of participants who discontinued or withdrew from the study was higher in the Ragwitek group (10%) than the placebo group (3.7%). The frequency of discontinuations due to an AE was higher in the Ragwitek group (3.9%) than in the placebo group (1.0%).

Participant discontinuation by treatment group is provided in Table 11 (please see the Reviewer Comment in Section 6.1.11.4 for commentary on the imbalance of discontinuations between the treatment groups).

Table 11. Study P008: Participant Disposition by Treatment Group (ASaT population)

Participant Disposition	Ragwitek (N= 512) n (%)	Placebo (N=510) n (%)	Total (N=1,022) n (%)
Participants Who Completed the Study	461 (90.0)	491 (96.3)	952 (93.2)
Participants Who Discontinued the Study	51 (10.0)	19 (3.7)	70 (6.8)
Primary Reason for Study Discontinuation	--	--	--
Adverse Event	20 (3.9)	5 (1.0)	25 (2.4)
Lost to Follow-Up	5 (1.0)	4 (0.8)	9 (0.9)
Non-Compliance with Study Drug	5 (1.0)	1 (0.2)	6 (0.6)
Protocol Violation	2 (0.4)	1 (0.2)	3 (0.3)
Withdrawal by Parent/ Guardian	9 (1.8)	4 (0.8)	13 (1.3)
Withdrawal by Participant	10 (2.0)	4 (0.8)	14 (1.4)
Death	0	0	0

Source: Adapted from BLA 125478/293/0, Study P008 CSR, Section 14, Table 14.1-1, p.84.
Abbreviations: ASaT= All Subjects as Treated, N= total number of participants in treatment group, n (%) = number (%) of participants experiencing at least one event, percentages are based on the number of participants in each treatment group

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Primary Efficacy Analysis

The primary efficacy assessment was the average TCS during the peak ragweed season.

Efficacy was demonstrated if the primary efficacy analysis met the pre-specified criteria for success. The criteria for success were pre-specified as: a treatment difference relative to placebo of at least -15% and the associated upper bound of the 95% confidence interval (CI) for this difference of at least -10% (i.e., no higher than -10%).

With regard to this primary endpoint, the average TCS during the peak RS was lower in the Ragwitek group compared to the placebo group with a treatment difference relative to placebo [based on the least square (LS) means] of -38.3% (95% CI: -46.0%, -29.7%). The primary efficacy analysis was based on all observed data and no missing values. The results of the primary efficacy analysis in the FAS population are displayed in Table 12.

Table 12. Study P008: Primary Analysis of the Primary Efficacy Endpoint: Average TCS during the Peak Ragweed Season by Treatment Group (FAS population)

Primary Endpoint	**Ragwitek** N= 460	**Placebo** N= 487	**Treatment Difference (Absolute) (Ragwitek – Placebo)** LS Mean (95% CI) [1]	**p-value [1]**	**Treatment Difference Relative to Placebo Estimate** % (95% CI) [2]
TCS Peak Season LS Mean (SD)	4.39 (3.85, 4.94)	7.12 (6.57, 7.67)	-2.73 (-3.45, -2.00)	<0.001	-38.3 (-46.0, -29.7)

Source: Adapted from BLA 125478/293/0, Study P008 CSR, Section 11.1.1, Table 11-1, p. 49.
Abbreviations: TCS = total combined score (DSS + DMS), DSS=Daily Symptom Score, DMS=Daily Medication Score, RS = ragweed pollen season, N = number of participants included in the analyses, SD = standard deviation, LS Mean = least square mean, CI = confidence interval
[1] Absolute treatment difference is of the LS means of the treatment groups and is based on the ANOVA model, which included fixed effects of treatment, baseline asthma status, age group (5 through 11 years of age and 12 through 17 years of age), pollen season, and pollen region nested within pollen season.
[2] Treatment difference relative to placebo was estimated as: (LS mean of Ragwitek - LS mean of placebo) / (LS mean of placebo) * 100%, where LS mean was based on the ANOVA model. Confidence interval was calculated by the bootstrap method using 10,000 iterations. No missing data was imputed.

Reviewer Comment:
Primary efficacy outcome results of Study P008 demonstrated a 38.3% reduction in total combined score (daily symptom and medication scores) during peak ragweed season in the Ragwitek treatment group relative to that of the placebo group thereby meeting the pre-specified criteria of success (which were based on a minimally important clinical difference) and demonstrating effectiveness of Ragwitek compared to placebo based on total combined score during peak ragweed season.

Sensitivity Analyses of the Primary Efficacy Endpoint

The results of the sensitivity analysis in the PP population are displayed in Table 13.

Table 13. Study P008: Sensitivity Analysis of the Primary Efficacy Endpoint: Average TCS during the Peak Ragweed Season by Treatment Group (PP population)

Primary Endpoint	Ragwitek N= 415	Placebo N= 439	Treatment Difference (Absolute) (Ragwitek – Placebo) LS Mean (95% CI) [1]	p-value [1]	Treatment Difference Relative to Placebo Estimate % (95% CI) [2]
TCS Peak RS LS Mean (SD)	4.39 (3.79, 4.98)	7.21 (6.60, 7.81)	-2.82 (-3.45, -2.00)	<0.001	-39.11 (-46.02, -29.66)

Source: Adapted from BLA 125478/293/0, Study P008 CSR, Section 11.1.1, Table 11-2, p. 50.
Abbreviations: TCS = total combined score (DSS + DMS); DSS=Daily Symptom Score; DMS=Daily Medication Score; RS = ragweed pollen season; N = number of participants included in the analyses; SD = standard deviation; LS Mean = least square mean; CI = confidence interval
[1] Absolute treatment difference is of the LS means (LS means for each treatment group are not listed in the table) of the treatment groups and is based on the ANOVA model, which included fixed effects of treatment, baseline asthma status, age group (5 through 11 years of age and 12 through 17 years of age), pollen season, and pollen region nested within pollen season.
[2] Treatment difference relative to placebo was estimated as: (LS mean of Ragwitek - LS mean of placebo) / (LS mean of placebo) * 100%, where LS mean was based on the ANOVA model. Confidence interval was calculated by the bootstrap method using 10,000 iterations. No missing data was imputed.

Reviewer Comment:
The per protocol (PP) population excluded participants from the FAS population who met pre-specified protocol violations that may substantially affect the results of the primary efficacy endpoint. Ten participants met pre-specified protocol violations and were excluded from the PP population (Study P008 CSR, Appendix 16.2.3). The pre-specified protocol violations that were met by these 10 participants were as follows:

- *Participants unable to meet medication washout requirements,*
- *Participants who took prohibited medications as defined in the protocol, with the exception of antihistamines. Participants who have taken antihistamines (other than Applicant provided rescue medications) will be considered protocol violators if they have taken the medication for 2 or more consecutive days between Visit 6 and Visit 8.*

Despite exclusion of these 10 participants from the PP population, results of this sensitivity analysis based on the PP population were consistent with and supportive of the results of the primary efficacy analysis based on the FAS population [treatment difference relative to placebo: -39.11% (95% CI: -46.02, -29.66), p-value<0.001].

The results of the primary analysis were corroborated by 4 supportive analyses based on the FAS population: the LDA model, the non-parametric method (observed data only), and the ANOVA model with multiple imputation method and with LOCF (data not shown).

Additional sensitivity analyses based on the FAS population were conducted where: only data entered in the e-diary on the same day (without recall) were included and non-study provided allergy rescue medication were included (data not shown). These analyses confirmed the primary analysis results.

6.1.11.2 Analyses of Secondary Endpoints

Key Secondary Efficacy Analyses

The key pre-specified secondary efficacy endpoints were average TCS during the entire RS, average rhinoconjunctivitis DSS during the peak RS, and average rhinoconjunctivitis DMS during the peak RS. Results are displayed in Table 14, Table 15, and Table 16, respectively.

Table 14. Study P008: Analyses of the Key Secondary Efficacy Endpoints by Treatment Group (FAS population): Total Combined Score Entire Ragweed Season

Key Secondary Endpoint	**Ragwitek** (N= 466)	**Placebo** (N= 491)	**Treatment Difference (Absolute) (Ragwitek – Placebo)** LS Mean (95% CI) [1]	**p-value [1]**	**Treatment Difference Relative to Placebo Estimate** % (95% CI) [2]
TCS Entire RS LS Mean (SD)	3.88 (3.44, 4.33)	5.75 (5.30, 6.20)	-1.86 (-2.46, -1.27)	<0.001	-32.4 (-40.7, -23.3)

Source: Adapted from BLA 125478/293/0, Study P008 CSR, Section 11.1.2, Table 11-3, p. 52.
Abbreviations: TCS = total combined score (DSS + DMS), DSS=Daily Symptom Score, DMS=Daily Medication Score, RS = ragweed pollen season, N = number of participants included in the analyses, SD = standard deviation, LS Mean = least square mean, CI = confidence interval
[1] Absolute treatment difference is of the LS means of the treatment groups and is based on the ANOVA model, which included fixed effects of treatment, baseline asthma status, age group (5 through 11 years of age and 12 through 17 years of age), pollen season, and pollen region nested within pollen season.
[2] Treatment difference relative to placebo was estimated as: (LS mean of Ragwitek – LS mean of placebo) / (LS mean of placebo) * 100%, where LS mean was based on the ANOVA model. Confidence interval was calculated by the bootstrap method using 10,000 iterations.

Table 15. Study P008: Analyses of the Key Secondary Efficacy Endpoints by Treatment Group (FAS population): Daily Symptom Score Peak Ragweed Season

Key Secondary Endpoint	Ragwitek (N= 468)	Placebo (N= 494)	Treatment Difference (Absolute) (Ragwitek – Placebo) LS Mean (95% CI) [1]	p-value [1]	Treatment Difference Relative to Placebo Estimate % (95% CI) [2]
DSS Peak RS LS Mean (SD)	2.55 (2.24, 2.86)	3.95 (3.63, 4.26)	-1.40 (-1.81, -0.99)	<0.001	-35.4 (-43.2, -26.1)

Source: Adapted from BLA 125478/293/0, Study P008 CSR, Section 11.1.2, Table 11-4, p. 53.
Abbreviations: TCS = total combined score (DSS + DMS); DSS=Daily Symptom Score; DMS=Daily Medication Score; RS = ragweed pollen season; N = number of participants included in the analyses; SD = standard deviation; LS Mean = least square mean; CI = confidence interval
[1] Absolute treatment difference is of the LS means of the treatment groups and is based on the ANOVA model, which included fixed effects of treatment, baseline asthma status, age group (5 through 11 years of age and 12 through 17 years of age), pollen season, and pollen region nested within pollen season.
[2] Treatment difference relative to placebo was estimated as: (LS mean of Ragwitek - LS mean of placebo) / (LS mean of placebo) * 100%, where LS mean was based on the ANOVA model. Confidence interval was calculated by the bootstrap method using 10,000 iterations.

For the key secondary efficacy endpoint of DMS peak season (Table 16), the zero-inflated log-normal model was used to analyze the average rhinoconjunctivitis DMS (estimated means presented below) for the FAS population during the peak RS (as pre-specified in the protocol) because greater than 30% of participants had a daily rhinoconjunctivitis DMS equal to zero during the peak RS.

Table 16. Study P008: Analyses of the Key Secondary Efficacy Endpoints by Treatment Group (FAS population): Daily Medication Score Peak Ragweed Season

Key Secondary Endpoint	Ragwitek (N= 460)	Placebo (N= 487)	Treatment Difference (Absolute) (Ragwitek – Placebo) Estimated Mean (95% CI) [1]	p-value [1]	Treatment Difference Relative to Placebo Estimate % (95% CI) [2]
DMS Peak RS Estimated Mean (SD)	2.01 (1.57, 2.46)	3.85 (3.14, 4.57)	-1.84 (-2.60, -1.08)	<0.001	-47.7 (-59.8, -32.5)

Source: Adapted from BLA 125478/293/0, Study P008 CSR, Section 11.1.2, Table 11-5, p. 54.
Abbreviations: TCS = total combined score (DSS + DMS); DSS=Daily Symptom Score, DMS=Daily Medication Score, RS = ragweed pollen season, N = number of participants included in the analyses, SD = standard deviation, CI = confidence interval
[1] Absolute treatment difference is of the estimated means of the treatment groups and is based on the zero-inflated log-normal model, which included fixed effects of treatment, baseline asthma status, age group (5 through 11 years of age and 12 through 17 years of age), pollen season, and pollen region nested within pollen season.
[2] Treatment difference relative to Placebo was estimated as (Estimated Mean of Ragwitek – Estimated Mean of Placebo) / (Estimated Mean of Placebo) * 100%, where Estimated Mean was based on the zero-inflated log-normal model. Confidence interval was calculated by the bootstrap method using 10,000 iterations.

Reviewer Comment:
Total and daily scores for the key secondary efficacy endpoints of TCS entire RS, DSS peak RS, and DMS peak RS were lower in the Ragwitek group compared to the placebo group (and these treatment differences were significant with respect to p-value). Although reduction in the total combined score for the entire RS (key secondary endpoint, relative treatment difference estimate: -32.4%) was slightly lower than that of the TCS peak RS (primary endpoint, relative treatment difference estimate: -38.3%), the reduction was relatively similar, suggesting that Ragwitek is effective in reducing TCS over the entire ragweed season.

6.1.11.3 Subpopulation Analyses

The average TCS during the peak RS was further analyzed by the subgroups of baseline asthma status, age group, gender, race, ICS use, allergen sensitization type, geographic region (US, Canada, Europe), pollen counts, and local application site reactions (see Table 17). These subgroups were examined to determine if any baseline factor had a notable influence on overall efficacy of Ragwitek.

Table 17. Study P008: Subgroup Analysis of Average TCS during the Peak Ragweed Season (FAS population: ANOVA Model- Observed Data Only)

Subgroup	Ragwitek n, mean ± SD	Placebo n, mean ± SD	Treatment Difference, Absolute LS Mean (95% CI)	Treatment Difference, Relative to Placebo % (95% CI)
Age	--	--	--	--
5 through 11 years of age	195, 5.24 (6.91)	193, 7.73 (8.00)	-2.38 (-3.63, -1.12)	-34.05 (-47.62, -16.11)
12 through 17 years of age	265, 4.25 (5.34)	294, 7.08 (6.92)	-2.92 (-3.80, -2.03)	-42.23 (-51.75, -31.41)
Gender	--	--	--	--
Male	293, 4.55 (6.22)	309, 7.48 (7.65)	-2.89 (-3.78, -1.99)	-40.94 (-50.29, -30.19)
Female	167, 4.88 (5.80)	178, 7.11 (6.87)	-2.50 (-3.73, -1.27)	-35.57 (-49.00, -21.13)
Race	--	--	--	--
Caucasian	426, 4.86 (6.21)	456, 7.57 (7.48)	-2.80 (-3.57, -2.04)	-38.65 (-46.94, -30.03)
Non-Caucasian	34, 2.22 (3.06)	31, 3.90 (4.19)	-1.02 (-3.19, 1.16)	-31.15 (-82.67, 58.10)
Baseline Asthma	--	--	--	--
Yes	196, 3.49 (4.11)	6.24 (6.6)	-2.87 (-3.87, -1.86)	-43.61 (-54.86, -31.4)
No	264, 5.55 (7.06)	283, 813 (7.79)	-2.61 (-3.65, -1.58)	-33.81 (-43.83, -21.67)
ICS Use at Baseline	--	--	--	--
Yes	61, 2.59 (2.96)	64, 4.87 (5.44)	-3.15 (-4.86, -1.44)	-60.08 (-81.39, -36.28)
No	399, 4.99 (6.35)	423, 7.71 (7.55)	-2.74 (-3.54, -1.94)	-38.04 (-46.33, -28.49)
Allergen Sensitization Type	--	--	--	--
Ragweed Only	104, 4.71 (5.52)	117, 10.46 (9.04)	-5.47 (-7.29, -3.64)	-60.75 (-74.81, -45.39)
Ragweed + Others	356, 4.66 (6.23)	370, 6.35 (6.46)	-1.9 (-2.67, -1.12)	-29.03 (-38.69, -17.93)
Geographic Region	--	--	--	--
US	3.21 (4.44)	4.79 (4.63)	-1.59 (-2.92, -0.26)	-34.82 (-56.76, -6.1)
Canada	2.35 (2.48)	3.97 (4.16)	-1.59 (-2.54, -0.65)	-40.76 (-54.54, -20.19)
Europe	6.07 (7.06)	9.71 (8.32)	-3.62 (-4.74, -2.5)	-38.78 (-47.75, -28.53)

Source: Adapted from BLA 125478/293/0, Study P008 CSR, Section 14, Table 14.2-10, p 204-207.
Abbreviations: n= number of participants, SD= standard deviation, LS mean= least square mean, CI= confidence interval, ICS= inhaled corticosteroid use, US= United States

Reviewer Comment:
In general, consistent trends in efficacy were observed across the subgroups. Of note, TCS during the peak RS was notably reduced to a greater extent in the Ragwitek group for the subgroup of participants with asthma with ICS use at baseline (-60.8%) compared to the subgroup of participants with asthma with no ICS use at baseline (-38.04%) and for the subgroup of participants mono-sensitized to ragweed (-60.75%) compared to the subgroup of participants who were polysensitized to ragweed pollen and other allergens (-29.03%). Polysensitization to allergens is generally more common (as was seen within the study population of Study P008), and the decrease in reduction of TCS seen in this subgroup is most likely due to concurrent allergic symptoms due to the presence of other allergens to which the participants were sensitized. Nevertheless, an approximately 30% reduction in TCS during peak RS was still observed in the subgroup of participants that were polysensitized, which is a clinically meaningful effect.

6.1.11.4 Dropouts and/or Discontinuations

Participant disposition, including discontinuations, for Study P008 are shown in Table 11 (Section 6.1.10.1.3).

The percentage of participants who discontinued or withdrew from the study was higher in the Ragwitek group (n= 51 out of 512, 10%) than in the placebo group (n= 19 out of 510, 3.7%). The primary reasons for study discontinuation were AEs (Ragwitek group: 3.9%; placebo group: 1%) and withdrawal (withdrawal by participant: Ragwitek group: 2%; placebo group: 0.8%; withdrawal by parent/guardian: Ragwitek group: 1.8%; placebo group: 0.8%). In the Ragwitek group, the most reported AE resulting in discontinuation of study intervention was throat irritation, which occurred in 3 participants (0.6%). Most of the discontinuations due to AEs were assessed by the investigators to be of mild or moderate intensity.

Compliance with the study intervention was high across the treatment groups, with the majority of participants (87.8%) being >90% compliant. Most participants received treatment for at least 28 days (96.1%) and for at least 20 weeks (84.5%).

Reviewer Comment:
The discontinuation rates were imbalanced between the Ragwitek group (10.0%) and the placebo group (3.7%). The Applicant noted that the percentage of participants in the Ragwitek group throughout the study was numerically lower than the placebo group at the corresponding duration in exposure, which contributed to the higher discontinuation rate seen in the Ragwitek group.

In the protocol and SAP for Study P008, the Applicant assumed a 15% attrition rate based on earlier studies conducted with Ragwitek (thus, of the 500 participants planned for randomization in each treatment group, 425 participants per arm were determined to be necessary to achieve 90% power to, in turn, meet the pre-specified statistical criteria for success). Therefore, the planned, powered sample size was already adjusted for this attrition rate, and the primary efficacy analysis was based on all observed data and no missing values. Since a 15% discontinuation rate was assumed and taken into account for sample size

calculations prior to the start of Study P008 (the discontinuation rate for Study P008 was 13.7%) and a large number of participants were exposed to Ragwitek (n=461) and placebo (n=491) even after discontinuations were taken into account, it is unlikely that the imbalance in the discontinuation rate between the two treatment groups affected interpretation of the results.

Twenty participants in the Ragwitek group and 5 participants in the placebo group discontinued due to AEs; the frequency was higher in the treatment group (3.9% to 1.0%, Ragwitek to placebo group). Of the twenty participants in the Ragwitek group, 11 of the participants discontinued due to gastrointestinal adverse events (see Section 6.1.12.7 for a listing of the participants with adverse events resulting in discontinuation).

6.1.11.5 Exploratory and Post Hoc Analyses

Tertiary Efficacy Analyses

The tertiary endpoints were the average rhinoconjunctivitis DSS during the entire RS, change from baseline in IgE level against *Ambrosia artemisiifolia* at Visit 6 and at Visit 8, and change from baseline in IgG4 level against *Ambrosia artemisiifolia* at Visit 6 and at Visit 8.

The average rhinoconjunctivitis DSS during the entire RS was observed to be lower in the Ragwitek group (LS mean= 2.27) than the placebo group (LS mean= 3.26) (absolute difference of the LS means of -0.99) with a treatment difference relative to placebo of -30% (95% CI -38.6, -20.7) (see Study P008 CSR, Section 14, Table 14.2-16, p. 214).

In terms of change in IgE level, in the Ragwitek group, there was a marked increase in serum specific IgE levels from Visit 2 (baseline) to Visit 6 (pre-season), which leveled off during the ragweed season (between Visits 6 and 8). There was little change in the placebo group between baseline and Visit 6, with a marked increase in serum specific IgE at Visit 8, after participants were exposed to ragweed pollen naturally in their environment. At Visit 6, the change from baseline in IgE levels was observed to be higher in the Ragwitek group than the placebo group. At Visit 8, the change from baseline in IgE levels was similar across the treatment groups.

In terms of change in serum-specific IgG level, in the Ragwitek group, there was a marked increase in IgG4 levels from Visit 2 (baseline) to Visit 6 (pre-season), which leveled off during the ragweed season (between Visits 6 and 8). There was little change in the placebo group between baseline and Visit 6, with a small change in IgG4 levels during the ragweed season (natural exposure to ragweed pollen). At both Visit 6 and Visit 8, the change from baseline in IgG4 levels against *Ambrosia artemisiifolia* was observed to be higher in the Ragwitek group than the placebo group.

Exploratory Analyses

- The exploratory endpoints centered around asthma and were: average Asthma DSS during the peak RS and the entire RS (all participants), average daily number of puffs of as-needed SABA used during the peak RS and the entire RS (participants with asthma only), and average weekly number of nights with nocturnal awakening due to asthma symptoms requiring SABA use during the peak RS and the entire RS (participants with asthma only).The average asthma

DSS during the peak RS and the entire RS were observed to be lower in the Ragwitek group than the placebo group.

- For participants with asthma, the average daily use of SABA was observed to be lower in the Ragwitek group than in the placebo group during the peak RS and the entire RS. A sensitivity analysis that included non-study-provided rescue medication showed similar results for the peak RS and the entire RS.
- For participants with asthma, the average weekly number of nights with nocturnal awakening due to asthma symptoms requiring SABA was observed to be lower in the Ragwitek group than in the placebo group during the peak RS and the entire RS.

Reviewer Comment:
As noted in Section 2, a large percentage of asthmatics also have AR/ ARC. Based on the results of these exploratory analyses, it appears that treatment with Ragwitek in participants with short ragweed pollen allergy may provide possible relief from asthma symptoms and lead to decreased daily SABA use and nocturnal awakening due to asthma symptoms requiring SABA use.

6.1.12 Safety Analyses

6.1.12.1 Safety Assessment Methods and Categorization of Adverse Events

The safety population was composed of all randomized participants who received at least one dose of treatment [mentioned in Section 6.1.10.1 as the All Subjects as Treated population (ASaT) and herein referred to as the safety population].

AEs in Study P008 were coded using MedDRA version 21.1 and were defined as: any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure; any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the investigational product is also an adverse event.

In all trials, participants were supplied comment cards to capture information on AEs, compliance, and concomitant medication. All adverse events that occurred after the consent form was signed but before randomization were reported by the investigator if they caused the participant to be excluded from the trial or were the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. All adverse events (duration of AE, severity of AE, relationship of timing of AE to the use of investigational product, action taken and/or outcome, and seriousness) that occurred from the time of randomization through 14 days following cessation of treatment were recorded by the investigator at each study visit on the AE case report forms (CRF) from comment cards. The investigator followed all participants with non-serious and serious adverse events for outcome.

Serious adverse events (SAEs) were defined as any adverse event occurring at any dose or during any use of the investigational product that results in death, is life threatening, results in persistent or significant disability/incapacity, results in or prolongs an existing inpatient hospitalization, is a congenital anomaly/birth defect, or can be

classified as “other important medical event” (note: other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously). In addition to the above criteria, adverse events of cancer and overdose, although not considered SAEs per the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) definition of SAEs, were considered SAEs by the investigator and were reportable to the Applicant in the SAE timeframe.

The scale used by the investigator for intensity grading of adverse events is displayed in Table 18.

Table 18. Study P008: Adverse Event Intensity Grading Scale used by Investigator

Intensity	Description
Mild	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)

Source: Study P008 Protocol, Section 7.2.4, Table 7, p. 57-58.

Safety of the investigational product (IP), Ragwitek, was assessed in the safety population by evaluation of: adverse events [data collected through e-diaries and comment cards (which also captured compliance and concomitant medication use) or through direct inquiry by study staff (at study visits)], pre-specified local application site reactions (data collected passively throughout the trial and data collected actively through solicitation for the first 28 days of treatment through a data collection tool termed the SLIT report card), vital signs (data collected at study visits throughout the trial), pulmonary function testing (data collected at specific study visits), and physical examination (data collected at the screening study visit and at the end of season/ discontinuation study visit).

Adverse Events of Special Interest

Selected AEs (non-serious or serious) were pre-specified as ‘adverse events of special interest’ (AESIs) and as ‘events of clinical interest’ as they were considered critical for the evaluation of the safety profile for which collection of additional data was determined to be necessary. The AEs designated as AESIs were “pre-specified local application site reactions” (common with sublingual administration of allergen to allergic participants). The AEs designated as events of clinical interest were systemic allergic reactions including anaphylactic reactions, events treated with epinephrine, severe local swelling or edema of the mouth and/or throat, severe treatment-related asthma exacerbations, eosinophilic esophagitis, an overdose of the investigational product, or abnormal liver function tests. AESIs were reported for the time period beginning at randomization through 14 days following cessation of treatment, whether related to the investigational product or not (see Section 6.1.12.5 for data on AESIs).

Reviewer Comment:
The Applicant used the term "pre-specified local application site reactions" for those reactions that were pre-specified. Since the term "local" describes areas of the body proximal to the site of administration, the term "application site" has been removed. The list of pre-specified adverse reactions is listed below under the subheading entitled, "Pre-specified Local Adverse Reactions".

Pre-specified local adverse reactions were collected both throughout the entire duration of the trial, in an unsolicited manner, via electronic diaries and study visits (herein referred to as 'pre-specified unsolicited local adverse reactions') and for the 1st 28 days of the trial, in a solicited manner, via a SLIT report card (herein referred to as 'pre-specified solicited local adverse reactions'). Since the Applicant reported data on pre-specified local adverse reactions in general (which included both the solicited and unsolicited adverse reactions under this terminology), use of the terminology "pre-specified local adverse reactions" will include both those that were unsolicited (over the full duration of the trial) and those that were solicited (over the first 28 days of the trial). Data on pre-specified solicited local adverse events (1st 28 days only) were provided by the Applicant with review of the PI and will be provided as a subset of the collective pre-specified local adverse event data below (see subsection entitled, "Pre-specified Solicited Local Adverse Reactions").

Finally, AEs designated by the Applicant as 'AESIs' (pre-specified unsolicited and solicited local adverse reactions) and 'events of clinical interest' (list above) will be herein collectively referred to as AESIs (thereby removing the term 'events of clinical interest').

Pre-specified Local Adverse Reactions
Local adverse events associated with the sublingual route of administration of allergen immunotherapy identified by the World Allergy Organization (WAO) as local adverse reactions include the following MedDRA (version 14.1) preferred terms: dysgeusia, oral pruritus, lip swelling, oral pruritus, mucosal edema, ear pruritus, swollen tongue, glossodynia, mouth ulceration, tongue ulceration, throat irritation, pharyngeal edema, nausea, abdominal pain upper, vomiting, abdominal pain, and diarrhea. [17]

The following local adverse reactions occurring within the first 60 minutes after investigational product intake were pre-specified for prospective collection as follows:

- ear pruritus
- oral pruritus
- tongue pruritus
- lip edema/swelling
- mouth edema/swelling
- tongue edema/swelling
- oropharyngeal edema/swelling

- palatal edema/swelling
- pharyngeal edema/throat tightness
- throat irritation

Pre-specified local adverse reactions were characterized further by collecting information on onset, duration in minutes (for AEs that occurred on Day 1), and duration in days (for AEs that occurred on Days 2 to Day 28).

Pre-specified solicited local adverse reactions were collected for the first 28 days of the trial via the SLIT report card. Pre-specified unsolicited local adverse reactions were collected for the duration of the trial via electronic diaries and study visits.

Intensity of pre-specified local adverse reactions due to SLIT was assessed by 2 different methods which defined intensity as mild, moderate, or severe: assessment of intensity grading as determined by the investigator (Table 18) and assessment of intensity grading as determined by the WAO grading system for local adverse events due to SLIT (Table 19). [17]

Table 19. World Allergy Organization Grading System for Local Adverse Events due to Sublingual Immunotherapy

Intensity	Grade	Description
Mild	1	Not troublesome; does not result in use of symptomatic treatment; no discontinuation of SLIT
Moderate	2	Troublesome; results in use of symptomatic treatment; no discontinuation of SLIT
Severe	3	Troublesome; results in use of symptomatic treatment; discontinuation of SLIT

Source: Study P008 Supplemental Statistical Analysis Plan, Section 3.2.5.2, p. 18.
Abbreviations: SLIT= sublingual immunotherapy, AE= adverse event
Note: The original WAO Grading System for Local Adverse Events due to SLIT is displayed in this table. This grading system was modified for Study P008 in that participants were not asked to indicate if they considered the AE "troublesome" or "not troublesome".

Reviewer Comment:
Thorough evaluation of local and systemic allergic reactions in the pediatric population for this investigational SLIT product was appropriate as these are known adverse reactions to SLIT (which occur due to exposure of an allergic population to the allergen to which they are allergic).

Of note, descriptions for each of the intensities (mild, moderate, severe) in the intensity grading scale used by the investigator (Table 18) specify degree of interference with activity, while those of the WAO Grading System (Table 19) specify whether symptomatic treatment was used and whether SLIT was continued ; therefore, intensity of pre-specified local

adverse events (the only category of adverse events for which the WAO Grading System was used in addition to the investigator grading scale) reported in the CSR for Study P008 is specified by the grading scale used for each particular assessment (intensity descriptors such as "by the investigator" or "per WAO criteria" were provided by the Applicant proceeding the intensity grade of a given pre-specified local adverse reaction (see end of subsection on Pre-specified Local Adverse Reactions in Section 6.1.12.5).

6.1.12.2 Overview of Adverse Events

Nearly three-quarters of participants (74.6%) reported at least 1 AE. The Ragwitek group reported a higher number of AEs, IP-related AEs, and discontinuations due to AEs than the placebo group. Overall, 48.7% of participants experienced AEs determined to be related to the investigational product. The most frequently reported IP-related AEs (>20%) were throat irritation, oral pruritus, and ear pruritus, all of which occurred more often in the Ragwitek group than in the placebo group. The proportions of participants with SAEs (<2%) and IP-related SAEs (<1%) were low and comparable between the 2 groups. There were no deaths in this study. In general, the intensities of AEs as assessed by the investigators were mostly mild in severity. An overview of adverse events is provided in Table 20.

Table 20. Study P008: Overview of Adverse Events (Safety population)

Adverse Event Category	Ragwitek (N= 513) n (%)	Placebo (N=509) n (%)	Total (N=1,022) n (%)
with one or more AEs	420 (81.9)	342 (67.2)	762 (74.6)
with no AEs	93 (18.1)	167 (32.8)	260(25.4)
with IP-related AEs[1]	338 (65.9)	160 (31.4)	498 (48.7)
with non-serious AEs	420 (81.9)	340 (66.8)	760 (74.4)
with serious AEs	7 (1.4)	9 (1.8)	16 (1.6)
with serious IP-related AEs[2]	3 (0.6)	1 (0.2)	4 (0.4)
with dose modification due to an AE[3]	55 (10.7)	34 (6.7)	89 (8.7)
who died	0 (0.0)	0 (0.0)	0 (0.0)
discontinued IP due to an AE	20 (3.9)	5 (1.0)	25 (2.4)
discontinued IP due to an IP-related AE	17 (3.3)	2 (0.4)	19 (1.9)
discontinued IP due to a serious AE	2 (0.4)	4 (0.8)	6 (0.6)
discontinued IP due to a serious IP-related AE	2 (0.4)	1 (0.2)	3 (0.3)

Source: BLA 125478/293/0, Study P008 CSR, Section 12.1.1, Table 12-1, p. 58.
Abbreviations: AE= adverse event, IP= investigational product, N= total number of participants in treatment group, n (%) = number (%) of participants experiencing at least one event, percentages are based on the number of participants in each treatment group
[1] Determined by investigator to be related to the IP
[2] Defined as one of the following actions taken: dose reduced, dosing interrupted, treatment withdrawn
[3] One serious drug-related AE (oral pruritus in the Ragwitek group) was associated with an overdose; this AE did not meet ICH criteria for seriousness

Data for participants with 'non-serious AEs' (of mild, moderate, or severe intensity) that were IP-related were provided in the CSR (see Study P008 CSR, Section 14 Supplemental Tables and/ or Figures, Section 14.3.1.2, Table 14.3-10, p. 289).
Of the participants in the Ragwitek (n= 513) and placebo (n= 509) groups (n= 513), 48.7% were noted have one or more IP-related AEs [Ragwitek group: 65.9% (n= 338);

placebo group: 31.4% (n= 160)], of which 43.4% were graded as mild [Ragwitek group: 56.9% (n= 292); placebo group: 29.9% (n= 152)], 5.0% were graded as moderate [Ragwitek group: 8.4% (n= 43); placebo group: 1.6% (n= 8)], and 0.3% were graded as severe [Ragwitek group: 0.6% (n= 3); placebo group: 0% (n=0)]. The following AEs were graded as severe: oral pruritus (Ragwitek group, n=1), laryngitis (Ragwitek group, n=1), and eczema (Ragwitek group, n=1).

The most frequently reported AEs in ≥2% of participants were throat irritation, oral pruritus, and ear pruritus; the proportion of participants with these AEs was higher in the Ragwitek group than in the placebo group (Table 21).

Table 21. Study P008: Summary of Most Frequent Relevant Adverse Events* in ≥2% of Participants by System Organ Class and Preferred Term (Safety population)

System Organ Class Preferred Term	Ragwitek (N= 513) n	Ragwitek (N= 513) (%)	Placebo (N=509) n	Placebo (N=509) (%)	Total (N=1,022) n	Total (N=1,022) (%)
Ear and Labyrinth Disorders	**184**	**(35.9)**	**40**	**(7.9)**	**224**	**(21.9)**
Ear pruritus	177	(34.5)	35	(6.9)	212	(20.7)
Eye Disorders	**31**	**(6.0)**	**33**	**(6.5)**	**64**	**(6.3)**
Eye pruritus	14	(2.7)	18	(3.5)	32	(3.1)
Gastrointestinal Disorders	**317**	**(61.8)**	**155**	**(30.5)**	**472**	**(46.2)**
Abdominal pain	16	(3.1)	12	(2.4)	28	(2.7)
Abdominal pain upper	54	(10.5)	30	(5.9)	84	(8.2)
Aphthous ulcer	15	(2.9)	7	(1.4)	22	(2.2)
Diarrhea	26	(5.1)	21	(4.1)	47	(4.6)
Enlarged uvula	33	(6.4)	2	(0.4)	35	(3.4)
Glossitis	24	(4.7)	7	(1.4)	31	(3.0)
Glossodynia	64	(12.5)	13	(2.6)	77	(7.5)
Lip edema	13	(2.5)	0	(0.0)	13	(1.3)
Lip pruritus	17	(3.3)	1	(0.2)	18	(1.8)
Lip swelling	66	(12.9)	7	(1.4)	73	(7.1)
Mouth swelling	18	(3.5)	0	(0.0)	18	(1.8)
Nausea	70	(13.6)	43	(8.4)	113	(11.1)
Oral pain	64	(12.5)	16	(3.1)	80	(7.8)
Oral pruritus	247	(48.1)	62	(12.2)	309	(30.2)
Stomatitis	34	(6.6)	6	(1.2)	40	(3.9)
Swollen tongue	56	(10.9)	4	(0.8)	60	(5.9)
Tongue pruritus	23	(4.5)	3	(0.6)	26	(2.5)
Tongue ulceration	12	(2.3)	5	(1.0)	17	(1.7)
Vomiting	22	(4.3)	15	(2.9)	37	(3.6)
Nervous System disorders	**63**	**(12.3)**	**65**	**(12.8)**	**128**	**(12.5)**
Dysgeusia	21	(4.1)	12	(2.4)	33	(3.2)
Headache	45	(8.8)	49	(9.6)	94	(9.2)
Respiratory, Thoracic, Mediastinal Disorders	**315**	**(61.4)**	**191**	**(37.5)**	**506**	**(49.5)**
Asthma	15	(2.9)	25	(4.9)	40	(3.9)
Cough	30	(5.8)	30	(5.9)	60	(5.9)
Nasal congestion	11	(2.1)	14	(2.8)	25	(2.4)
Oropharyngeal pain	25	(4.9)	29	(5.7)	54	(5.3)
Pharyngeal edema	58	(11.3)	8	(1.6)	66	(6.5)
Rhinorrhea	16	(3.1)	17	(3.3)	33	(3.2)
Sneezing	16	(3.1)	16	(3.1)	32	(3.1)
Throat irritation	254	(49.5)	98	(19.3)	352	(34.4)

Source: BLA 125478/293/0, Study P008 CSR, Section 12.1.1, Table 12-2, p. 59.

Abbreviations: N= total number of participants in treatment group, n (%) = number (%) of participants experiencing at least one event, percentages are based on the number of participants in each treatment group
* all adverse events (Solicited Local Adverse Reactions and Unsolicited Adverse Events)

Reviewer Comment:
Adverse reactions reported in ≥5% of adults were throat irritation, oral pruritus, ear pruritus, oral paresthesia, mouth edema, and tongue pruritus. Adverse reactions reported in ≥5% of children and adolescents 5 through 17 years of age (see totals in Table 19) were: throat irritation, oral pruritus, ear pruritus, lip swelling, glossodynia, nausea, oral pain, pharyngeal edema, swollen tongue, abdominal pain upper, stomatitis, and enlarged uvula. While terminology for many of the reported adverse events overlap in meaning, the following symptoms were reported by ≥5% of children and adolescents that were not reported by ≥5% of adults: lip swelling, glossodynia, nausea, swollen tongue, upper abdominal pain, stomatitis, and enlarged uvula. Thus, these adverse events appear to be more common in children and adolescents than in adults.

6.1.12.3 Deaths

There were no deaths in Study P008.

6.1.12.4 Nonfatal Serious Adverse Events

The proportion of participants with SAEs was low (1.6% overall) in both treatment groups (Ragwitek group: 1.4%; placebo group 1.8%). The most frequently reported SAE was asthma, which occurred only in the placebo group (0.6%, n= 3). SAEs in the Ragwitek group other than those listed in Table 19 below were categorized in the SOCs of Infections and Infestations (0.6%, n=3) and Injury, Poisoning, and Procedural Complications (0.4%, n=2). Serious AEs determined to be related to the investigational product are summarized in Table 22, with low incidence (<1%) overall.

Table 22. Study P008: Serious Adverse Events Related to the Investigational Product (Safety population)

System Organ Class Preferred Term	**Ragwitek (N= 513) n (%)**	**Placebo (N= 509) n (%)**	**Total (N= 1,022) n (%)**
Participants with one or more IP-related SAEs	3 (0.6)	1 (0.2)	4 (0.4)
Participants with no IP-related SAEs	510 (99.4)	508 (99.8)	1018 (99.6)
Gastrointestinal Disorders	**1 (0.2)**	**0 (0.0)**	**1 (0.1)**
Oral pruritus	1 (0.2)	0 (0.0)	1 (0.1)
Immune System Disorders	**1 (0.2)**	**1 (0.2)**	**2 (0.2)**
Hypersensitivity	1 (0.2)	1 (0.2)	2 (0.2)
Infections and Infestations	**1 (0.2)**	**0 (0.0)**	**1 (0.1)**
Laryngitis	1 (0.2)	0 (0.0)	1 (0.1)

Source: BLA 125478/293/0, Study P008 CSR, Section 12.2.1.2, Table 12-6, p. 65.
Abbreviations: SAE= serious adverse event, N= total number of participants in treatment group, n (%) = number (%) of participants experiencing at least one event, percentages are based on the number of participants in each treatment group

Narratives of Participants with IP-related SAEs [Ragwitek Group (n=3)]
The participant with the IP-related SAE of oral pruritus was a 17-year-old female with a history of ARC, atopic dermatitis, asthma, drug allergy, and food allergy. On Day 64, the participant experienced 2 minutes of oral pruritus after accidentally taking 2 doses of study medication (meeting the protocol definition of overdose which was pre-specified as an SAE). The symptom was mild in intensity as no treatment was administered and resolved that day.

The participant with the IP-related SAE of hypersensitivity was an 11-year-old female with history of ARC and cluster headache. The participant experienced various local allergic reactions within 60 minutes after administration of study medication beginning on Day 1. These allergic reactions occurred on and off for the next 25 days: the participant was treated with loratadine on Day 4 for lip swelling, on Days 9 and 10 for stomatitis, on Days 15 and 16 for swollen tongue, and from Days 22 to 25 for throat irritation and swelling. All local allergic reactions resolved by Day 25 and all were considered related to study medication by the investigator. On day 26, the participant experienced a rash on the abdomen and cheeks which generalized over the body and face as the day progressed. The participant was treated at home with IM dexamethasone and PO loratadine and the rash decreased in intensity but did not resolve. On Day 27 the rash increased again to the same intensity as on the previous day. The participant was treated at home with IM dexamethasone and PO loratadine and the rash decreased by the evening. On Day 28 no new rash was present, and the event was reported to the investigator, who diagnosed it as hypersensitivity (SAE, systemic allergic reaction of urticaria) of moderate in intensity and an SAE of 'other important medical event'. On Day 29 the participant was examined at the study site and localized face and extremity hyperemia with mild itching and single urticaria elements on the abdomen were noted. The participant's general condition was reported as mild and loratadine was prescribed by an allergist as follow-up therapy. The study site contacted the participant's caregiver periodically as follow-up support. Hypersensitivity resolved on Day 32. The participant received the last dose of study medication on Day 25 and discontinued from the study due to hypersensitivity on Day 29, with last contact on Day 41. The investigator considered hypersensitivity related to study medication.

The participant with the IP-related SAE of laryngitis was a 10-year-old male with a history of ARC, asthma, and headache. On Day 126 (during ragweed season) the participant experienced nasal congestion, neck pruritus, laryngitis, and a feeling of a lump in the throat approximately 30 minutes after taking study medication that evening; there was no severe throat swelling. On that day the participant also experienced a headache, lasting 4 hours, vomiting (resolved that day), and worsened allergic rhinitis symptoms (all nonserious AEs). The participant was treated at home with albuterol and loratadine for laryngitis symptoms, mometasone furoate for blocked nose, and dipyrone for headache. The participant did not improve and was hospitalized on Day 126 with symptoms of laryngitis (throaty voice and barking cough); the participant did not have an infection (axillary temperature 36.5°C). No laboratory tests or x-rays were performed. The participant was treated with inhaled racemic epinephrine hydrochloride and sodium chloride for laryngitis (Days 126 to 127). The investigator assessed the event of laryngitis as severe in intensity and related to study medication (the investigator could not exclude that the symptoms were related to the study medication). On Day 132 the Applicant identified the laryngitis as a suspected unexpected serious adverse reaction (SUSAR) and study medication was unblinded by the Applicant. On Day 139 the

participant discontinued from the study due to laryngitis (SUSAR and drug-related SAE met protocol specified discontinuation criterion), with the last dose administered on Day 126. The participant completed the follow-up visit on Day 153.

6.1.12.5 Adverse Events of Special Interest (AESI)

AESIs were designated as the following: pre-specified local adverse reactions (including pre-specified solicited local adverse reactions for the first 28 days and pre-specified unsolicited local adverse reactions for the duration of the study), systemic allergic reactions including anaphylactic reactions, events treated with epinephrine, severe local swelling or edema of the mouth and/or throat, severe treatment-related asthma exacerbations, eosinophilic esophagitis, an overdose of the investigational product, or abnormally levels of liver function tests. AESIs were reported for the time period from randomization through 14 days following cessation of treatment, whether considered related to the investigational product or not. An overview of AESIs is displayed in Table 23.

Table 23. Study P008: Overview of Adverse Events of Special Interest (Safety population)

AESIs	Ragwitek (N= 513) n (%)	Placebo (N= 509) n (%)	Total (N= 1,022) n (%)
Pre-specified Local Adverse Reactions	331 (64.5)	137 (26.9)	468 (45.8)
Systemic Allergic Reactions including Anaphylaxis	3 (0.6)	1 (0.2)	4 (0.4)
Events Treated with Epinephrine	1 (0.2)	1 (0.2)	2 (0.2)
Severe local swelling or edema of the mouth and/or throat	0 (0.0)	0 (0.0)	0 (0.0)
Severe IP-related asthma exacerbations	0 (0.0)	0 (0.0)	0 (0.0)
Eosinophilic Esophagitis	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal liver function lab values	0 (0.0)	0 (0.0)	0 (0.0)
Overdose without adverse effect	6 (1.2)	5 (1.0)	11 (1.1)

Source: Adapted from BLA 125478/293/0, Study P008 CSR, Section 12.2.3, p. 68-77.
Abbreviations: AESIs= adverse events of special interest, IP= investigational product, N= total number of participants in treatment group, n (%) = number (%) of participants experiencing at least one event, percentages are based on the number of participants in each treatment group

Pre-specified Local Adverse Reactions

Pre-specified local adverse reactions, including both solicited and unsolicited local adverse reactions, are provided in Table 24. Pre-specified solicited local adverse reactions are provided in Table 25 and pre-specified unsolicited local adverse reactions are provided in Table 26.

A higher number of participants in the Ragwitek group reported pre-specified local adverse reactions compared to the placebo group. In the Ragwitek group, the most frequently reported pre-specified local adverse reactions were throat irritation, oral

pruritus, and ear pruritus. Most of the pre-specified local adverse reactions were reported as mild in intensity by the investigator. With the exception of the oral pruritus event discussed in Section 6.1.12.4, no pre-specified local adverse reactions were reported as an SAE.

Table 24. Study P008: Pre-specified Local Adverse Reactions (Safety population)

System Organ Class Preferred Term	**Ragwitek (N= 513) n (%)**	**Placebo (N= 509) n (%)**	**Total (N= 1,022) n (%)**
Participants with one or more local adverse reactions	331 (64.5)	137 (26.9)	468 (45.8)
Participants with no local adverse reactions	182 (35.5)	372 (73.1)	554 (54.2)
Ear and Labyrinth Disorders	**177 (34.5)**	**35 (6.9)**	**212 (20.7)**
Ear pruritus	177 (34.5)	35 (6.9)	212 (20.7)
Gastrointestinal Disorders	**264 (51.5)**	**67 (13.2)**	**331 (32.4)**
Lip edema	13 (2.5)	0 (0.0)	13 (1.3)
Lip swelling	66 (12.9)	7 (1.4)	73 (7.1)
Mouth swelling	18 (3.5)	0 (0.0)	18 (1.8)
Mouth edema	3 (0.6)	0 (0.0)	3 (0.3)
Oral pruritus	247 (48.1)	62 (12.2)	309 (30.2)
Palatal edema	4 (0.8)	0 (0.0)	4 (0.4)
Palatal swelling	1 (0.2)	0 (0.0)	1 (0.1)
Swollen tongue	56 (10.9)	4 (0.8)	60 (5.9)
Tongue edema	8 (1.6)	0 (0.0)	8 (0.8)
Tongue pruritus	23 (4.5)	3 (0.6)	26 (2.5)
Respiratory, Thoracic, Mediastinal Disorders	**261 (50.9)**	**104 (20.4)**	**365 (35.7)**
Oropharyngeal swelling	1 (0.2)	0 (0.0)	1 (0.1)
Pharyngeal edema	58 (11.3)	8 (1.6)	66 (6.5)
Throat irritation	254 (49.5)	98 (19.3)	352 (34.4)
Throat tightness	3 (0.6)	0 (0.0)	3 (0.3)

Source: BLA 125478/ 293, Study P008 CSR, Section 12.2.3.1.1, Table 12-9, p. 69.
Abbreviations: N= total number of participants in treatment group, n (%) = number (%) of participants experiencing at least one event, percentages are based on the number of participants in each treatment group

After the first dose of study treatment, the time to onset of pre-specified local adverse reactions in the Ragwitek group occurred at a median of 1 day to 10 days; the median varied from 1 day to 8 days in the placebo group. In general, the events with irritation or pruritus were more common and had earlier median onsets than the events with swelling and/or edema in both treatment groups. In the Ragwitek group, the median duration of pre-specified local adverse reactions varied from 10.5 to 25.0 minutes after administration of the first dose of study intervention; the median duration in the placebo group varied from 7.5 to 33.0 minutes. In general, the events with swelling persisted longer than the events without swelling (i.e., itch or irritation) in both treatment groups. Median duration of pre-specified local adverse reactions over Day 2 to Day 14 varied from 1.0 to 2.5 days in both the Ragwitek and placebo groups. Over Day 15 to Day 28, the Ragwitek group median durations varied from 1.0 to 5.0 days, and the placebo group varied from 1.0 to 2.5 days. For both day ranges, the majority of the median durations was 1 day. Most participants experienced pre-specified local adverse reactions of short duration at the start of treatment, with fewer pre-specified local adverse reactions occurring in the second half of the first 28 days of treatment.

In the assessment by the investigator, 45.6% of participants reported pre-specified local adverse reactions of SLIT, the majority (93.6%) of which were considered to be mild in intensity by the investigator. Assessment using the modified WAO criteria showed similar results. In the Ragwitek group, one incidence of swollen tongue was assessed as severe using the modified WAO criteria but was not assessed as severe by the investigator, while one incidence of oral pruritus was assessed as severe by the investigator but was not assessed as severe using the modified WAO criteria.

Pre-specified Solicited Local Adverse Reactions (Day 1 through Day 28)
Pre-specified solicited local adverse reactions collected during the first 28 days of the study via the SLIT report card are provided in Table 25. Please see Section 6.1.12.1 for the pre-specified list of adverse reactions.

The participants in Study P008 were instructed to report local adverse events for the first 28 days of treatment using the SLIT report card listing 16 pre-defined patient-friendly terms. During visit 3 the SLIT report card was reviewed and any adverse event data from the SLIT report card was entered into the electronic case report form (eCRF) based on appropriate assessment made by the investigator. Based on this assessment, the adverse event data was entered into the eCRF using a free text field and the adverse event was marked in the clinical database as having originated from the SLIT report card. Fifty-one preferred terms (PTs) were marked in the clinical database as originating from the SLIT report card. However, some of these PTs did not match the clinical picture of the pre-defined patient-friendly terms. Therefore, from the 51 PTs, the Sponsor identified 28 PTs that each corresponded to a pre-defined patient-friendly term listed in the SLIT report card. These 28 terms were then grouped under the pre-defined patient- friendly terms used in the SLIT report card (information on specific term groupings above was provided by the Applicant in STN 125478/293/13, not shown here). The remaining 23 preferred terms (chest pain, dysphagia, dyspnea, eye pruritus, eye swelling, mouth injury, nasal congestion, oral disorder, oral mucosal eruption, oral mucosal erythema, oropharyngeal pain, panic reaction, paresthesia oral, pharyngeal paresthesia, pharyngeal ulceration, retching, sensation of foreign body, throat tightness, tongue eruption, tongue injury, tongue pruritus and urticaria) were assessed by the Sponsor to be of a different clinical or anatomical nature than the pre-defined patient-friendly terms listed in the SLIT report card and thus not included in the Table 25 (Table 2 of the PI). However, these adverse reactions are included in Table 26 (Table 3 of the PI) if they occurred in ≥1% of the participants in either treatment group.

Table 25. Study P008: Pre-specified Solicited Local Adverse Reactions from Day 1 through Day 28 on SLIT Report Card (Safety population)

System Organ Class Preferred Term	**Ragwitek (N= 513) %**	**Placebo (N= 509) %**
Ear and Labyrinth Disorders	**--**	**--**
Itching in the ear	33.9	6.3
Gastrointestinal Disorders	**--**	**--**
Itching in the mouth	47.8	11.2
Mouth pain	18.9	4.5
Swelling of the lips	13.8	1.2

System Organ Class Preferred Term	**Ragwitek (N= 513) %**	**Placebo (N= 509) %**
Nausea	11.5	3.3
Swelling of the tongue	11.3	0.8
Stomach pain	10.1	4.5
Swelling of the uvula/ back of the mouth	9.9	0.4
Mouth ulcer/ sore in the mouth	8.4	2.2
Tongue ulcer/ sore on the tongue	6.8	2.2
Diarrhea	2.7	1.2
Vomiting	1.2	0
Nervous System Disorders	--	--
Taste alteration/ food tastes different	3.9	2.0
Respiratory, Thoracic, Mediastinal Disorders	**--**	**--**
Throat irritation/ tickle	48.3	17.7
Throat swelling	10.7	1.6

Source: Prescribing Information dated as revised 4/2021, Ragwitek, Section 6, Table 2, p. 6.
Abbreviations: N= total number of participants in treatment group, %= percentage of participants experiencing at least one event, percentages are based on the number of participants in each treatment group

Pre-specified Unsolicited Local Adverse Reactions (duration of Study P008)
Pre-specified unsolicited local adverse reactions collected for the duration of the study and recorded in e-diaries and reported at study visits are provided in Table 26 which contains all adverse reactions reported in 1% or more in at least one treatment group, except the solicited adverse reactions in Table 25 (Table 2 in the PI). Please see Section 6.1.12.1 for the pre-specified list of adverse reactions.

Table 26. Study P008: Pre-specified Unsolicited Local Adverse Reactions (Safety population)

System Organ Class Preferred Term	**Ragwitek (N= 513) %**	**Placebo (N= 509) %**
Ear and Labyrinth Disorders	**--**	**--**
Ear pruritus	4.5	0.2
Gastrointestinal Disorders	**--**	**--**
Oral pruritus	7.8	1.0
Tongue pruritus	4.5	0.4
Lip swelling	1.9	--
Paresthesia oral	1.9	0.4
Mouth swelling	1.8	--
Dysphagia	1.6	0.2
Nausea	1.6	0.4
Oral pain	1.6	0.4
Swollen tongue	1.4	--
Respiratory, Thoracic, and Mediastinal Disorders	**--**	**--**
Throat irritation	7.6	1.6
Oropharyngeal pain	1.8	0.4
Sneezing	1.6	0.4
Pharyngeal edema	1.2	**--**
Rhinorrhea	1.2	0.4
Skin and Subcutaneous Tissue Disorders	**--**	**--**

System Organ Class Preferred Term	**Ragwitek (N= 513) %**	**Placebo (N= 509) %**
Pruritus	1.2	0.2

Source: Prescribing Information dated as revised 4/2021, Ragwitek, Section 6, Table 3, p. 7.
Abbreviations: N= total number of participants in treatment group, %= percentage of participants experiencing at least one event, percentages are based on the number of participants in each treatment group

Systemic Allergic Reactions including Anaphylactic Reactions

Reviewer Comment:

- *The Applicant reported systemic allergic reactions using the term 'hypersensitivity' throughout the Study P008 CSR.*
- *Definitions for systemic allergic reaction and anaphylaxis (severe systemic allergic reaction) were not explicitly provided in the protocol or CSR for Study P008. The lack of provision of definitions did not prevent the monitoring or ascertainment of systemic allergic reactions. The safety monitoring was adequate and performed by qualified health care professionals who were able to monitor for and diagnose anaphylaxis.*

The proportion of participants with hypersensitivity was low (≤0.6%) in both treatment groups [3 in the Ragwitek group (2 were related to IP and 1 was unrelated to IP) and 1 in the placebo group] (Table 23). There were no incidences of anaphylaxis (severe systemic allergic reaction) during treatment; 1 event occurred pre-randomization in the placebo group (cause of anaphylaxis in this participant was not provided in the adverse event narratives).

Systemic Allergic Reactions Related to IP

Three participants (2 in the Ragwitek group and 1 in placebo) had IP-related systemic allergic reactions.

- One participant (Ragwitek group) reported hypersensitivity events (skin/face/neck itching eye itching/swelling, sneezing, runny/itching nose, neck/abdomen redness) beginning on Day 6 (i.e., outside of ragweed pollen season) that resolved by Day 26. The events were considered mild in intensity by the investigator, were treated on two occasions with an antihistamine, and resolved within minutes to less than an hour. This participant subsequently discontinued from the study on Day 34 due to persistent local allergic symptoms (i.e., mild swollen tongue).
- One participant (Ragwitek group) reported hypersensitivity (i.e., urticaria/ generalized rash on body and face) on Day 26 (i.e., outside of ragweed pollen season), The event was considered moderate in intensity and serious by the investigator (see detailed narrative in Section 6.12.1.4), was treated with antihistamine and systemic corticosteroids, and resolved in one week. This participant discontinued the study due to this event.
- One participant (Ragwitek group) reported the AEs of dyspnea and pruritus (cheeks, arms, legs) on Day 1 (i.e., outside the ragweed pollen season) after taking the first dose of Ragwitek. These events were assessed by the investigator as moderate and mild in intensity, respectively, and IP-related. Both AEs resolved within 2 hours without

treatment and did not recur upon restarting trial medication 1 week later. The participant subsequently completed the study.

Reviewer Comment:
This case was captured through a search conducted for AEs that fulfilled the Modified Sampson Criteria for diagnosis of anaphylaxis to detect cases of potential systemic allergic reactions that may not have been identified by the investigator. [18] While this case was considered a systemic allergic reaction, the Applicant did not diagnose the combination of these 2 events as anaphylaxis (i.e., a severe systemic allergic reaction); the reviewer agrees with this assessment based on the description of the two events above (self-resolution, lack of objective data to determine severity of dyspnea).

- One participant (placebo group) reported hypersensitivity (i.e., hives/ papular rash with itching on hands, body, and lower limbs) on Day 7 (i.e., outside of ragweed pollen season) that was considered moderate in intensity and serious by the investigator. The event was treated with an antihistamine and systemic corticosteroids and resolved in one week. This participant discontinued the study due to this event.

Systemic Allergic Reactions Unrelated to IP
One participant in the Ragwitek group reported hypersensitivity (i.e., urticaria/ redness and itching on skin of the thorax after ingestion of strawberries) on Day 6, assessed as not IP-related by the investigator. The event was considered mild in intensity by the investigator, was treated with antihistamines, and resolved on Day 7.

Reviewer Comment:
The rate of systemic allergic reactions in this study was similar to the rate of systemic allergic reactions due to AIT in the allergic population (0.2-0.3%).

Events Requiring Epinephrine
Adverse events treated with epinephrine were designated as AESIs since systemic epinephrine use may be a surrogate for a more severe AE. Two participants (1 in the Ragwitek group and 1 in the placebo group) reported AEs that were treated with epinephrine (any route) (Table 23). Self-injectable epinephrine was provided to participants in countries where it was a regulatory requirement. None of these participants used the self-injectable epinephrine to treat an AE.

- One participant (Ragwitek group) experienced an SAE of laryngitis on Day 126 (see Section 6.1.12.4 for detailed narrative), for which the participant was hospitalized and treated with inhaled (racemic) epinephrine; the laryngitis resolved in 2 days. The event was considered to be related to study intervention and severe in intensity by the investigator. This event was identified as a suspected unexpected serious adverse reaction, and the treatment assignment was unblinded by the Applicant during the conduct of the study to satisfy safety reporting requirements. The participant was discontinued from the study due to the premature unblinding of study intervention as well as the protocol-specified discontinuation criterion of IP-related serious AE. The treatment assignment

remained blinded to the participant and to all personnel directly responsible for study conduct, including the investigator, other site personnel, and Applicant personnel. The participant was not excluded from any analysis populations.

- One participant (placebo group) experienced urticaria on Day 136 that was considered by the investigator to be moderate in intensity and not related to study intervention. The participant visited the emergency room and received treatment including intramuscular epinephrine. The event resolved in a week, and the participant subsequently completed the study.

Other AESIs

In terms of the other AEs designated as AESIs (Table 23), no events of severe local swelling or edema of the mouth and/or throat were reported; no events of severe treatment-related asthma exacerbations were reported; no events of eosinophilic esophagitis were reported; no abnormal liver function laboratory values were reported that met the predetermined criteria for a drug induced liver injury (and no increases in liver enzymes or other liver-related effects were reported as AEs). The most frequently reported AESI in both treatment groups was overdose (defined as taking more than 1 tablet per day of study treatment) without adverse effect (Ragwitek group, n=6; placebo group, n=5; approximately 1% in both groups). There was one overdose that occurred in the Ragwitek group (participant took 1 extra dose of Ragwitek), which resulted in oral pruritus of mild intensity. No treatment was required as the event resolved 2 minutes after onset.

Reviewer Comment:
Of the 11 participants who were reported as having overdosed, 9 participants were recorded as having accidentally overdosed, and 2 participants were recorded as having intentionally overdosed. Per the adverse event narratives document, of the participants that were recorded as having accidentally overdosed, one participant reported taking extra doses on several days seeking relief of general allergy symptoms, and the other participants or their parents/ guardians reported taking extra doses on a given days due to memory lapse of already having taken the daily dose earlier that day. Most of these participants were 12 through 17 years of age; however, three participants were 7 through 10 years of age. Of the two participants that were recorded as having intentionally overdosed, one (14 years of age) decided to omit the daily dose one night so that usual adverse effects were not experienced at bedtime and took two doses 12 hours apart the next day, and the other (13 years of age) took two doses 12 hours apart on one day due to lack of witness available for the 30-minute observation period post-dose the previous day.

6.1.12.6 Clinical Test Results

Not applicable.

6.1.12.7 Dropouts and/or Discontinuations due to Adverse Events

Overall, 2.4% of participants reported AEs resulting in study discontinuation, with more events reported in the Ragwitek group (3.9%, n= 20) than in the placebo group (1.0%, n=5). The intensities of discontinuations due to AEs as assessed by the investigators were mostly mild and moderate.

In the Ragwitek group, the most reported AE resulting in discontinuation was throat irritation, which occurred in 3 participants (0.6%), followed by pharyngeal edema (0.4%, n= 2), swollen tongue (0.4%, n=2), tongue ulceration (0.4%, n=2), lip swelling (0.4%, n=2), glossodynia (0.4%, n=2), and dysphagia (0.4%, n=2). The following AEs resulted in discontinuation in 1 participant each (0.2%): ear pruritus, cheilitis, enlarged uvula, gingival ulceration, mouth swelling, nausea, oral disorder, oral pain, oral pruritus, tongue edema, asthenia, chest pain, pyrexia, hypersensitivity, laryngitis, headache, fear of disease, eczema, and urticaria.

In the placebo group, the most reported AE resulting in discontinuation was asthma (0.4%, n=2). Other AEs resulting in discontinuation in 1 participant each (0.2%) were: hypersensitivity, conduct disorder, and sneezing.

6.1.13 Study Summary and Conclusions

Efficacy data from the phase 3 study P008 show that treatment with Ragwitek (12 Amb a 1 U) resulted in a lower average TCS over the peak RS relative to placebo of -38.3% [treatment difference relative to placebo -38.3%; 95% confidence interval (-46.0, -29.7)] which met the pre-specified criteria for success. As discussed in Section 6.1.11, the success criteria for this trial [a treatment difference relative to placebo of at least -15% and the associated upper bound of the 95% confidence interval (CI) for this difference of at least -10% (i.e., no higher than -10%)] were chosen to reflect a minimal clinically important difference in symptoms and medication usage due to short ragweed pollen allergen. The results of the primary analysis (FAS population) were corroborated by sensitivity analyses in the FAS population, a sensitivity analysis in the PP population, and subgroup analyses in the FAS population. Lower average scores were similarly demonstrated for each of the key secondary endpoints (treatment difference relative to placebo): average TCS during the entire RS, average rhinoconjunctivitis DSS during the peak RS, and average rhinoconjunctivitis DMS during the peak RS.

Safety data from Study P008 revealed that the majority (81.9%) of participants in the Ragwitek group reported at least 1 adverse event (AE) over the course of the study and that the proportion of participants with AEs was comparable between the 2 age groups. The most frequently reported adverse events in the Ragwitek group were throat irritation, oral pruritus, and ear pruritus.

Discontinuation from the study due to an AE occurred in 3.9% of participants in the Ragwitek group and 1.0% in the placebo group. In the Ragwitek group, the most reported AE resulting in discontinuation was throat irritation, which occurred in 3 participants (0.6%), followed by pharyngeal edema (0.4%, n= 2), swollen tongue (0.4%, n=2), tongue ulceration (0.4%, n=2), lip swelling (0.4%, n=2), glossodynia (0.4%, n=2), and dysphagia (0.4%, n=2). The following AEs resulted in discontinuation in 1 participant each (0.2%): ear pruritus, cheilitis, enlarged uvula, gingival ulceration, mouth swelling, nausea, oral disorder, oral pain, oral pruritus, tongue edema, asthenia, chest pain, pyrexia, hypersensitivity, laryngitis, headache, fear of disease, eczema, and urticaria.

The incidence of SAEs overall was low (<2%) and similar in the Ragwitek and placebo groups.

AESIs were pre-specified solicited and unsolicited local adverse reactions, systemic allergic reactions including anaphylaxis, events treated with epinephrine, severe edema of the mouth and/or throat, severe drug-related asthma exacerbations, EoE, abnormal liver function values, and overdose without adverse effect. The rates of local adverse events that are known to occur with sublingual immunotherapy (SLIT) (pre-specified solicited and unsolicited local adverse events), however, was higher in the Ragwitek group (64.5%, n= 331) compared to the placebo group (26.9%, n=137), with a similar distribution of rates for pre-specified solicited local adverse reactions. Pre-specified solicited local adverse reactions were of mild intensity, transient (onset within the first 10 days of treatment), and of short duration (median of 30 minutes). Rates of systemic allergic reactions were low [Ragwitek group: 0.6% (n=3); placebo group: 0.2% (n=1)]; no cases of severe systemic allergic reactions (anaphylaxis) occurred during treatment. Two events were treated with epinephrine (one participant in the placebo group was treated with systemic epinephrine for urticaria, and one participant in the Ragwitek group was treated with inhaled racemic epinephrine for laryngitis). There were no cases of severe local edema of the mouth and/or throat, severe drug-related asthma exacerbations, eosinophilic esophagitis, or abnormal liver function values. The most frequently reported AESI in both treatment groups was overdose (defined as taking more than 1 tablet per day of study treatment) without adverse effect (approximately 1% in both groups; Ragwitek group, n=6; placebo group, n=5). There was one overdose that occurred in the Ragwitek group (participant took 1 extra dose of Ragwitek), which resulted in oral pruritus of mild intensity which self-resolved; most cases of overdose were unintentional and were of two doses taken on the same day due to a result of memory lapse with regard to having already taken the daily dose.

Overall, the AE profile appeared similar in participants with and without asthma at baseline and those who did and did not use inhaled corticosteroids (ICS). Of the participants with asthma, about one-third had ICS use at baseline; a higher proportion of participants using ICS at baseline in the Ragwitek group reported AEs compared with those in the placebo group.

The clinical data from Study P008 support the safety and effectiveness of Ragwitek in children and adolescents 5 through 17 years of age.

7. Integrated Overview of Efficacy

An integrated overview of efficacy is not applicable to this review as only one study (Study P008) contributed efficacy data for the pediatric population. Please see Section 6.1.11 for efficacy results.

8. Integrated Overview of Safety

An integrated overview of safety is not applicable to this review, as only one study (Study P008) contributed safety data for the pediatric population. Please see Section 6.1.12 for safety results.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No case of exposure to Ragwitek (or to placebo) during pregnancy was reported during clinical studies. These data were not sufficient to determine the presence or absence of Ragwitek-associated risks during pregnancy.

> *Reviewer Comment:*
> *Pregnancy was an exclusion criterion for studies in the clinical development program for Ragwitek; therefore, there are no data on safety of use of Ragwitek by pregnant women. Practice parameters for administration of allergen immunotherapy (developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology) state, "allergen immunotherapy can be continued but usually is not initiated in the pregnant patient and discontinuation of immunotherapy should be considered if the pregnancy occurs during the build-up phase and the patient is receiving a dose unlikely to be therapeutic." [19] This advice is based on of the risk of systemic allergic reactions and the possible respective effect on the mother and/or fetus. Since Ragwitek can lead to anaphylaxis, which can cause a dangerous decrease in blood pressure, and in turn could result in compromised placental perfusion and significant risk to a fetus, it is preferable to avoid initiating allergen immunotherapy during pregnancy.*

9.1.2 Use During Lactation

The safety of Ragwitek in women who are lactating has not been established.

> *Reviewer Comment:*
> *Lactation was an exclusion criterion for studies in the clinical development program for Ragwitek; therefore, there are no data on safety of use of Ragwitek in lactating women.*

9.1.3 Pediatric Use and PREA Considerations

The study reviewed in this supplemental BLA submission was a post-marketing requirement under the Pediatric Research Equity Act (PREA; Section 505B of the Federal Food, Drug, and Cosmetic Act), which requires that FDA consider the utility of studying use of an investigational drug product in all pediatric subpopulations. The pediatric study plan was proposed during phase 3 of clinical development in adults (see STN 125478.0.5 Request for Pediatric Study Waivers and Deferrals, dated June 27, 2013). At that time, FDA's Pediatric Review Committee (PeRC) and CBER agreed with the Applicant's request for:

- a waiver for pediatric studies assessing the safety and efficacy of ragweed AIT for the treatment of ragweed-pollen induced allergic rhinitis with or without conjunctivitis in children less than 5 years of age on the basis that "the product does not represent a meaningful therapeutic benefit over existing therapies in this population and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested. (The justification provided for this waiver was as follows: seasonal allergic rhinitis typically does not develop until at least 2 years of age, and at least two seasons of pollen allergen exposure are needed before it becomes clinically relevant Therefore, the number of patients with induced allergic rhinitis, caused by

allergens such as short ragweed, is very small in this age group. As recommended in the allergen immunotherapy treatment guideline, using allergen immunotherapy to treat allergic rhinitis in children under the age of 5 years is considered a Special Consideration. Allergen immunotherapy for inhalant allergens is usually not considered in the very young because there might be difficulty in communicating with the child regarding systemic reactions.)

- a deferral for pediatric studies assessing the safety and efficacy of ragweed AIT for the treatment of ragweed-pollen induced allergic rhinitis with or without conjunctivitis in children and adolescents 5 to 17 years of age until after approval of the Biologic License Application (BLA) for licensure of Ragwitek in adults

Reviewer Comment:
The Pediatric Study Plan (PSP) was discussed throughout clinical development with the Pediatric Review Committee (PeRC), who agreed with this plan. This reviewer also agrees with the rationale for requests for waiver and deferrals.

A meeting was held with FDA's Pediatric Review Committee during the BLA review cycle in which the findings of Study P008 and CBER's proposed release of the Applicant from the requirement to conduct Study P009 as initially proposed in the pediatric study plan were discussed (see Section 2.5 for further details). Briefly, after review of the data from Study P008, which supports use of Ragwitek in this age range and in which no new safety signals were identified that would require additional evaluation in this age group, CBER proposed to the Pediatric Review Committee (PeRC) that the Applicant be released from Study P009. PeRC agreed with the assessments provided by CBER with regard to the adequacy of the safety and efficacy data to support approval of Ragwitek for licensure in children and adolescents 5 through 17 years of age and with regard to release of the Applicant from the PMR Study P009. The Pediatric Review Committee determined that Study P008 fulfills the Applicant's PMR for pediatric studies assessing the safety and efficacy of Ragweed AIT for the treatment of ragweed-pollen induced allergic rhinitis with or without conjunctivitis.

9.1.4 Immunocompromised Patients

The safety and effectiveness of Ragwitek have not been established in immunocompromised individuals.

9.1.5 Geriatric Use

The pre-licensure clinical studies in the clinical development program included individuals ≥ 65 years of age; however, very few participants greater than 65 years of age were exposed to Ragwitek in these pre-licensure clinical studies. Data were insufficient to adequately evaluate safety and efficacy in the population > 65 years of age. Consequently, the indication for use in adults was limited to adults 18 through 65 years of age.

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

Not applicable.

10. CONCLUSIONS

Efficacy data from phase 3 Study P008 provide substantial evidence of effectiveness for Ragwitek in the treatment of ragweed-induced allergic rhinitis/rhinoconjunctivitis. Efficacy data show that treatment with Ragwitek (12 Amb a 1 U) resulted in a lower average total combined score over the peak ragweed season relative to placebo of -38.3% [treatment difference relative to placebo -38.3%; 95% confidence interval (-46.0, -29.7)] (primary efficacy endpoint), which met the pre-specified statistical criteria for success for this trial. These pre-specified criteria for success were a treatment difference relative to placebo of at least -15% and the associated upper bound of the 95% confidence interval (CI) for this difference of at least -10% (i.e., no higher than -10%)] and were chosen to reflect a minimal clinically important difference in symptoms and medication usage due to short ragweed pollen allergen. Lower average scores were similarly demonstrated for each of the key secondary endpoints (treatment difference relative to placebo): total combined score during the entire ragweed season, rhinoconjunctivitis daily symptom score during peak ragweed season, and rhinoconjunctivitis daily medication score during peak ragweed season.

Ragwitek was generally safe, with an AE profile characterized by frequent but transient local adverse reactions (assessed as mild or moderate in intensity) and rare systemic allergic reactions and epinephrine use. The higher incidence of the local adverse events seen in the Ragwitek group was communicated in labeling and will be monitored in routine post-marketing activities.

While a limitation of the results of Study P008 is generalizability to non-Caucasian populations due to the lack of racial diversity (possibly due to the enrollment of participants by study sites outside of the United States), post-licensure PMR Study P008 demonstrates that Ragwitek is safe and effective in children and adolescents 5 through 17 years of age.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 27 below summarizes the risk-benefit considerations for Ragwitek.

Table 27. Summary of Risk-Benefit Analysis of Ragwitek

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• IgE-mediated short ragweed pollen allergy is the chief cause of late summer and fall ARC in the US. • ARC is among the most common chronic conditions affecting both children and adults and affects up to 60 million children and adults in the US. • ARC can have a major impact on quality of life and is often associated with asthma, rhinosinusitis, and sleep disturbances. • ARC commonly coexists with asthma, which typically develops after allergic rhinitis.	• ARC is prevalent in the US pediatric population. • ARC impacts quality of life. • In a subset of patients, ARC precedes and contributes to allergic asthma.
Unmet Medical Need	• Currently available treatment for short ragweed pollen-induced ARC in pediatric age groups includes allergen avoidance, pharmacologic therapy (intranasal corticosteroids or oral, ocular, or intranasal antihistamines), and SCIT with short ragweed pollen allergen extract. o Allergen avoidance requires staying indoors with windows closed during ragweed pollen season which is usually hard to achieve and sustain. o Combined pharmacologic therapy regimens provide temporary relief from allergic symptoms and may be sufficient for a subset of mildly affected ARC patients but may not be effective in all patients and are not disease-modifying. o SCIT with ragweed pollen allergen extract offers the potential to reduce allergic symptoms and decrease the need for symptomatic treatment by increasing an individual's immune tolerance to a specific allergen but causes a substantial burden on the individual due to the level of discomfort associated with injections and local reactions, the inconvenience of the frequency of administration of the injections, the inconvenience of delivery (required to occur in a monitored healthcare setting due to the risk of systemic allergic reactions), and the risk of local and systemic allergic reactions (which are more common with SCIT than with SLIT).	• Because of the convenience of SLIT administration, its availability is expected to increase the use of immunotherapy to treat ARC in children and adolescents 5 through 17 years of age. • Ragwitek may have a significant impact on overall quality of life in this population.
Clinical Benefit	• Efficacy data from Study P008 in children and adolescents 5 through 17 years of age show that treatment with Ragwitek resulted in a lower average TCS over the peak RS of Ragwitek relative to placebo of -38.3%, as well as lower scores for Ragwitek relative to placebo of: average TCS during the entire RS, average rhinoconjunctivitis DSS during the peak RS, and average rhinoconjunctivitis DMS during the peak RS. • It is uncertain whether the treatment effect of Ragwitek is maintained beyond one or multiple courses of treatment.	• The totality of evidence for Ragwitek in children and adolescents 5 through 17 years of age supports effectiveness of Ragwitek for treatment of short ragweed pollen allergy and suggests clinically meaningful benefit. • Sublingual allergen immunotherapy may be disease-modifying.

	• The clinical study population had substantially less morbidity than patients who will be prescribed Ragwitek, which, in particular includes those with moderate to severe asthma.	
Risk	• The most common adverse events in children and adolescents are local adverse reactions which are frequent, of mild to moderate intensity, transient, and commonly occur during the first month of treatment. • The most substantial risks of Ragwitek are life threatening local or systemic allergic reactions. However, systemic allergic reactions (including anaphylaxis) and events requiring use of epinephrine were rare. • Although occurrence of EoE was not reported in the pre-licensure clinical study of Ragwitek in children and adolescents, EoE is known to be associated with SLIT products.	• The safety profile of Ragwitek is acceptable in children and adolescents 5 through 17 years of age and is justified by the clinical benefit. • The risk of severe systemic allergic reaction is low. • Patients should be educated on the potential risk of systemic allergic reactions and on the technique of epinephrine auto-injector self-administration. • Further studies are needed to characterize the incidence of EoE in patients taking SLIT products.
Risk Management	• The ragweed-allergic patient population in which this product is intended for use and the healthcare providers who manage allergy patients generally have good understanding of risks, signs and symptoms, and management of allergic reactions. • Ragwitek should be prescribed along with a prescription for injectable intramuscular epinephrine in case of systemic reactions. • The Ragwitek PI includes a boxed warning about severe allergic reactions. • Risk of severe and serious adverse events may decrease in the second and subsequent treatment years. • Patients should be warned about the potential risk of eosinophilic esophagitis and directly contact a health care professional if any signs or symptoms of EoE occur.	• The first dose of Ragwitek should be taken in a healthcare setting by a provider who is experienced in the treatment of and equipped to treat systemic allergic reactions. • Use of product labeling (PI and MG) and the PVP plan to communicate the potential for serious local adverse reactions , severe systemic allergic reactions, and EoE and to educate patients or parents/ guardians on how to manage these risks could adequately mitigate the risk of local adverse reactions, systemic allergic reactions, and EoE.

11.2 Risk-Benefit Summary and Assessment

Allergic rhinitis (AR) and ARC are among the most common chronic conditions affecting both children and adults. ARC can have a major impact on quality of life and is often associated with and can potentially impact asthma, rhinosinusitis, and sleep disturbances. IgE-mediated ragweed pollen allergy is the chief cause of late summer and fall ARC in the US. The most abundant of the three species of ragweed that predominate in the US is short ragweed. There is a high degree of cross-reactivity among the ragweed species, therefore, immunotherapy with the allergenic extract of one species is often effective against ragweed pollen allergens of other species of ragweed.

Current treatment options for ragweed pollen-induced ARC include allergen avoidance (which requires staying indoors during ragweed pollen season and is usually hard to achieve and sustain), combined pharmacologic therapy regimens of intranasal steroids and oral, intranasal, or ocular antihistamines (which provide temporary relief from allergic symptoms, but which may not be effective in all patients and are not disease-modifying), and SCIT with ragweed pollen allergen extract [which, while it offers the potential to reduce allergic symptoms and decrease the need for symptomatic treatment by increasing an individual's immune tolerance to a specific allergen, causes a substantial burden on the individual due to: the level of discomfort associated with SCIT, the inconvenience of the frequency of administration of the injections due to duration of treatment, the inconvenience of delivery of SCIT (which is required to occur in a monitored healthcare setting due to the risk of systemic allergic reactions), and the risks of occurrence of local and systemic allergic reactions].

Data on effectiveness of SLIT products suggest that SLIT may be a viable alternative to SCIT with the added benefits of self-administration due to a lower incidence of severe or serious adverse events (including systemic allergic reactions) compared to SCIT. Although local adverse reactions of mild to moderate intensity at or around the site of administration (pruritus of the tongue, mouth, throat, and ears; edema of the tongue, mouth, throat) are relatively common with SLIT, the most common adverse reactions occurring in patients who receive SCIT are also local adverse reactions at the injection site (e.g., erythema, itching, swelling, tenderness, pain).

The data from Study P008, submitted to the BLA in support of licensure of Ragwitek in children and adolescents 5 through 17 years of age, demonstrate a clinically meaningful benefit of Ragwitek for the treatment of short ragweed-induced allergic rhinitis with or without conjunctivitis in children and adolescent 5 through 17 years of age in that a lower average total combined score (sum of daily symptom and daily medication scores) was seen in participants treated with Ragwitek compared to those treated with placebo (estimate of treatment difference relative to placebo: -38%). The safety profile of this product was characterized by frequent but expected transient local adverse reactions that were mild or moderate in intensity and rare systemic allergic reactions and epinephrine use. Participants with mild to moderate asthma had a safety profile similar to participants without asthma. Based on the submitted data, the risks of treatment with Ragwitek appear to be modest and adverse reactions tend to be self-limited. However, because of the small risk of systemic allergic reactions and local allergic reactions, patients should be prescribed auto-injectable epinephrine. Furthermore, the Ragwitek PI includes a boxed warning about severe allergic reactions. In addition, while no cases of

EoE were seen in this study, EoE remains a known risk with sublingual AIT products; to mitigate this risk, product labeling (Prescribing Information and Medication Guide) is used to communicate the potential for development of EoE. While the duration of treatment effect after discontinuation of Ragwitek has not been studied, the addition of Ragwitek as the first sublingual AIT product for treatment of seasonal short ragweed pollen allergy to the currently available treatments for ragweed pollen allergy provides another treatment option for children and adolescents 5 through 17 years of age in the US with ragweed pollen allergen-induced ARC that is effective, safe, and possibly less burdensome than currently available treatment options. Given the clinical benefit associated with the consistent treatment effect and the modest risks of treatment with Ragwitek observed in Study P008, the overall risk-benefit assessment for Ragwitek is favorable for its intended use.

11.3 Discussion of Regulatory Options

The safety and efficacy data from Study P008 are sufficient to support approval of Ragwitek for the treatment of short-ragweed pollen-induced ARC in children and adolescents 5 through 17 years of age; therefore, consideration of other regulatory options was not necessary.

11.4 Recommendations on Regulatory Actions

The data submitted to this supplemental BLA support licensure of Ragwitek in children and adolescents 5 through 17 years of age.

11.5 Labeling Review and Recommendations

CBER and the Applicant reached concurrence on the revised PI (dated 4/2021) and revised MG (dated 4/2021) for Ragwitek.

The following are the major changes that were made to the most recent version of the PI (revised June 2019).

- Section 1 (Indications and Usage) was revised to indicate that the product is approved for use in persons 5 through 65 years of age.
- Section 5 (Warnings and Precautions) was revised to eliminate subsection 5.2 (Epinephrine) since epinephrine is not in and of itself a warning or precaution.
    - All relevant information originally listed in subsection 5.2 was moved to subsection 5.1 (Severe Allergic Reactions).
    - The list of medications that inhibit or potentiate epinephrine was removed as this information is listed in a comprehensive fashion in several PIs for the various brands of epinephrine; reference to the drug interactions section of the PI for epinephrine was, therefore, added in subsection 5.1.
- Section 6 was revised to include data from Study P008.
    - Since local adverse reactions were solicited in the pediatric study population (Study P009) (this data was not collected in this manner in the studies in the adult clinical development program), solicited adverse reactions collected in the first 28 days of Study P008 were displayed separately (PI, Section 6, Table 2) from unsolicited adverse reactions (PI, Section 6, Table 3). Due to this intentional separation of data, the data contained in these tables are exclusive to the PI (data enumeration with respect to these separate datasets of adverse events led to slightly

different percentages in these tables in the PI compared to the tables in this review).

- Section 14 was revised to include efficacy data from Study P008.
- The MG was revised to include adverse events in children and adolescents 5 through 17 years of age.
- Language in the PI and MG was adapted from adults only to include adults, children, adolescents, and their parents/guardians.

11.6 Recommendations on Post-marketing Actions

Additional post-marketing safety studies are not recommended. Routine pharmaco-vigilance measures are adequate.