Application Type	Original BLA
STN	125478
CBER Received Date	March 11, 2013
PDUFA Goal Date	N/A
Division / Office	DBPAP/OVRR
Priority Review	N/A
Reviewer Name(s)	Ronald L. Rabin, MD
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Merck Sharp & Dohme Corp
Established Name	Short Ragweed Pollen Allergen Extract (*Ambrosia artemisiifolia)*
(Proposed) Trade Name	RAGWITEK
Pharmacologic Class	Allergenic extract
Formulation	Tablet
Dosage Form and Route of Administration	Sub-lingual (placed beneath the tongue until dissolved)
Dosing Regimen	1 tablet (12 Amb a 1-U), once per day
Indication and Intended Population	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 adults 18 through 65 years of age. RAGWITEK is not indicated for the immediate relief of allergic symptoms.

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Glossary

AAAAI	American Academy of Allergy, Asthma and Immunology
ACAAI	American College of Allergy, Asthma and Immunology
AIT	Allergy Immunotherapy tablet
ALK	ALK-Abello A/S
Amb a 1 U	Units of Amb a 1, the major allergen of short ragweed
ANOVA	Analysis of Variance
AR/ARC	Allergic Rhinitis/Allergic Rhinoconjunctivitis
CI	Confidence interval
CSR	Clinical Study Report
DBPC	Double-Blind Placebo-Controlled
DMS	Daily medication score
DSS	Daily symptom score
EMA	European Medicines Agency
EU	European Union
RPS	Ragweed pollen season
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroids
IMP	Investigational Medical Product (either treatment drug or placebo)
ITT	Intention-To-Treat
LDA	Longitudinal data analysis
LABA	Long-acting beta2-agonist
MCID	Minimal Clinically Important Difference
ND	Not Determined
Ph. Eur.	European Pharmacopoeia
PMS	Postmarketing surveillance
RC	Rhinoconjunctivitis
RCS	Rhinoconjunctivitis combined score
RQLQ(s)	Rhinoconjunctivitis Quality of Life Questionnaire with standardized activity(activities)
SAE	Serious Adverse Event
SCIT	Subcutaneous Immunotherapy
SEM	Standard Error of the Mean
SLIT	Sublingual Immunotherapy
SmPC	Summary of Product Characteristics
SPT	Skin Prick Test
TCS	Total Combined Score
WAO	World Allergy Organization

1. Executive Summary

Background

MK-3641 (also referred to in IND documents as SCH 39641) is a fast-dissolving--less than 10 seconds--sublingual tablet for oromucosal delivery. The active substance is a natural pollen extract which is partially purified from extract from short ragweed (Ambrosia artemisiifolia) pollen. MK-3641 is not approved for sale or marketed anywhere in the world.

The submitted BLA is for licensure of MK-3641 at a dose of 12 Amb a 1-U in the US with the proposed indication "as immunotherapy for diagnosed ragweed pollen induced allergic rhinitis, with or without conjunctivitis, in adults 18 years of age and older." The sponsor asserts that they have demonstrated safety and efficacy for this proposed indication. RAGWITEK is the proposed U.S. proprietary name, which is acceptable to the Agency.

Because the allergen Amb a 1 accounts for the great majority of allergenic activity in short ragweed extracts, the potency of the extracts is defined according to the concentration of this major allergen. The unitage is Amb a 1 units (Amb a 1-U), in which 1 Amb a 1-U is roughly equivalent to 1 mcg of Amb a 1. The current method of measurement is to compare an extract to a CBER reference with a defined potency by radial immunodiffusion assay[1]. If approved, the strength of each RAGWITEK tablet will be 12 Amb a 1-U.

Unless specifically stated, the word "RAGWITEK" in this document refers to the 12 Amb a 1-U tablet.

Upon approval of RAGWITEK, adults and children will take 1 tablet sublingually, daily for a time period prior to the ragweed pollen season (RPS, which runs from August through October in the mid-Atlantic region of the United States), and then throughout the RPS. The time period prior to the RPS proposed by the sponsor is 8 weeks prior to RPS, but CBER will require that the instructions for drug administration are consistent with the US Phase 3 studies in which subjects took the RAGWITEK for at least 12 weeks prior to the anticipated RPS. The first dose is taken at the physician's office, and the remaining doses are taken at home.

Overview of Submitted Studies

The BLA includes summaries of one Phase 1 dose-ranging study, two randomized DBPC Phase 2/3 studies for efficacy and safety, and two short-term studies for safety:

- RT-01, a Phase 1 study conducted in the US of 53 subjects ages 18 to 50 years, who took placebo or RAGWITEK (3, 6, 12, 24, or 50 Amb a 1-U) for 28 days outside of ragweed season. RT-01 was completed in March, 2007. This study will not be reviewed in this document.

- P05233 was a Phase 2/3 safety and efficacy study conducted in the US and Canada of 565 subjects ages 18 to 50 years who took placebo or RAGWITEK (6

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

or 12 Amb a 1-U) for approximately 52 weeks beginning ~16 weeks prior to the 2010 ragweed season. P05233 was completed in May, 2011.

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

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

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

There are no postmarketing studies to report, as this product is not licensed or marketed anywhere in the world.

Assessment of Efficacy

As discussed in detail in Section 6 of this document, clinical scores are the critical measures of efficacy in allergy immunotherapy. The primary clinical score in the pivotal North American studies is the total combined score (TCS) which comprises the daily symptom score (DSS) and the daily medication score (DMS), all of which are averaged over the RPS. The DSS comprises six symptoms of ARC, which may be scored 0-3, for a range of DSS between 0 (no symptoms) to 18 (all six symptoms severe). The DMS ranges from 0-36. The maximum TCS is 54. Table 1 shows the mean difference and 95% CI (in percentage) and statistical significance between the treatment and placebo groups in the two efficacy studies.

Table 1. Primary efficacy endpoint data from the two North American studies that demonstrated efficacy of RAGWITEK

Protocol	TCS RAGWITEK	TCS Placebo	Difference (%)	95% CI (%)	P-value
P05233	6.22	8.46	-26.5	-38.7, -14.6	0.0002
P05234^	6.41	8.46	-24.2	-36.5%, -11.3%	0.0015

Adapted from original BLA submission 125478, Module 5: Summary of Clinical Efficacy.

CBER considers the point estimate of the improvement in the TCS of ~25% over placebo as clinically significant, and the lower upper limits of the 95% CI of < -10% as statistically acceptable. Therefore, Protocols P05233 and P05234 met their primary endpoints.

Assessment of Safety

The North American and European safety data base includes 1707 adults over 18 years of age who have taken at least one dose of RAGWITEK, either at 1.5 Amb a 1-U strength n = 196), 6 Amb a 1-U strength (n = 454), or 12 Amb a 1-U strength.(n = 1057). In the clinical studies, there were 757 Placebo subjects.

Data from clinical trials demonstrate that RAGWITEK may cause allergic reactions, which are associated with sublingual administration of natural ragweed pollen allergen to sensitized subjects. There were no episodes of anaphylactic shock or of treatment-related death during the clinical trials. The occurrence of systemic allergic events including anaphylactic reactions was low and of mild to moderate severity. Safety data from clinical trials support the sponsor's assertion that after the first dose is administered under medical supervision, RAGWITEK, Amb a 1-U daily, is safe for self-administration at home.

Upon licensure, however, the general patient population will include many patients who would have been excluded from these studies, including children and adults with moderate or severe asthma. In fact, European post-marketing studies have revealed the incidence of at least 24 treatment-related SAE. These SAE included five episodes of anaphylaxis, four of which required epinephrine injections. Eight of the 24 SAE included in their description "asthma." Eight of the SAE occurred with the first dose of RAGWITEK.

Therefore, while SLIT with this product is a safe alternative to SCIT, there must be a statement in the package insert to the effect that the safety profile observed in study populations cannot be applied to patients who would not fit the entry criteria of these studies, and caution must be observed when administering the product to patients with pre-existing diseases, or asthma of greater than mild severity.

Pediatric Research and Equity Act

This product was presented to the Pediatric Review Committee (PeRC) on March 19, 2014. PREA was waived for children less than 5 years of age because seasonal allergies are uncommon in this population, and therefore few, if any, patients less than 5 years of age would be eligible for allergen immunotherapy for seasonal short ragweed pollen allergy.

The sponsor also requested that the indication for children and adolescents be deferred. The following studies will be performed as a postmarketing requirement:

1. A study for safety and efficacy in 1000 children and adolescents that is randomized 1:1 (RAGWITEK: Placebo) in which subjects will be exposed to RAGWITEK for a total of approximately 24 weeks (12 weeks before onset of ragweed season and during ragweed season).
2. A study for safety in which 500 subjects ages 5-18 will be treated with RAGWITEK or Placebo (randomized 2:1) for 28 days outside of ragweed pollen season.

These proposals are acceptable.

Pharmacovigilance

The sponsor proposes to routine Pharmacovigilance in accordance with ICH Guidance E2E. Expedited AE and periodic safety reports will be submitted to FDA. These events are subject to enhanced surveillance: allergic reactions including severe laryngopharyngeal disorders, autoimmune disease, and anaphylaxis. CBER agrees with the proposed plan. In addition, enhanced pharmacovigilance through questionnaires

sent to healthcare professionals will be collected to supplement information on health outcomes of interest reported with early dose exposure

In addition, the sponsor has agreed to two postmarketing studies. The first will be a post-market claims-based study to further describe the safety profile of RAGWITEK in marketed use in the United States. Outcomes of interest in this study will include serious allergic reactions and eosinophilic esophagitis. The study will enroll all new users of RAGWITEK identified through claims data from a large US health insurance database for a period of at least three years from launch of . The study observation period will be for at least 3 years and until at least 10,000 patients are accrued between both post-market studies. Outcomes of interest identified through claims data will be verified using medical record review.

To capture events within the first seven days of therapy, the sponsor commits to conduct a post-market electronic medical record study to further describe the safety profile of RAGWITEK in marketed use in the United States. Outcomes of interest in this study will include serious allergic reactions and eosinophilic esophagitis. The study will enroll all new users of RAGWITEK identified through electronic medical records in a large US integrated health system for a period of at least three years from launch of RAGWITEK. The study observation period be last for at least 3 years and until at least 10,000 patients are accrued between both post-market studies. This study will include early exposures to RAGWITEK, including administration through starter packs provided in physician offices as well as all subsequent exposures.

CBER agrees with the proposed plan.

Proposed Package Insert

The proposed indication in the original BLA submission is phrased:
"RAGWITEK is indicated as immunotherapy for the treatment of diagnosed ragweed pollen induced allergic rhinitis, with or without conjunctivitis, in adults 18 to 65 years of age"

The final version of the package insert will read:

> 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 adults 18 through 65 years of age.

RAGWITEK is not indicated for the immediate relief of allergic symptoms.

Reviewer's Conclusions

The sponsor has demonstrated that RAGWITEK is safe and effective for the treatment of ARC due to short ragweed pollen allergy in adults ages 18-65. Please see complete summary comments at the end of this document.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Background

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

In addition to allergen avoidance (e.g. staying indoors during ragweed pollen season), current treatment options include pharmacologic therapy such as oral antihistamines and nasal corticosteroids, which provide temporary relief from allergy symptoms, but are not effective in all patients, and are not disease-modifying.

Another treatment option for ARC is immunotherapy. Classically, immunotherapy involves the administration of gradually increasing doses of the allergen over a period of time to desensitize the patient. It is the only known treatment that modifies the immune response and treats the cause rather than the symptoms. In the United States, the only licensed route of administration is subcutaneous injection (SCIT). Despite the documented benefits of SCIT, only 5% of the US population with allergic rhinitis, asthma, or both receive SCIT because of its discomfort, the risk of local and systemic allergic reactions, and the inconvenience of frequent injections which should be administered only in the health care setting.

An alternative to SCIT is sublingual immunotherapy (SLIT). As its name implies, the medication is kept beneath the tongue where it is absorbed into the mucosa. Though complex and not fully characterized mechanisms, administration of allergens through the oral, gingival, or sublingual mucosa can decrease the allergic response thus desensitizing the patient by modifying disease at least temporarily if not permanently (i.e. inducing tolerance). In addition, and perhaps most importantly, the incidence of severe or serious AE associated with SLIT is significantly lower than with SCIT such that SLIT may be self-administered at home while safe use of SCIT requires administration in a clinic that is capable of responding to systemic allergic reactions. A recent Cochrane review suggested that SLIT is a viable alternative to SCIT with a significantly lower risk profile and little difference in overall efficacy (Radulovic S., Calderon M. A., Wilson D., Durham S. Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev. 2010;12:CD002893).

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (herein referred to as Merck or Sponsor), in collaboration with ALK-Abelló A/S (herein referred to as ALK), has developed a sublingual pharmaceutical formulation of MK-3641 in tablet form. MK-3641 is a fast-dissolving (e.g., less than 10 seconds), sublingual tablet for oromucosal delivery for the treatment of ARC due to ragweed pollen allergy. MK-3641 is manufactured with the same technology as used for GRASTEK®, its Timothy grass tablet (recently approved in the US and approved under the name GRAZAX® in the EU). Unlike GRASTEK®, RAGWITEK is not approved anywhere in the world.

The dose is 12 Amb a 1-U per tablet, one tablet sublingually per day. There is no “ramp up” dosing. The sponsors assert that the data support an optimal preseason induction period of at least twelve weeks with a minimum eight week induction period. Treatment is to continue throughout the ragweed pollen season (RPS), which in runs from August through October or November in the mid-Atlantic region of the United States.

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

Pharmacologic agents used to treat AR

Table 2 summarizes the efficacy of pharmacologic agents used to treat ARC. A short discussion of each agent follows the table. The primary sources for the discussion Greiner N and Hellings PW et al. *The Lancet* 178:2112; 2012, and , Sanjay NM, Shah JH, and Thennati, R. Internat Immunopharm 11:1646; 2011.

Table 2. Pharmacologic agents to treat ARC

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.	Rh	Sn, Co, It	Op
Corticosteroids	i.n./p.o.	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

Sn—sneezing, Rh—rhinorrhea, It—nasal itching, Op—ophthalmic symptoms, Co—nasal congestion.

Adapted from: Sanjay NM, Shah JH, and Thennati, R. *Internat Immunopharm* 11:1646; 2011

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 subjects 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 there are occasional results of AE 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 AE associated with systemic corticosteroid therapy.

2.3 Safety and Efficacy of Pharmacologically Related Products

Currently, there are no products approved for SLIT in the US. Allergen immunotherapy is approved only for administration by SCIT—subcutaneous immunotherapy.

Subcutaneous Immunotherapy (SCIT) for the treatment of AR
Immunotherapy involves the administration of gradually increasing doses of the allergen over a period of time to desensitize the subject. It is the only known treatment that modifies the immune response and treats the cause rather than the symptoms. In the US, the only licensed route of administration is subcutaneous injection (SCIT).

In November, 2011, the Laboratory of Immunobiochemistry reported to the Allergic Products Advisory Committee (APAC) a summary of safety data associated with SCIT. From submissions to the Adverse Events Reporting System (AERS) database, 195 adverse events after SCIT between 1987 and 2009 were reported, of which 43% were either “allergic” or “anaphylaxis,” and 19.4% of which resulted in hospitalizations. During this time period there have been 15 deaths, but significantly, no deaths have been reported due to SCIT in the years 2008-2011 (Epstein et al, Ann Allergy Asthma Immunol 110 (2013) 274e278). Severe asthma is a known risk factor for SAE and death due to immunotherapy. When administered by qualified and trained clinicians in the clinic setting, SCIT is considered safe and effective. Because of its discomfort, the risk of local and systemic allergic reactions, and the inconvenience of frequent injections, however, only 5% of US patients with allergic rhinitis, asthma, or both receive SCIT.

Sublingual Immunotherapy (SLIT) for the treatment of AR in the US vs. Europe
There are no products approved for administration by SLIT in the US. A survey of European and American practices (Cox and Jacobsen, *Ann Allergy Asthma Immunol* 103:451; 2009) revealed that in 2009, 5.9% of allergists were prescribing SLIT. For this "off-label" use, allergenic extracts prepared and FDA-approved for SCIT would be placed under the tongue (presumably) with a syringe. Worldwide, SLIT use is highly variable, and appears to be increasing.

> The Cochrane Review of SLIT published in 2010 (Radulovic S., et al. Cochrane Database Syst Rev. 2010;12:CD002893) includes a meta-analysis of 60 randomized controlled clinical trials of SLIT, in which 2333 SLIT and 2256 placebo participants were studied. Symptom and medication scores were both improved, and in contrast to SCIT, none of the trials reported severe systemic reactions or anaphylaxis, and none of the systemic reactions that were reported required the use of epinephrine. When compared directly with SCIT, SLIT appeared to be associated with fewer SAE (summarized in Reference 8; AHRQ Publication No. 13-EHC061-EF). The combined experience, therefore, supports at least equivalent efficacy of SLIT compared to SCIT for ARC, and suggests that SLIT has a better safety profile.
>
> Because SLIT is tolerated better than SCIT and can be self-administered at home, it is expected that subjects with immunotherapy who declined SCIT because of anticipated AE or the required commitment to physician office visits will elect to undergo immunotherapy with SLIT.
>
> As stated in the Executive Summary of the AHRQ Publication, however, subjects included in clinical studies of SLIT included only subjects with ARC with or without mild asthma. "Hence, although it may appear . . . that sublingual immunotherapy may be safer than subcutaneous immunotherapy, the safety data from these subgroups of subjects *must not be extrapolated to the more severely affected subjects*" (emphasis added).

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

There is no previous experience with RAGWITEK outside of the five clinical trials performed during clinical development of this product.

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

<u>March 24, 2006 (IND 12970, Original Submission)</u>
ALK-Abello proposed RT-01, a Phase 1 dosing study of RAGWITEK, 12 subjects per dose, ranging from 3-100 Amb a 1-U. After satisfaction of Clinical Hold items, the study was allowed to proceed on May 20, 2006. Based on the results of this study (IND 12970, Amendments 13 and 18), the sponsors ruled out use of doses greater than 12 Amb a 1-U per day.

<u>September 20, 2007 (IND 12970, Amendment 11)</u>
Transfer of file from ALK-Abello to Schering Plough.

December 10, 2007
Schering Corp requested a Type C meeting to propose two studies:

- Study P05234, a single -season DBRPC study of safety and efficacy in subjects age of 12 years or older who are allergic to ragweed pollen. The study was to test the safety and efficacy of three doses of ragweed sublingual tablet, 1.5, 6, and 12 Amb a 1 U vs. placebo in 800 subjects (200 subjects per group). Treatment will be discontinued at the end of the ragweed season.

- Study P05233, a 5 year DBRPC study of 3 years treatment and two years follow up in ragweed-allergic subjects aged 12 years or older. The objective of the study will be to evaluate the efficacy and safety of two doses of ragweed tablet 6 and 12 Amb a 1 U vs. placebo at the end of Year 1 ragweed season in 1350 subjects (450 subjects per group). Safety data from the first 12 months of treatment will be included in the first year evaluation, and efficacy will be based on data obtained through Year 3 ragweed season. Long-term efficacy and disease modifying effect was to be evaluated at the end of the ragweed season for Years 4 and 5.

October 1, 2008 (IND 12970, Amendment 21)
Schering Plough submitted Protocol P05234, a Phase 2/3 efficacy and safety study of RAGWITEK in adults 18-50 years of age randomized equally to placebo or to one of three doses of RAGWITEK (1.5, 6 or 12 Amb a 1-U). Subjects were treated for 12 weeks prior to ragweed pollen season, throughout RPS, and (after the proposal was amended) for a total of 52 weeks. The primary endpoint was the average TCS over the entire ragweed pollen season. The study was to be conducted in 2009. After satisfaction of Clinical Hold issues, the study was allowed to proceed.

October 2, 2008 (IND 12970, Amendment 22)
Schering Plough submitted Protocol P05233, a Phase 2/3 efficacy and safety study of RAGWITEK in adults 18-50 years of age randomized equally to placebo or to one of three doses of RAGWITEK (6 or 12 Amb a 1-U). Subjects were treated for 12 weeks prior to ragweed pollen season, throughout RPS, and (after the proposal was amended) for a total of 52 weeks. The primary endpoint was the average TCS over the entire ragweed pollen season. The study was to be conducted in 2009. After satisfaction of Clinical Hold issues, the study was allowed to proceed.

October 7, 2009 (IND 12970, Amendment 27)
Schering Plough submitted Protocol P06081, a Safety of RAGWITEK in Adult Subjects ≥ 50 years of age. Subjects with ragweed induced ARC were treated with either placebo or 6 or 12 Amb a 1-U for 28 days outside of RPS. The study was allowed to proceed.

November 4, 2009 (IND 12970, Amendment 29)
Schering Plough merged with Merck, Sharp and Dohme. Merged company referred to as Merck, Sharp and Dohme.

December 2, 2010 (IND 12970, Amendment 45)
Schering Plough proposed changing the primary endpoint of P05233 and P05234 from TCS of the entire ragweed season to the TCS of the peak ragweed season. On or about May 5, 2011, CBER concurred with the change in the primary endpoint of these two safety and efficacy trials.

June 6, 2011 (IND 12970, Amendment 53)
Final Study report of study P060801 submitted.

June 15, 2011, (IND 12970, Amendment 56)
Schering Plough submitted Protocol P05751, a Safety of RAGWITEK in Adult Subjects ≥ 18 years of age. Subjects with ragweed induced ARC were treated with either placebo or 6 or 12 Amb a 1-U for 28 days outside of RPS. The study was allowed to proceed.

September 21, 2012 (IND 12970, Amendment 78)
Pre-BLA package submitted with study results from P05233.

November 29, 2012 Pre-BLA meeting with Merck
Minutes of meeting communicated to Merck on December 19, 2012 in which CBER concurred that data were appropriate for BLA submission.

March 11, 2013
BLA submitted to CBER.

Information Requests (IR) following the original submission were sent to the sponsor, and responses submitted to the BLA file.

Table 3. Information Requests (IR) and BLA Amendment Responses to BLA 125478

IR Date	CBER Representative(s)	Reviewer Requester for Info	IR Summary	BLA Amendment Response (by sequence #)	Reviewed by/Concurrence that Response is Acceptable
5/24/2013	K. Rivers	R. Rabin, C. Wernly, J. Sun,	Request for PSP	STN# 125478/0.5 Seq#: 0005	R. Rabin,
8/2/2013	K. Rivers	R. Rabin	Request for pediatric study plan timeline justification	STN# 125478/0.7 Seq#: 0007	R. Rabin
12/13/2013	K. Rivers	T. Khurana	Request for copies of diary cards and subject comment cards	STN# 125478/0.11 Seq#: 0011	R. Rabin
1/07/2014	E. Valenti	R. Rabin	Request for summary of adverse event data in subjects receiving Ragwitek.	Response received via email 1/7/2014	R. Rabin
1/10/2014	K. Rivers	R. Rabin	Request for summary of clinical data regarding treatment interruptions and discontinuation, and synonymous adverse events	Response received via email January 13, 2014 STN# 125478/0.16 Seq#: 0016	R. Rabin
1/14/2014	K. Rivers	R. Rabin	Request for clinical data summarizing then number of subjects receiving any dosage strength of Ragwitek by age group	Response received via email 1/14/2014	R. Rabin
1/15/2013	K. Rivers	R. Rabin	Request regarding the proposed pediatric study plan	Response received via email February 14, 2014 STN# 125478/0.18 Seq#: 0018	R. Rabin
2/27/14	K. Rivers	R. Rabin	Response to 2/14/14 submission which included an amended proposal for clinical studies of pediatric subjects	STN# 125478/0.24 Seq#: 0024	R. Rabin

2.6 Other Relevant Background Information

None

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was complete.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Clinical Investigator (CI) Site Issues

A review was conducted of testing records, regulatory binders, study specific standard operating procedures, and general study conduct. In addition, source documents were reviewed and compared to the data tables submitted by the sponsor in the application. Individual site observations are listed below:

- Study Site 01: The inspection did not result in the issuance of a Form FDA 483 and received a final classification of “no action indicated.”

- Study Site 80: The inspection did not result in the issuance of a Form FDA 483 and received a final classification of ”no action indicated.”.

- Study Site 91: The inspection resulted in the issuance of a Form FDA 483. The findings included protocol violations and documentation errors. The violation of greatest concern is that subjects were not documented as observed for the required 30 minutes after dosing, and in several instances, study comment cards, which documented the use of rescue medications, adverse events, and missed doses were not signed and dated as reviewed for compliance. The inspection received a final classification of “voluntary action indicated.”

OTHER ISSUES

1. Inspection of the sponsor/monitor was conducted at the Merck and Company, Inc., Springfield, New Jersey 07081 location by the NWJ-DO between April 17, 2012 and May 02, 2012. At close of the inspection, a Form FDA 483 was issued for failing to conduct study site monitoring visits within the time frame of six to eight weeks as is specified in the sponsor’s Site Monitoring Visit Plan. The inspection received a final classification of ”voluntary action indicated.”.

2. Site 63 was inspected after notification by the sponsor of protocol violations. The inspection received a final classification of OAI (Official Action Indicated) and an Untitled Letter was issued to the clinical investigator. The observations cited are as follows:

3. Failure to fulfill the general responsibilities of an investigator;

4. Failure to obtain legally effective informed consent from a subject or the subject’s legally authorized representative;

5. Failure to prepare and maintain accurate and complete case histories for subjects enrolled in the study, with respect to observations and data pertinent to the study;

6. Failure to maintain source documents and records pertinent to an investigation for a period of two years following approval of a marketing application or discontinuance of the investigation and notification of the FDA, and;

7. Failure to assure that an IRB complying with the applicable regulatory requirements would be responsible for the initial and continuing review and approval of a clinical study.

The sponsor reported that all 5 subjects from Study Site 63 were excluded from the Full Analysis Set (FAS) and the All Subjects as Treated Set (ASaT).

3.3 Financial Disclosures

On Form 3454, the sponsor certified that the following statement is correct: “As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).”4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

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

4.1 Chemistry, Manufacturing, and Controls

(b) (4)

(b) (4)

(b) (4) is measured by the (b) (4) The release and shelf life acceptance criteria are (b) (4) of IHR. The specification for the potency value is (b) (4)

The drug product (DP) is a tablet. The excipient substances in the drug product are listed in the table below. The DP is fully addressed in the CMC review of this product.

Table 5. Sponsor's description of Drug Product
Quantitative Composition of SCH 39641 Tablet, 2800 BAU

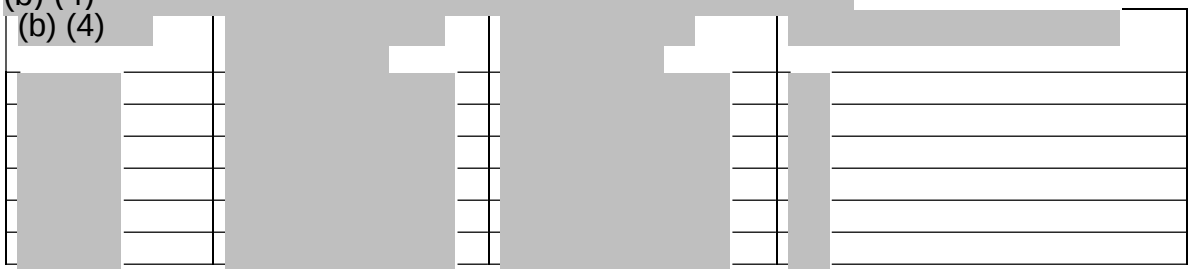
Ingredient	Quality Standard	Function	Amount per Tablet
MK 3641 (b) (4)	In-house	Active ingredient	12 Amb a 1-U
Gelatin (Fish, (b) (4))	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Mannitol	(b) (4)	(b) (4)	(b) (4)
Sodium Hydroxide	(b) (4)	(b) (4)	(b) (4)
Purified Water	(b) (4)	(b) (4)	(b) (4)
(b) (4)			(b) (4)
(b) (4)			(b) (4)

a (b) (4)
b (b) (4) Unit weight may vary slightly
Extracted from the original BLA SBLA STN 125478/000; Module 2.3.P, Page 1

4.2 Assay Validation

The DP is a tablet that contains the (b) (4) that is standardized in Amb a 1-U to the In House Reference Standard. The product substance is measured for potency using the (b) (4) . In March, 2014, Merck submitted to CBER samples for validation of potency testing. CBER tested the samples in March 2014, and the results of testing of (b) (4) lots is shown in Table 6.

(b) (4)



4.3 Nonclinical Pharmacology/Toxicology

Animal reproduction studies were not performed with RAGWITEK.

A toxicity study with the *Ambrosia artemesiifolia* extract (RAGWITEK) in mice dosed up to four to five weeks revealed no safety issues at doses up to 70 Amb a 1-U/day which is approximately six-fold based on absolute value or 11666-fold based on 1-U/kg the human dose of 12 Amb a 1-U/day.

No animal reproductive and development studies were performed with RAGWITEK to assess its teratogenic potential. Animal reproductive and development study reports conducted using *Phleum pratense* (Timothy Grass), were submitted. These reports are irrelevant and were not reviewed under this application as they were not conducted using the product, *Ambrosia artemisiifolia*. Thus, a Pregnancy Category C, instead of B, was included in Section 8.1 of the package insert (PI).

A core of genetic studies has not been performed with the product. These studies, which are designed to identify genotoxic hazard, include: (1) a test for gene mutation in bacteria, (2) an *in vitro* assessment of chromosome damage, and (3) an in vivo test for chromosome damage. A combined in vivo comet assay and micronucleus test in rats was performed with the product. Negative results from only one assay could not constitute that the product does not pose an overall genotoxic risk for humans.

Impairment of fertility of the product has not been investigated in animals.

4.4 Clinical Pharmacology

No clinical pharmacology studies were performed, and in general, are not relevant to this class of product.

4.4.1 Mechanism of Action

Independent of route, allergen immunotherapy is a therapeutic vaccination intended to re-orient the immune response away from the production of allergen-specific IgE antibodies and towards either desensitization or tolerance of the allergen (temporary or permanent state of no immune response) or towards a different immune response that generates a different class of antibodies. The mechanisms by which the immune response is reoriented are complex, incompletely understood, and may differ among a heterogeneous population of humans. Descriptions of these mechanisms of allergen immunotherapy are beyond the scope of this document.

4.4.2 Human Pharmacodynamics (PD)

The sponsors submitted a clinical study report in which allergen-specific IgG_4 responses were measured as a parameter of pharmacodynamics. Because pharmacodynamics

generally refers to direct responses to a drug that reflect its mechanism of action, CBER does not agree that these serologic responses may be considered a pharmacodynamic parameter. CBER does not consider pharmacodynamic studies to be relevant to this form of therapy.

4.4.3 Human Pharmacokinetics (PK)

Human PK studies were not performed, and in general, are not relevant to this form of therapy.

4.5 Statistical

The statistical reviewer analyzed efficacy and safety/tolerability datasets provided by the applicant in this submission. Analysis of the primary study endpoints, select relevant secondary endpoints and the safety/tolerability data included in this submission were verified to be consistent with the sponsor's results. The data analysis was performed utilizing SAS version 8.2 and/or JMP version 9 and was based upon the pre-specified Statistical Analysis Plan (SAP) incorporating appropriate models proposed by the sponsor. In the case of studies performed under US-IND the Statistical Analysis Plan and models associated with primary and secondary endpoints were explicitly agreed to by the Agency. The results of the statistical analysis were confirmed independently by the reviewing statistician and illustrate the safety/tolerability and efficacy of this sublingual ragweed immunotherapy product.

4.6 Pharmacovigilance (PV)

The PV plan was submitted and reviewed in a document submitted to the file on September 17, 2013 by Dr. Patricia Rohan. Based upon the submitted information and current clinical knowledge, at this time, CBER agrees that routine pharmacovigilance as proposed by the sponsor is appropriate should this product be licensed.

Postmarketing commitments are reviewed in Section 11.6.

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

5.1 Review Strategy

The primary document reviewed was the original BLA submission, the Pre-BLA submission and documents generated during review of IND 12970.

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

The source of clinical data used for review is BLA submission, including the final study reports contained within the submission. Most of the data that support this submission are found in Module 5 of the original submission of BLA 125478.

The BLA includes a total of five clinical trials that comprise the MK-3641 Clinical Program conducted to evaluate the efficacy and safety of MK-3641:

- One Phase 1 dosing trial (RT-01) in adults which is not extensively reviewed in this document.
- Two Phase 2 safety trials in adults with AR (P05751 and P06081);
- Two Phase 2/3 efficacy and safety studies in adults (P05233 and P05234)

5.3 Table of Studies/Clinical Trials

Table 7. List of studies included in the BLA submission.

Phase 1

Study/ Protocol#	# Sites/ Countries Location	Objective	Subjects (Study Drug /Placebo)	Tx* Duration	Study Dates
RT-01	2 sites; San Antonio TX, and Normal IL	Safety, Dose ranging; 3, 6, 12, 24, 50 Amb a 1-U	Adults 18-50y 40/13	28 days	June 2006 through Mar 2007
P05751	72 sites 58 in US 14 Canada	Safety 12 Amb a 1-U versus Placebo	Adults 18-50y (610/304)	28 days	Dec, 2011 through Apr, 2012
P06081	30 sites in the US	Safety 6, 12 Amb a 1-U versus Placebo	Adults 50 years or older (66/65/65)	28 days	Nov, 2009 through Feb 2010
P05233	80 sites 67 US 13 Canada	Efficacy/Safety 6, 12 Amb a 1-U versus Placebo	Adults 18-50 (188, 186, 186)	52 weeks	Sep 2009 through May 2011
P05234	114 sites 72 US 12 Canada 20 Hungary 8 Ukraine 2 Russia	Efficacy/Safety 1.5, 6, 12 Amb a 1-U versus Placebo	Adults 18-50 (197, 195, 194, 198)	52 weeks	Sep 2009 through May 2011

5.4 Consultations

None

5.4.1 Advisory Committee Meeting

This BLA was presented before the Allergic Products Advisory Committee on January 28, 2014. The committee voted unanimously that the available data are adequate to

support the safety of RAGWITEK when administered to persons 18-65 years of age with the understanding that auto-injectable epinephrine will be available to patients at home.

APAC members proposed additional studies in the following sets of subjects to define more clearly safety and/or efficacy:

1. Adults > 65 years of age (primarily safety)
2. Pregnant women
2. Children and adults with moderate to severe asthma
3. Children and adults with food or latex allergy
4. Racial or ethnic subpopulations (e.g. African-American, Hispanic)
5 Monitor patients who have gastrointestinal symptoms for eosinophilic esophagitis and related diseases
6. Efficacy on subjects who are sensitive to additional environmental allergens (e.g. ragweed, trees)
7. Safety for those receiving concomitant SCIT
8. Longer duration of treatment to test for disease modifying effect

APAC members also suggested

1. Long term studies to addressed sustained effectiveness not only on allergy to ragweed but to tracking the appearance of hew hypersensitivities
2. Tracking the effect of immunotherapy on viral-induced wheezing

5.4.2 External Consults/Collaborations
None

6. Discussion of Individual Studies/Clinical Trials

General concepts regarding safety and anticipated AE
In order to comprehend the review strategy and interpret the data that support safety of allergen immunotherapeutics, it is necessary to understand the AE that are anticipated with this class of products.

Allergen immunotherapy is essentially a therapeutic vaccination that currently consists of administration of an extract of the allergen to which an individual is sensitive in order to either desensitize (temporary and dependent on continued therapy) or tolerize (permanent loss of sensitization) the patient to the allergen. By definition, therefore, the drug substance is at least a component of the offending substance, and consequently, the AE that are expected to occur are those associated with allergic responses.

In general, allergic responses to administration of an allergenic extract are either local or systemic, or both. Local allergic responses to SCIT are centered on the injection site and include redness, swelling, itching and pain. Because the SCIT injection site is on the upper arm, there is little danger that the local reaction may be serious or life threatening.

Local allergic responses to SLIT include redness, swelling, itching and pain around the lips and throat, but may also include swelling of the uvula and hoarseness, and because some of the extract is swallowed, symptoms related to the gastrointestinal system such as abdominal pain and diarrhea. By contrast to SCIT, the anatomic nature of SLIT is such that local swelling (of the uvula or within the larynx) may obstruct the airway. In practice, serious or life threatening local reactions to SLIT have been very rare, and none occurred during the clinical trials with RAGWITEK.

Systemic reactions are not uncommon with SCIT, occurring in up to 5% of patients during the course of therapy. Most systemic reactions are mild or moderate and consist of generalized itching with or without hives, cough, or mild exacerbations of asthma. Rarely, systemic reactions may include severe asthma exacerbations and anaphylactic shock, both of which may be fatal. When administered by a trained health professional, these SAE are very rare. SLIT, on the other hand, is associated with fewer systemic reactions, and life-threatening SAE after SLIT are exceedingly rare to date. In addition to convenience of home administration of SLIT, this lower level of risk adds considerable advantage to SLIT over SCIT (for review, see the immunotherapy practice parameters of the American Academy of Allergy, Asthma, and Immunology [AAAAI] *J Allergy Clin Immunol* 127:S1; 2011).

Relevant study parameters, variables, and endpoints to demonstrate efficacy of allergenic extracts for desensitization to environmental allergens

In order to interpret the data that support efficacy of allergen immunotherapeutics, it is necessary to understand the unique variables associated with allergy to environmental substances, and in particular, to seasonal allergens.

By definition, natural exposure to seasonal allergens is dependent on region. Birch pollen, for example, is the major tree allergen in Northern Europe, while olive tree pollen is most important in Southern Europe. Ragweed is found throughout North America, but not in Europe. Grass pollens, particularly Timothy grass, are present in Europe and North America.

While the season in which these pollens are most prevalent is relatively constant within a region (e.g. tree pollen season is late winter/spring, ragweed pollen season is late spring/summer) the onset and end of each season varies with region, and varies year to year in the same region. (One remarkable exception to this variation of onset is ragweed pollen in the mid-Atlantic region, which begins on August 15, 16, 17, or 18 of each year with precipitously high pollen levels.) In addition, weather patterns that vary from year to year (rainfall for example) will in turn cause pollen levels to vary within the same region. Since the magnitude of symptoms in any allergic individual varies with these pollen levels, the severity of allergic disease experienced by that individual varies from year to year. Therefore, the ability to measure the efficacy of therapy is adversely impacted by this variability among regions, and among years in the same region. These variables also impact upon the comparison within individual study subjects of their level of illness between a baseline and treatment season; paired data may be confounded by a high pollen season the first (baseline) year and low the next (treatment) year or vice versa.

Similar to many autoimmune and auto-inflammatory diseases, there is not one clinical parameter that serves as an index of disease severity. Further complicating measurement of allergenic therapeutics, is that although allergen-specific IgE mediates these allergic symptoms, serum levels of IgE cannot serve as a biomarker for response to therapy. The lack of any biomarker requires clinical scoring of symptoms, medication usage, or both (so-called combined scoring) as a primary endpoint. These measurements obviously are not ideal because clinical scores include some element of subjectivity, and therefore contribute to variability and to the statistical complexity of these studies.

There are multiple clinical scoring algorithms that may be used to demonstrate proof of efficacy of immunotherapy. While of these scoring systems consider only symptoms or quality of life, others consider medication usage. So-called “combined scores” take both symptoms and medication usage into account. CBER considers combined scoring systems the best parameter of efficacy because they account for differences in individual subjects’ threshold for tolerating symptoms. Simply stated, of two individuals with the same severity of ARC symptoms, one may choose to take medications to relieve those symptoms and the other may choose to “stick it out.” Ideally, despite this choice, they would each have the same combined symptom and medication score.

Currently CBER does not mandate the method by which the sponsor will combine symptom and medication scores. For the pivotal Phase 3 study, the sponsors used for the primary efficacy endpoint the Total Combined Score (TCS), which is the sum of each daily symptom score (DSS) and daily medication score (DMS) divided by the duration (in days) of the ragweed pollen season (RPS).

The DSS is the sum of six individual rhinoconjunctivitis (RC) symptom scores with possible values of 0 (symptom is absent) to 3 (symptom is severe). The six RC symptoms that are scored are: (runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes). Therefore, the maximum DSS is 18.

The DMS is the sum of scores that are assigned to each medication in the table below.

Table 8. **Scoring of Rescue Medication Usage (RMS)**
RHINOCONJUNCTIVITIS

STEP	Rescue Medication	Score/Dose Unit	Maximum Daily Score
1a	Loratadine RediTabs tablet 10 mg – 1 tablet QD	6 per tablet	6
1b	Olopatadine hydrochloride 0.1% ophthalmic solution -1 drop in the affected eye BID	1.5 (per drop)	6
2	Mometasone furoate monohydrate nasal spray 50 mcg - 2 sprays in each nostril QD	2 (per spray)	8
3	Prednisone tablet 5 mg (Day 1 - 1 mg/kg/day, Max 50 mg/day)	1.6 (per tablet)	16a
3	Prednisone tablet 5 mg (Day 2+ - 0.5 mg/kg/day, Max 25 mg/day)	1.6 x 2 (per tablet)	16a
	Maximum daily rhinoconjunctivitis medication score		36

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The TCS is the sum of the DSS (maximum 18) and the DMS (maximum 36). The maximum TCS is 54. This method of calculation of the TCS as a primary efficacy endpoint is acceptable to CBER, and was used for the U.S. pivotal studies.

6.1 Trial #1: Protocol P05233

A multicenter, double-blind, randomized, placebo-controlled, parallel group study evaluating the efficacy and long-term safety of ragweed (Ambrosia artemisiifolia) sublingual tablet (SCH 39641) in adult subjects with a history of ragweed-induced rhinoconjunctivitis with or without asthma

6.1.1 Objectives (Primary, Secondary, etc) Protocol P05233

Primary Objective:
To evaluate the efficacy of ragweed sublingual tablet (SCH 39641) versus placebo in the treatment of ragweed pollen-induced rhinoconjunctivitis based on the Total Combined Score (TCS), the sum of rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS) averaged over the peak ragweed pollen season (RPS).

Key Secondary Objectives:

1. The safety and to compare the following between the SCH 39641 and placebo groups:
2. The average TCS for the entire RPS
3. The average rhinoconjunctivitis DSS for the entire RPS.
4. The average rhinoconjunctivitis DMS for the entire RPS

6.1.2 Design Overview Protocol P05233

Protocol P05233 was a Phase 2/3 multicenter double blind, randomized, placebo-controlled parallel group study evaluating the efficacy and safety of short ragweed (*Ambrosia artemisiifolia*) pollen sublingual tablet (SCH 39641) in adults age 18-50 with a history of ragweed pollen induced ARC with or without asthma.

Subjects were treated once daily prior to the onset of RPS of 2010, throughout that RPS, and following the RPS for a total of ~52 weeks of treatment. Subjects were randomized equally to 6 or 12 Amb a 1-U tablets or to placebo (i.e. 1:1:1 randomization).

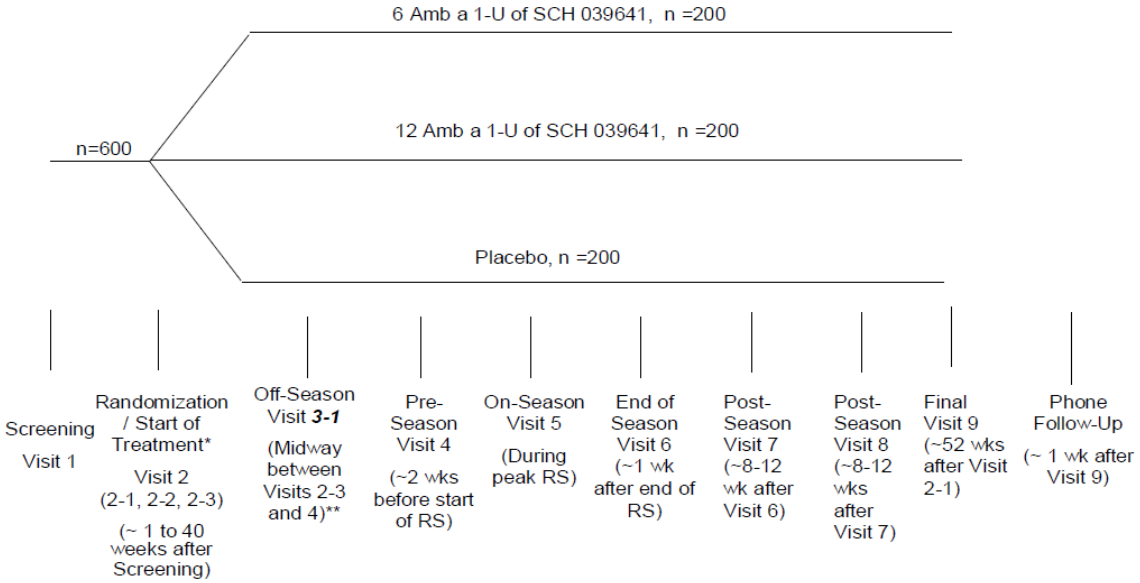
A total of 565 subjects were randomized in a 1:1:1 ratio to either 12 or 6 Amb a 1-U ragweed AIT or Placebo. In total, 565 subjects received double-blind treatment. There were 560 subjects included in the safety and efficacy analyses, treated with either 12 Amb a 1-U ragweed AIT (n=186) or 6 Amb a 1-U ragweed AIT (n=188) or placebo (n=186).

Subjects visited the study site for at least 11 visits during the treatment period: Screening, Randomization and On-site dosing of study drug or placebo (3 visits), Off-season, Preseason, On-season, End-of-season, Post-season (2 visits), and Final Visit, and at Unscheduled Visits as appropriate.

The first three doses of investigational medical product (IMP) were administered at the study site, and the subject was monitored at the site for 30 minutes following dosing. Subsequent administration of IMP was done once daily at home at approximately the same time each day. A follow-up telephone call between the site and the subjects was made daily for the first 4 doses of at-home administration of IMP and also once approximately 1 week after the Final Visit. Additional Off-season Visits were scheduled depending on how early the subjects attended the Randomization Visit, in relation to the anticipated start of the RS.

Efficacy and safety were assessed with a paper diary comment card to assist in capturing information between visits regarding IMP and rescue medication compliance, adverse events and use of concomitant medications. These data were applied towards measurement of the DSS and DMS, the sum of which is the TCS.

Figure 1: Study diagram for Protocol P05233



Extracted from the original BLA SBLA STN 125478/000; Module 5, CSR p05233, Vol 1, Page 43

Reviewer's comment: The study was well designed to determine efficacy and safety of the product.

The schedule of study visits is shown in Table 9.

Table 9. **Study Schedule including survey for AE of Protocol P05233**

Visit Name	1	2-1	2-2	2-3	3-1, 3-2, 3-3[a]	4	5	6	7	8	9		
Visit Description	Screening	Randomization[b]	Randomization[b]	Randomization[b]	Off-Season	Pre-season	On-Season	End-of-Season	Post-Season	Post-Season	Final	Phone Follow-Up	Uns[c,d]
Time Point		Approx 1 to 40 Wks After Visit 1	Approx 1 to 40 Wks After Visit 1	Approx 1 to 40 Wks After Visit 1	Midway Between Visits 2-3 and 4	Approx 2 Wks Before Start of RS	In Peak RS[e]	Approx 1 Wk After End of RS	Approx 8-12 Wks After V6	Approx 8-12 Wks After V7	Approx 52 Wks After V2-1	Approx1 Wk After V9	
Week[f]	-40 to -1	1	1	1	5-7	10-14	19-20	26-27	35-39	47-51	52	53	
Informed Consent[g]	X												
Inclusion/Exclusion Criteria	X	X											
Demography	X												
Body Height and Weight	X										X		
Medical History	X												
Assess/Record Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X[h]
Physical Examination	X										X		X[h]
Vital Signs	X	X	X	X	X	X	X	X	X	X	X		X[h]
Pulmonary Function Tests	X	X				X	X	X	X	X	X		X[h]
Safety Laboratory Assessments	X[i]							X			X		X[h]
Urine Pregnancy Test[j]	X[i]	X			X	X	X	X	X	X	X		X[h]
Skin Prick Test	X												
Specific IgE	X[i]												
Other Immunological Assessments	X					X	X	X			X		
Pharmacogenetic Sample Collection[k]								X					
IVRS	X[i]	X			X	X	X	X	X	X		X	X[h]
Issue/Review Subject's Paper Diary Comments Card	X	X	X	X	X	X	X	X	X	X	X		X[h]
Issue/Instruct in the Use of Electronic Diaries[l]		X											

Visit Name	1	2-1	2-2	2-3	3-1, 3-2, 3-3[a]	4	5	6	7	8	9		
Visit Description	Screening	Randomization[b]	Randomization[b]	Randomization[b]	Off-Season	Pre-season	On-Season	End-of-Season	Post-Season	Post-Season	Final	Phone Follow-Up	Uns[c,d]
Time Point		Approx 1 to 40 Wks After Visit 1	Approx 1 to 40 Wks After Visit 1	Approx 1 to 40 Wks After Visit 1	Midway Between Visits 2-3 and 4	Approx 2 Wks Before Start of RS	In Peak RS[e]	Approx 1 Wk After End of RS	Approx 8-12 Wks After V6	Approx 8-12 Wks After V7	Approx 52 Wks After V2-1	Approx1 Wk After V9	
Review /Discuss Electronic Diary Recordings			X	X	X	X	X	X					X[h]
Discontinue Electronic Diary								X					
Assess/Record AEs		X	X	X	X	X	X	X	X	X	X	X	X[h]
Examination of Oral Cavity		X	X	X	X	X	X	X	X	X	X		X[h]
Dispense Self- Injectable Epinephrine, Instruct to Use, Provide Educational Info and Written Anaphylaxis Emergency Action Plan		X											
Verify That Subject has Self-Injectable Epinephrine/ Instruct in Its Use			X	X	X	X	X	X	X	X			X[h]
Dispense IMP				X	X	X	X	X	X	X			X[h]
On-site Dosing of IMP		X	X	X									
Dispense PEF Meter, Train/Perform Measurements, Review Results (asthmatic subjects in countries where required)		X	X	X	X	X	X	X	X	X	X		X[h]
Dispense Allergy Rescue Medication						X	X						X[h]
Check/Collect IMP, Assess Compliance					X	X	X	X	X	X	X		X[h]
Check/Collect Allergy Rescue Medication, Assess Compliance							X	X					X[h]
Collect Self-Injectable Epinephrine													

Extracted from original BLA 125478/000, Module 5, CSR P05233; Pages 44-47 of 3030

6.1.3 Population Protocol P05233

Key Inclusion Criteria:

1. Subjects were 18 to 65 years of age, of either sex, and of any race.
2. Subject must have had a clinical history of significant allergic rhinoconjunctivitis to ragweed (with or without asthma) diagnosed by a physician and received treatment for their disease during the previous RPS.
3. Subject must have had a 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.
4. Subject must have been positive for specific IgE against *Ambrosia artemisiifolia* (≥ IgE Class 2) at the Screening Visit.
5. Subject must have had an FEV1 ≥70% of predicted value at the Screening Visit and requiring no more than 250 mcg fluticasone or its equivalent.
6. A subject's safety laboratory tests, vital signs and ECG conducted at the Screening Visit must have been within normal limits or clinically acceptable to the investigator/sponsor.

Key Exclusion Criteria:

1. Subject with a clinical history of symptomatic seasonal allergic rhinitis and/or asthma, having received regular medications due to another allergen during or potentially overlapping the RPS.
2. Subject with a clinical history of significant symptomatic perennial allergic rhinitis and/or asthma having received regular medication due to an allergen to which the subject is regularly exposed.
3. Severe asthma or asthma requiring medium or high dose inhaled corticosteroids.

6.1.4 Study Treatments or Agents Mandated by Protocol P05233

Table 10. Batch numbers used for treatments in Protocol 05233

	Ragweed AIT 6 Amb a 1-U	Ragweed AIT 12 Amb a 1-U	Placebo
	(b) (4)		

Extracted from the original BLA STN 125478/000; Module 5, CSR p05233, Page 59

6.1.5 Directions for Use Protocol P05233

Sublingual ingestion (tablet dissolves under tongue), 1 tablet per day.

6.1.6 Sites and Centers Protocol P05233

This study was performed at 67 sites in the United States and 13 sites in Canada.

6.1.7 Surveillance/Monitoring Protocol P05233

The safety variables assessed included: AE, VS, physical examinations, an ECG at screening, and safety laboratory assessments. AE were recorded on open-ended daily diary cards, which were collected at each study visit. Clinical data were recorded on a CRF for each visit.

Subjects were given rescue medication, use of which was recorded on the daily diary card. Subjects were withdrawn from the study according to the individual stopping criteria.

This study included a Data Safety Monitoring Committee (DSMC). The DSMC was established prior to the start of the treatment period to evaluate AE data and provide any recommendations regarding the conduct of the study to ensure that the safety of the subjects participating in the study was protected. The DSMC was developed to monitor trial conduct and safety data as outlined in a separate charter.

6.1.8 Endpoints and Criteria for Study Success Protocol P05233

The primary efficacy endpoint for the study was the Total Combined Score, which is the sum of the rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS) averaged over the peak ragweed pollen season (RPS).

(This endpoint was amended from the TCS over the entire RPS).

The key secondary endpoints were:

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

6.1.9 Statistical Considerations & Statistical Analysis Plan Protocol P05233

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

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

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

The analysis of safety results followed a tiered approach. Statistical tests were performed, and the 95% CIs and p-values were displayed for the Tier 1 AEs (any treatment-emergent AEs [TEAE], any TEAE leading to study discontinuation, pre-specified local application site reactions [oral pruritus, ear pruritus, throat irritation, and edema mouth], and serious hypersensitivity reaction). For Tier 2 events (that included any related AE, any serious AE, any serious and related AE, and individual AEs that occurred in at least four subjects in one or more of the groups), 95% CIs of the between-treatment groups differences of incidence rates were provided.

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

Please refer to the Statistical Review for more information.

6.1.10 Study Population and Disposition Protocol P05233

6.1.10.1 Populations Enrolled/Analyzed Protocol P05233

Full Analysis Set (FAS): All subjects randomized with at least one post treatment diary data entry following the Intent to Treat (ITT) International Conference on Harmonization (ICH) principle.

Per Protocol Set (PP): All subjects without major protocol deviations; equivalent to the efficacy-evaluable set.

All Treated Subjects: All subjects randomized and who have taken at least one dose of study drug or placebo.

6.1.10.1.1 Demographics Protocol P05233

Table 11 shows key demographic data from Study P05233. Subjects were equally distributed between the study drug and placebo groups for each of these variables, as well as weight, height, BMI, duration of ARC, tobacco history, and for asthmatics, the percent predicted FEV_1 at baseline (not shown).

Table 11. Key Demographics Study P05233

	RAGWEED AIT 6 Amb a 1-U n (%)	RAGWEED AIT 6 Amb a 1-U n (%)	Placebo n (%)	Total N (%)
Number of subjects each group	190 (100%)	187 (100%)	188 (100%)	565 (100%)
Sex				
Female	84 (44.2)	109 (58.3)	93 (49.5)	286 (50.6)
Male	106 (55.8)	78 (41.7)	95 (50.5)	279 (49.4)
Race				
White	151 (79.5)	153 (81.8)	139 (73.9)	443 (78.4)
Non-White	39 (20.5)	34 (18.2)	49 (26.1)	122 (21.6)
Asian	16 (8.4)	10 (5.3)	19 (10.1)	45 (8.0)
Black or African American	17 (8.9)	21 (11.2)	27 (14.4)	65 (11.5)
American Indian or Alaskan Native	2 (1.1)	1 (0.5)	0 (0.0)	3 (0.5)
Age (yrs)				
Mean (SD)	35.3 (9.00)	34.9 (9.41)	35.9 (9.13)	35.4 (9.17)
Median	36.0	36.0	37.0	37.0
Range	18-50	18-51	18-50	18-51
Asthma Status				
Asthmatics	37 (19.5)	42 (22.5)	43 (22.9)	122 (21.6)
Non-Asthmatics	153 (80.5)	145 (77.5)	145 (77.1)	443 (78.4)

From Original BLA 125478/000, Module 5, CSR P05233; Pages 88-89 of 3030

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population Protocol P05233

As shown above, approximately 20% of subjects in each group had asthma.

6.1.10.1.3 Subject Disposition Protocol P05233

Table 12. **Disposition of randomized study subjects Protocol P05233**

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

Extracted from original BLA STN 125478/000; Module 5, CSR p05233, Page 82

In addition, two sites were terminated from the study because of observed and significant departures from GCP.

- Site 63 had a total of five subjects randomized (two subjects received 6 Amb a 1-U short ragweed tablet, one subject received 12 Amb a 1-U short ragweed tablet, and two subjects received placebo). These subjects did not complete the trial and there were no reports of AEs, including severe or serious AEs, at this site. Sensitivity analyses were performed to include the five subjects from this site, and resulting data indicated that including these subjects had no impact on the safety and efficacy conclusions.

- Site 59 was terminated with three screen failures (subjects 001, 002, and 003), and no subjects were enrolled or treated with investigational drug. No adverse event data was reported from this site

6.1.11 Efficacy Analyses Protocol P05233

6.1.11.1 Analyses of Primary Endpoint and Key Secondary Endpoints Protocol P05233

The primary efficacy endpoint was the average Total Combined Score (TCS), the sum of the daily symptom score (DSS) and the (DMS), for each subject during the peak ragweed

pollen season 2010, divided by the number of subject diary recordings of that score during the entire ragweed pollen season.

The RPS was defined as the period from the first day of 3 consecutive recorded days with a pollen count of ≥10 grains/m^3, to the last day of the last occurrence of 3 consecutive recorded days with a pollen count ≥10 grains/m^3, inclusively. The peak of the RPS was defined as the15 consecutive recorded days within RS with the highest 15-day moving average pollen count for each site. The highest 15-day moving average was chosen from the period 14 days prior to the start of RS through 14 days after the end of RS. The final peak season, however, only included those days that fell within RS. There was only one unique peak season for each site.

The TCS is shown in Table 13 shows the TCS for the 12 Amb a 1-U and placebo groups and the change in the TCS, DSS, and DMS for the 12 Amb a 1-U study group relative to the placebo study group.

Table 13. **Change in the TCS, DSS, and DMS for the 12 Amb a 1-U study group relative to the placebo study group.**

	N	Adjusted Mean	Treatment Difference (RAGWITEK – Placebo) (95% CI)[a]	% difference relative to Placebo (95% CI)[b]	P-Value
TCS peak ragweed season (primary endpoint)					
12 Amb a 1-U	159	6.22	-2.24 (-3.41, -1.07)	-26.49 (-38.74, -14.59)	0.0002
Placebo	164	8.46	---	---	---
TCS entire ragweed season					
12 Amb a 1-U	160	5.21	-1.80 (-2.78, -0.82)	-25.66 (-37.55, -13.48)	0.0003
Placebo	166	7.01	---	---	---
DSS peak ragweed season					
12 Amb a 1-U	159	4.65	-0.94 (-1.70, -0.19)	-16.87 (-28.64, -4.62)	0.0144
Placebo	164	5.59	---	---	---
DSS entire ragweed season					
12 Amb a 1-U	160	4.05	-0.82 (-1.46, -0.18)	-16.85 (-28.47, -4.54)	0.0125
Placebo	166	4.87	---	---	---
DMS peak ragweed season					
12 Amb a 1-U	159	1.57	-1.30 (-1.95, -0.64)	-45.28 (-65.39, -26.99)	0.0001
Placebo	164	2.87	---	---	---
DMS entire ragweed season					
12 Amb a 1-U	160	1.16	-0.98 (-1.53, -0.44)	-45.86 (-65.53, -24.02)	0.0004
Placebo	166	2.15	---	---	---

From the original BLA STN 125478/000; Module 5, CSR p05233, Page 97-109

The [% Relative to Placebo (95% CI)] for the 6 Amb a 1-U dose was -20.8% (-34.1, -7.1), suggesting that the 12 Amb a 1 U dose is effective, while the 6 Amb a 1 U dose may not be effective.

6.1.11.2 Analyses of Secondary Endpoints Protocol P05233

Secondary endpoint analyses are included in Table 13, above.

6.1.11.3 Subpopulation Analyses Protocol P05233

Efficacy of subpopulations from both Protocols P05233 and P05234 are discussed in Section 7.1.7

6.1.11.4 Dropouts and/or Discontinuations Protocol P05233

No imputation of data was carried out in case of missing data but all available data was used to its full extent. This means that subjects who withdrew prior to the start of the ragweed pollen season did not contribute to the efficacy analyses.

6.1.11.5 Exploratory and Post Hoc Analyses Protocol P05233

None

6.1.12 Safety Analyses Protocol P05233

6.1.12.1 Methods Protocol P05233

The safety variables assessed included: AEs, vital signs, physical examinations, ECG at screening, and safety laboratory assessments. AEs were recorded on open-ended. diary cards collected at each study visit. The schedule of visits is shown in Table 9 (above).

6.1.12.2 Overview of Adverse Events Protocol P05233

A total of 81.3% (455/560) of subjects reported an AE during the study. AEs were reported by 85.5% in the 12 Amb a 1-U group, 80.9% in the 6 Amb a 1-U group, and 77.4% in the placebo group, indicating that the occurrence of AEs was similar across the three treatment groups. The most commonly reported AEs were oral pruritus, swollen tongue, tongue pruritus, throat irritation, nasopharyngitis, and ear pruritus. Approximately half of the subjects (293/560, or 52.3%) reported AEs that were considered by the investigator as possibly or probably related to study treatment, although it is notable that subjects in the active groups experienced more AEs assessed as treatment-related compared to the placebo group.

Treatment-related AE were noted in 68.8% of subjects in the 12 Amb a 1-U group, 59.6% of subjects in the 6 Amb a 1-U group, and 28.5% of subjects in the placebo group [14.3.1.6]. The AE included throat irritation, oral pruritus, ear pruritus, tongue pruritus, and swollen tongue, all of which have been observed in previous SLIT trials. These data are summarized in Table 14, and a listing of AE reported in > 2% of subjects is shown in Table 13.

Table 14. Summary of AE in Study P05233.

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

From the original BLA STN 125478/000; Module 5, CSR p05233, Page 142

Table 15. **Treatment-emergent AE that reported in >2% subjects, Protocol P05233**

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

The denominator for percentages is based on the number of subjects in each treatment group.
Subjects are counted once for each system organ class and preferred term.
Treatment-emergent adverse events (AEs) are new or worsening AEs reported on or after treatment start date through treatment stop date +30 days.
From the original BLA STN 125478/000; Module 5, CSR p05233, Pages 144-145

6.1.12.3 Deaths Protocol P05233

There were no deaths.

6.1.12.4 Nonfatal Serious Adverse Events Protocol P05233

Serious AEs were reported by nine subjects during the treatment period: 3 subjects (1.6%) in the 12 Amb a 1-U group (nephritis, appendicitis, lobar pneumonia, and hypoxia); 2 subjects (1.1%) in the 6 Amb a 1-U group (Pelvic mass and tonsillar hypertrophy); 4 subjects (2.2%) in the placebo group: (appendicitis, stab wound, cholelithiasis, and soft tissue injury).

There were no episodes of anaphylactic shock.

6.1.12.5 Adverse Events of Special Interest (AESI) Protocol P05233

AESI are severe local reactions, systemic reactions and administration of epinephrine, either self-administered or administered by a health care provider. All AESI for RAGWITEK are discussed in Section 8.4.8.

6.1.12.6 Clinical Test Results Protocol P05233

There were no clinical test results that reflect efficacy or are of concern regarding the safety of RAGWITEK.

6.1.12.7 Dropouts and/or Discontinuations Protocol P05233

A total of 37 subjects discontinued as a result of TEAEs: 15 subjects in the 6 Amb a 1-U group, 19 (10.2%) subjects in the 12 (8.0%) Amb a 1-U group, and 3 (1.6%) in the placebo group; these differences were statistically significant ($p \leq 0.001$ for the 12 Amb a 1-U group and $p=0.004$ for the 6 Amb a 1-U group, respectively)

AE leading to treatment discontinuations are shown in Tables 16-18.

Table 16. **Treatment Discontinuations in the 6 Amb a 1-U group**

Sex/Age/ Race	Onset/ End day	Adverse Events/ Preferred Terms	Severity	Relationship to treatment
F/27/W	1/-	Pruritus	Mild	Probably
M/37/W	14/14	Nausea Salivary hypersecretion	Moderate Severe	Probably Probably
M/50/W	16/16	Gingival edema Lip Swelling	Moderate Moderate	Probably Probably
M/46/B	47/57	Urticaria	Severe	Possibly
F/25/W	47/47	Glossitis Glossydynia	Moderate Moderate	Probably Probably
	47/47	Swollen Tongue Tongue Hemorrhage	Moderate	Probably
F/48/W	1/33	Throat Irritation	Moderate	Probably
M/43/A	14/22	Eye Swelling/Swelling Face	Moderate Moderate	Probably Probably
F/20/W	22/22	Abdominal Pain Lower Dysphagia Lip edema Tongue edema Face edema Pharyngeal edema	Moderate Moderate Moderate Moderate Moderate Severe	Probably Probably Probably Probably Probably Probably
M/39/W	8/12	Choking sensation	Mild	Probably
M/46/A	4/28	Swelling tongue	Mild	Probably
M/43/W	1/1	Nausea	Mild	Possibly
	1/1	Feeling hot	Mild	Possibly
	1/1	Dizziness	Mild	Possibly
M/32/A	3/36	Non-cardiac chest pain	Mild	Possibly
F/23/W	159/179	Stomatitis	Moderate	Possibly
	159/167	Acne	Moderate	Possibly
	176/179	Oral Pruritus	Moderate	Possibly
F/26/W	10/16	Tongue edema	Moderate	Probably

From the original BLA STN 125478/000; Module 5, CSR p05233, Pages 166-167

Table 17. **Treatment Discontinuations in the 12 Amb a 1-U group**

Sex/Age/ Race	Onset/ End day	Adverse Events/ Preferred Terms	Severity	Relationship to treatment
F/35/W	64/157	Seasonal Allergy	Moderate	Unlikely/Rx/Disc/DRG Discon
F/43/W	7/7	Palpitations	Moderate	Possibly
	7/7	Feeling Cold	Moderate	Possibly
M/32/W	12/18	Oral Pruritus	Moderate	Probably
	12/18	Tongue Pruritus	Moderate	Probably
	12/18	Pharyngeal Erythema	Moderate	Probably
	12/18	Pharyngeal Erythema	Moderate	Probably
	12/18	Throat Irritation	Moderate	Probably
F/21/W	7/28	Ear Pruritus	Mild	Probably
	7/28	Swollen Tongue	Mild	Probably
	11/28	Lip Swelling	Mild	Probably
	11/28	Palatal edema	Mild	Probably
	12/28	Dysphagia	Moderate	Probably
	12/28	Chest Discomfort	Moderate	Probably
	12/28	Pharyngeal edema	Moderate	Probably
F/39/W	1/3	Palatal edema	Mild	Probably
	1/1	Paresthesia Oral	Mild	Probably
	1/3	Tongue Disorder	Mild	Probably
	1/3	Tongue edema	Mild	Probably
	1/1	Fatigue	Mild	Probably
	1/3	Pharyngeal Erythema	Mild	Probably
	1/1	Flushing	Mild	Probably
F/48/W	20/27	Swollen tongue	Severe	Probably
	20/27	Oropharyngeal Swelling	Severe	Probably
	23/27	Ear Pruritus	Moderate	Probably
	23/27	Lip Swelling	Moderate	Probably
	23/27	Paresthesia oral	Moderate	Probably
	23/27	Paraesthesia	Moderate	Probably
F/18/W	1/1	Palatal Oedema	Moderate	Probably
	1/1	Tongue Pruritus	Mild	Probably
M/29/W	17/17	Swollen Tongue	Moderate	Probably
M/40/A	20/24	Gastritis	Moderate	Probably
M/32/A	72/83	Asthma	Moderate	Possibly
M/31/W	7/13	Abdominal Pain	Mild	Probably
	8/10	Pharyngeal edema	Moderate	Probably
	11/12	Pharyngeal edema	Severe	Probably
	12/12	Dysphagia	Severe	Probably
	12/12	Lip Swelling	Severe	Probably
	12/12	Oral Pruritus	Severe	Probably
	12/12	Tongue edema	Severe	Probably
	12/12	Tongue edema	Severe	Probably

Sex/Age/ Race	Onset/ End day	Adverse Events/ Preferred Terms	Severity	Relationship to treatment
	17/19	Pharyngeal Erythema	Mild	Probably
	7/13	Nausea	Mild	Probably
F/42/W	22/46	Nausea	Moderate	Probably
	22/46	esophageal Pain	Moderate	Probably
	22/46	Throat Irritation	Moderate	Probably
F/31/W	24/24	Swollen Tongue	Mild	Probably
M/35/W	274/294	Cough	Moderate	Possibly
F/37/W	6/11	Chest Discomfort	Severe	Probably
F/37/W	7/14	Tongue edema	Severe	Probably
F/19/W	12/25	Tongue edema	Moderate	Probably
	12/25	Oropharyngeal Discomfort	Moderate	Probably
	25/25	Dysphagia	Moderate	Probably
F/34/W	13/13	Swollen tongue	Severe	Probably

From the original BLA STN 125478/000; Module 5, CSR p05233, Pages 167-169

Table 18. Treatment Discontinuations in the Placebo group

Sex/Age/ Race	Onset/ End day	Adverse Events/ Preferred Terms	Severity	Relationship to treatment
F/29/W	116/122	Allergic pruritus	Moderate	Possibly/RX/Discon/ DRG Discon
	116/122	Allergic pruritus	Moderate	Possibly
	116/122	Rash	Moderate	Possibly
M/27/W	13/19	Disturbance in Attention	Moderate	Possibly
	13/19	Dizziness	Moderate	Possibly
	13/19	Asthma	Moderate	Possibly
M/49/W	196/215	Asthma	Moderate	Unlikely

From the original BLA STN 125478/000; Module 5, CSR p05233, Pages 169-170

6.1.13 Study Summary and Conclusions Protocol P05233

In Study P05233, RAGWITEK was most often associated with treatment related AE that are mild or moderate. Most often, these AE did not precipitate withdrawal from the study.

Study P05233 was well designed to meet its clinical endpoint, an improvement in the TCS in the RAGWITEK study drug group. The 12 Amb a 1-U dose appears to have greater efficacy than the 6 Amb a 1-U dose. The point estimate of that improvement of the 12 Amb a 1-U dose was was better than the minimal 15% considered acceptable by CBER, and the 95% Upper Limit of this difference was ≤ -10%. Therefore, the study met CBER's requirements for proof of efficacy.

The results of this study are considered pivotal for efficacy and safety of RAGWITEK for the treatment of adults with ARC due to sensitivity to ragweed pollen.

6.2 Trial #2: Protocol P05234

A multicenter, double-blind, randomized, placebo-controlled, parallel group study evaluating the efficacy and long-term safety of ragweed (Ambrosia artemisiifolia) sublingual tablet (SCH 39641) in adult subjects with a history of ragweed-induced rhinoconjunctivitis with or without asthma

6.2.1 Objectives (Primary, Secondary, etc) Protocol P05234

Primary Objective:
Identical to P05233

Key Secondary Objectives:
Identical to P05233

6.2.2 Design Overview Protocol P05234

Identical to P05233 except that P05234 included a 1.5 Amb a 1-U dosing group.

A total of 784 subjects were randomized in a 1:1:1:1 ratio to 12 Amb a 1-U (n=194), 6 Amb a 1-U (n=195), or 1.5 Amb a 1-U (197) dose, or to placebo (n=198).

Subjects visited the study site for at least 11 visits during the treatment period: Screening, Randomization and On-site dosing of study drug or placebo (3 visits), Off-season, Preseason, On-season, End-of-season, Post-season (2 visits), and Final Visit, and at Unscheduled Visits as appropriate.

The study schedule was identical to P05233.

Reviewer's comment: The study was well designed to determine efficacy and safety of the product.

6.2.3 Population Protocol P05234

Key Inclusion Criteria:
Identical to P05233

Key Exclusion Criteria:

1. Identical to P05233

6.2.4 Study Treatments or Agents Mandated by Protocol P05234

Table 19. Batch numbers used for treatments in Protocol 05233

	Ragweed AIT 1.5 Amb a 1-U	Ragweed AIT 6 Amb a 1-U	Ragweed AIT 12 Amb a 1-U	Placebo
Batch numbers	(b) (4)			

From the original BLA STN 125478/000; Module 5, CSR p05234, Page 4 of 3143

6.2.5 Directions for Use Protocol P05234

Sublingual ingestion (tablet dissolves under tongue), 1 tablet per day.

6.2.6 Sites and Centers Protocol P05234

This study was performed at 72 sites in the United States and 12 sites in Canada, 20 sites in Hungary, 8 sites in the Ukraine, and 2 sites in Russia.

6.2.7 Surveillance/Monitoring Protocol P05234

Identical to P05233

6.2.8 Endpoints and Criteria for Study Success Protocol P05234

Identical to P05233

6.2.9 Statistical Considerations & Statistical Analysis Plan Protocol P05234

Identical to P05233

6.2.10 Study Population and Disposition Protocol P05234

6.2.10.1 Populations Enrolled/Analyzed Protocol P05234

Identical to P05233

6.2.10.1.1 Demographics Protocol P05234

Table 27 shows key demographic data from Study P05234. Subjects were equally distributed between the study drug and placebo groups for each of these variables, as well as weight, height, BMI, duration of ARC, tobacco history, and for asthmatics, the percent predicted FEV_1 at baseline (not shown).

Table 20. **Key Demographics Study P05234**

	RAGWEED AIT 1.5 Amb a 1-U n (%)	RAGWEED AIT 6 Amb a 1-U n (%)	RAGWEED AIT 6 Amb a 1-U n (%)	Placebo n (%)	Total N (%)
Number of subjects each group	197	195	194	198	784
Sex					
Female	110 (55.8)	103 (52.8)	91 (46.9)	96 (48.5)	400 (51.0)
Male	87 (44.2)	92 (47.2)	103 (53.1)	102 (51.5)	384 (49.0)
Race					
White	176 (89.3)	169 (86.7)	173 (89.2)	168 (84.8)	686 (87.5)
Non-White	21 (10.7)	26 (13.3)	21 (10.8)	30 (15.2)	98 (12.5)
Asian	4 (2.0)	4 (2.1)	2 (1.0)	6 (3.0)	16 (2.0)
Black or African American	14 (7.1)	21 (10.8)	13 (6.7)	22 (11.1)	70 (8.9)
Multiracial	3 (1.5)	1 (0.5)	4 (2.1)	2 (1.0)	10 (1.3)
Age (yrs)					
Mean (SD)	Mean (SD)	36.2 (8.83)	36.9 (8.80)	35.6 (8.75)	36.7 (8.54)
Median	Median	37.0	38.0	36.5	38.0
Range	Range	18.0-50.0	18.0-50.0	19.0-50.0	18.0-51.0
Asthma Status					
Asthmatics	34 (17.3)	31 (15.9)	37 (19.1)	32 (16.2)	134 (17.1)
Non-Asthmatics	163 (82.7)	164 (84.1)	157 (80.9)	166 (83.8)	650 (82.9)

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6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population Protocol P05234

The number of asthmatics and non-asthmatics were balanced among the study groups (15.9%-17.3%).

6.2.10.1.3 Subject Disposition Protocol P05234

Table 21. **Disposition of randomized study subjects Protocol P05234**

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

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6.2.11 Efficacy Analyses Protocol P05234

6.1.11.1 Analyses of Primary Endpoint(s) Protocol P05234

The primary efficacy endpoint was the average Total Combined Score (TCS), the sum of the daily symptom score (DSS) and the (DMS), for each subject during the peak ragweed pollen season 2010, divided by the number of subject diary recordings of that score during the entire ragweed pollen season.

The RPS was defined as the period from the first day of 3 consecutive recorded days with a pollen count of ≥10 grains/m^3, to the last day of the last occurrence of 3 consecutive recorded days with a pollen count ≥10 grains/m^3, inclusively. The peak of the RPS was defined as the15 consecutive recorded days within RS with the highest 15-day moving average pollen count for each site. The highest 15-day moving average was chosen from the period 14 days prior to the start of RS through 14 days after the end of RS. The final peak season, however, only included those days that fell within RS. There was only one unique peak season for each site.

The TCS is shown in Table 22 shows the TCS for the 12 Amb a 1-U and placebo groups and the change in the TCS, DSS, and DMS for the 12 Amb a 1-U study group relative to the placebo study group.

Table 22. Change in the TCS, DSS, and DMS for the 12 Amb a 1-U study group relative to the placebo study group.

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

From original BLA STN 125478/000; Module 5, CSR p05234 Pages 101-116

The [% Relative to Placebo (95% CI)] for the 6 Amb a 1-U dose was -20.8% (-34.1, -7.1), suggesting that the 12 Amb a 1 U dose is effective, while the 6 Amb a 1 U dose may not be effective.

6.2.11.3 Subpopulation Analyses Protocol P05234

Efficacy of subpopulations from both Protocols P05233 and P05244 are discussed in Section 7.1.7

6.2.11.4 Dropouts and/or Discontinuations Protocol P05234

No imputation of data was carried out in case of missing data but all available data was used to its full extent. This means that subjects who withdrew prior to the start of the ragweed pollen season did not contribute to the efficacy analyses.

6.2.11.5 Exploratory and Post Hoc Analyses Protocol P05234

None

6.2.12 Safety Analyses Protocol P05234

6.2.12.1 Methods Protocol P05234

The safety variables assessed included: AEs, vital signs, physical examinations, ECG at screening, and safety laboratory assessments. AEs were recorded on open-ended. diary cards collected at each study visit. The schedule of visits is identical to the schedule for P05233 shown in Table 9.

This study included a Data Safety Monitoring Committee (DSMC). The DSMC was established prior to the start of the treatment period to evaluate AE data and provide any recommendations regarding the conduct of the study to ensure that the safety of the subjects participating in the study was protected. The DSMC was developed to monitor trial conduct and safety data as outlined in a separate charter.

6.2.12.2 Overview of Adverse Events Protocol P05234

A total of 75.1% of subjects reported an AE during the trial. The most commonly reported AEs were throat irritation, ear pruritus (13.8% to 7.1% in the ragweed AIT groups; 1.0% in the placebo group), oral pruritus (14.9% to 5.6% in the ragweed AIT groups; 1.0% in the placebo group), and headache (10.3% to 7.7% in the ragweed AIT groups; 10.6% in the placebo group).

Treatment-related AEs were noted in 54.1% of subjects in the 12 Amb a 1-U group, 51.8% of subjects in the 6 Amb a 1-U group, 40.3% in the 1.5 Amb a 1-U group, and 22.7% of subjects in the placebo group. These treatment-related AE included throat irritation, ear pruritus, oral pruritus, tongue pruritus, and paresthesia oral.

Table 23. **Adverse event Summary for Protocol P05234**

	Ragweed AIT 1.5 Amb a 1-U n (%)	Ragweed AIT 6 Amb a 1-U n (%)	Ragweed AIT 12 Amb a 1-U n (%)	Placebo n (%)	Total N (%)
Number of subjects in each group	196	195	194	198	793
Any Adverse Event	151 (77.0)	154 (79.0)	152 (78.4)	131 (66.2)	588 (75.1)
TEAEs	148 (75.5)	149 (76.4)	149 (76.8)	125 (63.1)	571 (72.9)
Treatment-Related Adverse Events[a]	79 (40.3)	101 (51.8)	105 (54.1)	45 (22.7)	330 (42.1)
Severe/Life-threatening Adverse Events	27 (13.8)	27 (13.8)	30 (15.5)	25 (12.6)	109 (13.9)
Serious Adverse Events[b]	5 (2.6)	4 (2.1)	4 (2.1)	1 (0.5)	14 (1.8)
Serious TEAEs	4 (2.0)	3 (1.5)	2 (1.0)	1 (0.5)	10 (1.3)
Serious Treatment-Related TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs Leading to Study Discontinuation	10 (5.1)	16 (8.2)	16 (8.2)	6 (3.0)	48 (6.1)
Treatment-Related TEAEs Leading to Study Discontinuation	4 (2.0)	12 (6.2)	14 (7.2)	4 (2.0)	34 (4.3)

From original BLA STN 125478/000; Module 5, CSR p05234 Page 149

The majority of subjects reporting treatment-emergent adverse events (TEAEs) during the treatment period (462/571, 80.9%) had their AEs assessed by the investigator as either mild or moderate in severity. Severe TEAEs were reported by 108 subjects:

- 5 subjects in the 12 Amb a 1-U group
- 6 subjects in the 6 Amb a 1-U
- 1 subject in the 1.5 Amb a 1-U group
- 2 subjects in the placebo group

Table 24 shows AE that occurred in more than 2% of study subjects in Protocol P05234.

Table 24. Treatment-emergent AE that reported in >2% subjects, Protocol 05234

	Number (%) of Subjects Ragweed AIT 1.5 Amb a 1-U (n=196)	Number (%) of Subjects Ragweed AIT 6 Amb a 1-U (n=195)	Number (%) of Subjects Ragweed AIT 12 Amb a 1-U (n=194)	Number (%) of Subjects Placebo (n=198)	Number (%) of Subjects Total (N=783)
Sujects Reporting Any Adverse Event	148 (75.5)	148 (76.4)	149 (76.8)	125 (63.1)	571 (75.6)
Ear and Labyrinth Disorders	20 (10.2)	29 (14.9)	29 (14.9)	4 (2.0)	82 (10.5)
Ear Pruritus	14 (7.1)	27 (13.8)	25 (12.9)	2 (1.0)	68 (8.7)
Eye Disorders	11 (5.6)	22 (11.3)	11 (5.7)	17 (8.6)	61 (7.8)
Conjunctivitis	2 (1.0)	4 (2.1)	1 (0.5)	1 (0.5)	8 (1.0)
Eye Pruritus	7 (3.6)	7 (3.6)	6 (3.1)	4 (2.0)	24 (3.1)
Gastrointestinal Disorders	60 (30.6)	91 (46.7)	87 (44.8)	27 (13.6)	265 (33.8)
Diarrhoea	1 (0.5)	7 (3.6)	5 (2.6)	4 (2.0)	17 (2.2)
Dyspepsia	3 (1.5)	6 (3.1)	7 (3.6)	0 (0.0)	16 (2.0)
Hypoaesthesia Oral	2 (1.0)	6 (3.1)	4 (2.1)	0 (0.0)	12 (1.5)
Lip Oedema	3 (1.5)	4 (2.1)	3 (1.5)	0 (0.0)	10 (1.3)
Lip Swelling	1 (0.5)	3 (1.5)	4 (2.1)	0 (0.0)	8 (1.0)
Nausea	2 (1.0)	7 (3.6)	3 (1.5)	5 (2.5)	17 (2.2)
Oral Pruritus	11 (5.6)	29 (14.9)	16 (8.2)	2 (1.0)	58 (7.4)
Paraesthesia Oral	10 (5.1)	15 (7.7)	9 (4.6)	5 (2.5)	39 (5.0)
Stomatitis	0 (0.0)	4 (2.1)	1 (0.5)	0 (0.0)	5 (0.6)
Swollen Tongue	11 (5.6)	12 (6.2)	15 (7.7)	1 (0.5)	39 (5.0)
Tongue Disorder	1 (0.5)	3 (1.5)	4 (2.1)	2 (1.0)	10 (1.3)
Tongue Oedema	8 (4.1)	15 (7.7)	12 (6.2)	0 (0.0)	35 (4.5)
Tongue Pruritus	13 (6.6)	19 (9.7)	18 (9.3)	3 (1.5)	53 (6.8)
Vomiting	1 (0.5)	8 (4.1)	2 (1.0)	1 (0.5)	12 (1.5)
General Disorders and Administration Site Conditions	12 (6.1)	22 (11.3)	13 (6.7)	9 (4.5)	56 (7.2)
Chest Discomfort	4 (2.0)	3 (1.5)	2 (1.0)	0 (0.0)	9 (1.1)
Pyrexia	0 (0.0)	5 (2.6)	3 (1.5)	2 (1.0)	10 (1.3)
Immune System Disorders	6 (3.1)	4 (2.1)	4 (2.1)	0 (0.0)	14 (1.8)
Allergy to Animal	4 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.5)

	Number (%) of Subjects Ragweed AIT 1.5 Amb a 1-U (n=196)	Number (%) of Subjects Ragweed AIT 6 Amb a 1-U (n=195)	Number (%) of Subjects Ragweed AIT 12 Amb a 1-U (n=194)	Number (%) of Subjects Placebo (n=198)	Number (%) of Subjects Total (N=783)
Infections and Infestations	70 (35.7)	72 (36.9)	69 (35.6)	77 (38.9)	288 (36.8)
Bronchitis	5 (2.6)	7 (3.6)	8 (4.1)	12 (6.1)	32 (4.1)
Gastroenteritis Viral	2 (1.0)	3 (1.5)	2 (1.0)	5 (2.5)	12 (1.5)
Influenza	4 (2.0)	2 (1.0)	3 (1.5)	3 (1.5)	12 (1.5)
Nasopharyngitis	31 (15.8)	28 (14.4)	33 (17.0)	35 (17.7)	127 (16.2)
Pharyngitis Streptococcal	4 (2.0)	1 (0.5)	6 (3.1)	3 (1.5)	14 (1.8)
Sinusitis	12 (6.1)	9 (4.6)	8 (4.1)	7 (3.5)	36 (4..6)
Upper Respiratory Tract Infection	9 (4.6)	18 (9.2)	9 (4.6)	9 (4.5)	45 (5.7)
Urinary Tract Infection	3 (1.5)	2 (1.0)	1 (0.5)	5 (2.5)	11 (1.4)
Viral Infection	1 (0.5)	0 (0.0)	1 (0.5)	4 (2.0)	6 (0.8)
Injury, Poisoning Procedural Complications	19 (9.7)	22 (11.3)	17 (8.8)	17 (8.6)	75 (9.6)
Procedural Pain	6 (3.1)	3 (1.5)	1 (0.5)	2 (1.0)	12 (1.5)
Musculoskeletal and Connective Tissue Disorders	18 (9.2)	14 (7.2)	12 (6.2)	17 (8.6)	61 (7.8)
Arthralgia	6 (3.1)	5 (2.6)	0 (0.0)	2 (1.0)	13 (1.7)
Back Pain	2 (1.0)	4 (2.1)	4 (2.1)	6 (3.0)	16 (2.0)
Myalgia	0 (0.0)	4 (2.1)	2 (1.0)	2 (1.0)	8 (1.0)
Neck Pain	0 (0.0)	0 (0.0)	4 (2.1)	2 (1.0)	6 (0.8)
Nervous System Disorders	27 (13.8)	24 (12.3)	24 (12.4)	29 (14.6)	104 (13.3)
Dizziness	3 (1.5)	2 (1.0)	2 (1.0)	4 (2.0)	11 (1.4)
Headache	15 (7.7)	12 (6.2)	18 (9.3)	20 (10.1)	65 (8.3)
Migraine	4 (2.0)	3 (1.5)	1 (0.5)	1 (0.5)	9 (1.1)
Sinus Headache	4 (2.0)	2 (1.0)	3 (1.5)	2 (1.0)	11 (1.4)
Pregnancy, Puerperium and Perinatal Conditions	4 (2.0)	2 (1.0)	1 (0.5)	0 (0.0)	7 (0.9)
Pregnancy	4 (2.0)	2 (1.0)	1 (0.5)	0 (0.0)	7 (0.9)
Psychiatric Disorders	3 (1.5)	3 (1.5)	7 (3.6)	6 (3.0)	19 (2.4)
Insomnia	1 (0.5)	1 (0.5)	4 (2.1)	2 (1.0)	8 (1.0)
Respiratory, Thoracic and Mediastinal Disorders	74 (37.8)	72 (36.9)	78 (40.2)	42 (21.2)	266 (34.0)
Cough	11 (5.6)	10 (5.1)	12 (6.2)	6 (3.0)	39 (5.0)
Dyspnoea	1 (0.5)	0 (0.0)	5 (2.6)	3 (1.5)	9 (1.1)
Nasal Congestion	4 (2.0)	8 (4.1)	8 (4.1)	3 (1.5)	23 (2.9)
Nasal Discomfort	1 (0.5)	0 (0.0)	3 (1.5)	4 (2.0)	8 (1.0)
Nasal Obstruction	4 (2.0)	1 (0.5)	1 (0.5)	6 (3.0)	12 (1.5)
Oropharyngeal Pain	14 (7.1)	5 (2.6)	9 (4.6)	4 (2.0)	32 (4.1)
Pharyngeal Oedema	1 (0.5)	1 (0.5)	4 (2.1)	0 (0.0)	6 (0.8)
Rhinitis Allergic	2 (1.0)	3 (1.5)	3 (1.5)	6 (3.0)	14 (1.8)
Rhinorrhoea	5 (2.6)	6 (3.1)	5 (2.6)	8 (4.0)	24 (3.1)

	Number (%) of Subjects Ragweed AIT 1.5 Amb a 1-U (n=196)	Number (%) of Subjects Ragweed AIT 6 Amb a 1-U (n=195)	Number (%) of Subjects Ragweed AIT 12 Amb a 1-U (n=194)	Number (%) of Subjects Placebo (n=198)	Number (%) of Subjects Total (N=783)
Sinus Congestion	4 (2.0)	1 (0.5)	1 (0.5)	0 (0.0)	6 (0.8)
Sneezing	10 (5.1)	6 (3.1)	8 (4.1)	4 (2.0)	28 (3.6)
Throat Irritation	28 (14.3)	42 (21.5)	41 (21.1)	11 (5.6)	122 (15.6)
Throat Tightness	4 (2.0)	2 (1.0)	6 (3.1)	1 (0.5)	13 (1.7)
Skin and Subcutaneous Tissue Disorders	16 (8.2)	31 (15.9)	20 (10.3)	22 (11.1)	89 (11.4)
Dermatitis Contact	0 (0.0)	4 (2.1)	2 (1.0)	3 (1.5)	9 (1.1)
Pruritus	4 (2.0)	9 (4.6)	4 (2.1)	5 (2.5)	22 (2.8)
Pruritus Generalized	3 (1.5)	7 (3.6)	2 (1.0)	0 (0.0)	12 (1.5)
Rash	3 (1.5)	5 (2.6)	2 (1.0)	2 (1.0)	12 (1.5)
Urticaria	1 (0.5)	4 (2.1)	4 (2.1)	5 (2.5)	14 (1.8)

The denominator for percentages is based on the number of subjects in each treatment group.
Subjects are counted once for each system organ class and preferred term.
Treatment-emergent adverse events (AEs) are new or worsening AEs reported on or after treatment start date through treatment stop date +30 days.
Data Source: [14.3.1.5]
From original BLA STN 125478/000; Module 5, CSR p05234 Pages 150-152

6.2.12.3 Deaths Protocol P05234

There were no deaths.

6.2.12.4 Nonfatal Serious Adverse Events Protocol P05234

There were no episodes of anaphylactic shock.

Serious adverse events were reported by 14 subjects: 13 subjects in the ragweed AIT groups and 1 subject in the placebo group. Similar numbers of SAEs were reported across the active treatment groups: 4 (2.1%) in the 12 Amb a 1-U group; 4 (2.1%) in the 6 Amb a 1-U group, and 5 (2.6%) in the 1.5 Amb a 1-U group.

- The SAE for the 1.5 Amb a 1-U group were: ligament rupture, abortion induced, abortion spontaneous, breast cancer, acute pancreatitis, and cholelithiasis.
- The SAE for the 6 Amb a 1-U group were: obstructive abdominal hernia with post-operative abscess, breast cancer, abortion spontaneous, and bronchitis.
- The SAE for the 12 Amb a 1-U group were: Diabetes Mellitus inadequate control, hydrocele, ovarian cyst, hypersensitivity.

The one SAE in the placebo group was chlamydial pneumonia.

The reviewer agrees with the assessment that each of these SAE are unlikely to be related to treatment.

6.2.12.5 Adverse Events of Special Interest (AESI) Protocol P05234

AESI are severe local reactions, systemic reactions and administration of epinephrine, either self-administered or administered by a health care provider. All AESI for RAGWITEK are discussed in Section 8.4.8.

6.2.12.6 Clinical Test Results Protocol P05234

There were no clinical test results that reflect efficacy or are of concern regarding the safety of RAGWITEK.

6.2.12.7 Dropouts and/or Discontinuations Protocol P05234

A total of 37 subjects discontinued as a result of TEAEs: 15 subjects in the 6 Amb a 1-U group, 19 (10.2%) subjects in the 12 (8.0%) Amb a 1-U group, and 3 (1.6%) in the placebo group; these differences were statistically significant ($p \leq 0.001$ for the 12 Amb a 1-U group and $p=0.004$ for the 6 Amb a 1-U group, respectively).

Four subjects from the 1.5 Amb a 1-U group withdrew from the study due to TEAE that were considered treatment related.

Table 25. Treatment Discontinuations in the 1.5 Amb a 1-U group

Sex/Age/ Race	Onset/ End day	Adverse Events/ Preferred Term(s)	Severity	Relationship/Status
M/41	35/54	Tongue, lip Edema	Mild	Probably related
M/33	17/40	Palatal, tongue edema	Moderate	Probably related
F/30/W	6/88	Abdominal Discomfort, headache	Moderate	Possibly related
F/29/	11/14	Swollen tongue	Moderate	Possibly related

Twelve subjects from the 6 Amb a 1-U group withdrew from the study due to TEAE that were considered treatment related.

Table 26. Treatment Discontinuations in the 6 Amb a 1-U group

Sex/Age/ Race	Onset/ End day	Adverse Events/Preferred Term(s)	Severity	Relationship/Status
F/29/W	8/9	Lip edema, pruritus generalized	Moderate	Probably related
F27/W	31/34	Tongue edema	Moderate	
M/47	Tongue edema	Pregnancy	Moderate	Possibly related
F/35	125/131	Oral Pruritus, Papule	Severe	Probably related
F/48	17/27	Angioedema	Moderate	Probably related
F/48	4/12	Oropharyngeal blistering	Moderate	Probably related
F/31	1/22 22/22	Oral pruritus Dysphagia, tongue edema, chest discomfort, throat tightness	Mild Moderate/ severe	Probably related Probably related
M/26	7/10	Chest, orophyngeal discomfort	Severe	Possibly related
F/31	6/6	Stomatitis Swollen tongue, rash	Moderate	Probably related
F/47	295/313	Lip, mouth edema; paresthesia oral	Moderate	Probably related
M/32	109/113	Lip edema	Moderate	Possibly related
F/34	2/4	Tongue edema	Moderate	Probably related

From the original BLA STN 125478/000; Module 5, CSR p05234, Pages 177-178

Thirteen subjects from the 12 Amb a 1-U group withdrew from the study due to TEAE that were considered treatment related. One subject with non-cardiac chest pain is included in this table because the Clinical Reviewer considers this event as "probably related" or "possibly related."

Table 27. Treatment Discontinuations in the 12 Amb a 1-U group

Sex/Age/ Race	Onset/ End day	Adverse Events/ Preferred Term(s)	Severity	Relationship/Status
F/44	12/14	Pharyngeal edema	Moderate	Probably related
F/34	9/9	Swollen Tongue	Moderate	Probably related
F/28	13/54	Swollen tongue, throat irritation	Moderate	Possibly related
M/32	19/28	Tongue edema	Moderate	Probably related
M/46	26/26	Dyspnea	Moderate	Possibly related
F/42	47/47	Lip swelling, swollen tongue	Severe	Probably related
M/40	15/16	Swollen tongue	Moderate	Probably related
M/19	5/7	Non-cardiac chest pain	Severe	Unlikely
M/42	105/145	Rash	Moderate	Probably related
M/32	1/24	Tongue edema, throat irritation	Moderate	Possibly related
M/42	7/?	Swollen tongue	Moderate	Probably related
F/44	8/14 13/14 14/14	Tongue edema Oropharyngeal discomfort, dysphagia	Moderate Severe Severe	Probably related
F/46	15/15	Hopoesthesia oral, swollen tongue	Mild	Probably related
F/46	3/9	Salivary gland enlargement	Moderate	Probably related

From the original BLA STN 125478/000; Module 5, CSR p05234, Pages 17-177

Four subjects from the Placebo group withdrew from the study due to TEAE that were considered treatment related.

Table 28. Treatment Discontinuations in the placebo group

Sex/Age/ Race	Onset/ End day	Adverse Events/ Preferred Term(s)	Severity	Relationship/Status
F/39	2/2	Angioedema	Moderate	Probably related
F/42	43/43	Throat irritation, pruritus	Mild	Possibly related
111/117	111/117	Rhinitis seasonal	Moderate	Possibly related
M/38	1/25 25/25	Headache Dyspnea	Mild	Probably related

From the original BLA STN 125478/000; Module 5, CSR p05234, Pages 178

6.2.13 Study Summary and Conclusions Protocol P05234

In Study P05234, RAGWITEK 12 Amb a 1-U was associated with treatment related AE that are predominantly mild or moderate. The rate of treatment-related AE was similar to the 6 Amb a 1-U dose, both of which were greater than placebo. The rate of treatment-related AE in response to the 1.5 Amb a 1 U dose was similar to placebo. Most often, the AE did not precipitate withdrawal from the study. There was one systemic reaction

(episode of anaphylaxis) in response to the RAGWITEK, which occurred after the first dose of therapy; this subject withdrew from the trial.

Study P05234 was well designed to meet its clinical endpoint, an improvement in the TCS in the RAGWITEK study drug group. The point estimate of that improvement was better than the minimal 15% considered acceptable by CBER, and the 95% Upper Limit of this difference was ≤ -10% for the 12 Amb a 1-U dose. Therefore, the study met CBER's requirements for proof of efficacy for the 12 Amb a 1-U dose.

The results of this study are considered pivotal for efficacy and safety of RAGWITEK for the treatment of adults with ARC due to sensitivity to ragweed pollen.

6.3 Trial #3: Protocol P05751

A 28-Day Study Evaluating the Safety of Ragweed (Ambrosia artemisiifolia) Allergy Immunotherapy Tablet (SCH39641/MK-3641) Treatment in Ragweed Allergic Adults

6.3.1 Objectives (Primary, Secondary, etc.) Protocol P05751

Primary Objective:
The primary objective of the trial was to assess the safety profile of short ragweed (*Ambrosia artemisiifolia*) AIT (MK-3641), as evidenced by the percentage of subjects treated with MK-3641 compared to placebo with treatment-emergent adverse events (AEs), in adult subjects with ragweed-induced rhinoconjunctivitis with or without asthma.

Key Secondary Trial Objective: The secondary objective of the trial was to assess the frequency of particular AEs expected to occur commonly with the local application of short ragweed AIT, namely, oral pruritus, ear pruritus, throat irritation, edema mouth, nasal passage irritation, eye pruritus, and skin pruritus. Additionally, discontinuations due to treatment-emergent AEs were evaluated.

6.3.2 Design Overview Protocol P05751

This was a multicenter, double-blind, randomized, placebo-controlled, parallel group study in subjects 18 years of age or older, of either gender, and of any race with a history of ragweed-induced rhinoconjunctivitis with or without asthma. The subjects were treated once daily with MK-3641, 12 Amb a 1-U ragweed sublingual tablet or placebo for approximately 28 days.

Prior to treatment initiation, each subject was supplied with self-injectable epinephrine for the treatment of acute severe systemic allergic reactions. Subjects were instructed on how and when to use the medication. Subjects completed at least 3 visits: Screening, Randomization, and a final study visit to occur at the end of study treatment (approximately Day 28).

The first dose of IMP was administered at the study site, and the subject was monitored for adverse events at the site for 30 minutes following dosing. Subsequent administration of IMP was done once daily at home at approximately the same time each day. A follow-up telephone call between the site and the subjects was made daily for the first 2 doses of at-home administration of IMP and approximately once weekly thereafter. A follow-up telephone contact occurred approximately 7 days after the final study visit.

Figure 2. Study Design of Protocol P05751

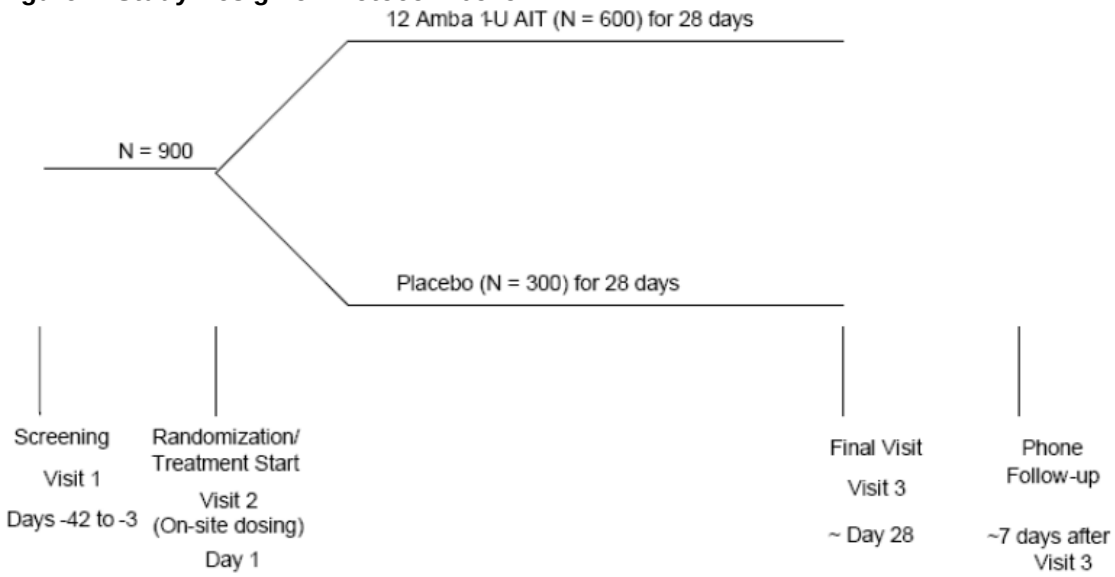

Table 29. Study Schedule of P05751

Visit Title	Screening	Randomization	Telephone Contact[a]	Final	Telephone Contact	Unscheduled[b]
Visit Number	Visit 1	Visit 2[c]	-	Visit 3[d]		
Scheduled Day	Days -42 to -3	Day 1		Day 28	Day 35	
Scheduling Window			±3 days[a]	±2 days	±5 days	
Informed Consent[e]	X					
Issue/Collect Subject Identification Card	X			X		
Medical History	X					
Inclusion/Exclusion Criteria	X	X				
Demography	X					
Body Height and Weight	X			X		
Assess/Record Concomitant Medications	X	X	X	X	X	X
Physical Examination	X			X		X
Vital Signs[f]	X	X		X		X
Pulmonary Function Tests	X	X		X		X
12-Lead Electrocardiogram (ECG)[g]	X					
Clinical Laboratory Tests[h]	X			X		
Serum Specific Immunoglobin E (IgE)[i]	X					
Urine Pregnancy Test[j]	X	X		X		X
Skin Prick Test	X					
Interactive Voice Response System (IVRS)	X	X			X	X
Immunologic Assessment/Serum Archive[k]	X			X		
Pharmacogenetic (PGt) Sample[l]				X		
Issue/Review Comment Card	X	X	X	X		X
Assess/Record Adverse Events (AEs)		X	X	X	X	X
Oropharyngeal Examination	X	Xm		X		X
Dispense Self- Injectable Epinephrine, Instruct in Its Use, Provide Educational Information and Written Anaphylaxis Emergency Action Plan		X				X
Verify That Subject has Self-Injectable Epinephrine/ Instruct in Its Use			X	X		X
On-Site Dosing of Investigational Medicinal Product (IMP)		X				
Dispense Study Medication		X				
Assess compliance			X	X		X
Collect Comment Cards				X		
Collect IMP				X		
Collect Self-Injectable Epinephrine				X		

From original BLA STN 125478/000; Module 5, CSR P05751, Page 30-32 of 1971

6.3.3 Population Protocol P05751

Key Inclusion Criteria

1. Each subject must have been at least 18 years of age. A subject may have been of either sex and any race/ethnicity.
2. Each subject must have had a clinical history of physician-diagnosed ragweed induced allergic rhinoconjunctivitis of 2 years duration or more, with or without asthma.
3. Each subject must have had a positive skin prick test response to *Ambrosia artemisiifolia* at the Screening Visit (at least 5 mm wheal).
4. Subject must have had an FEV1 ≥70% of predicted value at the Screening Visit and requiring no more than 250 mcg fluticasone or its equivalent.

Key Exclusion Criteria

1. A subject with unstable asthma, as judged by the clinical investigator, or a subject who had experienced an occurrence of any clinical deterioration of asthma that resulted in emergency treatment, hospitalization due to asthma, or treatment with systemic corticosteroids (but allowing short-acting beta2-agonists [SABA]) at any time within the 3 months prior to Screening.
2. Subject received an immunosuppressive treatment within 3 months prior to Randomization (except steroids for allergic symptoms other than asthma).
3. A subject with a history of anaphylaxis with cardiorespiratory symptoms.
4. A subject with a history of chronic urticaria or angioedema.
5. A subject who had current severe atopic dermatitis.

6.3.4 Study Treatments or Agents Mandated by Protocol P05751

Table 30. Batch numbers of Study Drug and Placebo Protocol P05751

Drug	MK-3641	Placebo
Strength	12 Amb a 1-U	Not Applicable
Batch Numbers	(b) (4)	

From original BLA STN 125478/000; Module 5, CSR P05751, Page 4 of 1971

6.3.5 Directions for Use Protocol P05751

One tablet sublingually daily.

6.3.6 Sites and Centers Protocol P05751

There were 72 sites; 58 sites in the US and 14 sites in Canada

6.3.7 Surveillance/Monitoring Protocol P05751

All Independent Ethics Committees (IECs) reviewed and approved the protocol and applicable amendments. All IECs, also referred to as an Ethical Review Committees (ERCs) or Institutional Review Boards (IRBs) used for this study meet the following definition of an “IEC” consistent with the definition outlined in the Food and Drug Administration Code of Federal Regulations (CFR) Title 21, Part 312.3. An IEC is a review panel responsible for ensuring the protection of the rights, safety, and well-being of human subjects/patients involved in this clinical investigation. All IECs used for this study were adequately constituted in accordance with local regulations to provide assurance of human subject/patient protection.

There was no DSMB for this study.

6.3.8 Endpoints and Criteria for Study Success Protocol P05751

The primary safety endpoint for this study was the proportion of subjects reporting treatment-emergent AEs.

The secondary endpoints were the proportion of subjects reporting local AEs that occur with application of this type of therapy, including oral pruritus, ear pruritus, throat irritation, edema mouth, eye pruritus, nasal passage irritation, and skin pruritus, and the frequency of discontinuations due to treatment-emergent AEs.

6.3.9 Statistical Considerations & Statistical Analysis Plan Protocol P05751

The sample size for the active-treatment arm in this study is based on exposure requirements of the short ragweed AIT program. Approximately 1600 subjects were to be screened. Approximately 900 subjects were to receive randomized treatment assignment in the trial with 600 subjects assigned to the active-treatment arm and 300 assigned to placebo.

With 600 subjects in the active-treatment arm and 300 subjects in the placebo arm, the study is powered for a difference (with 90% power at an alpha level of 0.05 [2-sided test]), and its corresponding half-width of the 95% confidence interval for placebo incidence rates range from 0.5% to 45.0%.

6.3.10 Study Population and Disposition Protocol P05751

6.3.10.1 Populations Enrolled/Analyzed Protocol P05751

Of 914 randomized subjects, 913 subjects took at least one dose of study medication and were included in the safety analysis.

6.3.10.1.1 Demographics Protocol P05751

Table 31. Demographics of subjects in Protocol P05751

	12 Amb a 1-U N=610	Placebo N=304	Total N=914
Sex (n,%)			
Female	345 (56.6)	177 (58.2)	522 (57.1)
Male	265 (43.4)	127 (41.8)	392 (42.9)
Race (n,%)			
White	494 (81.0)	227 (74.7)	721 (78.9)
Non-White	116 (19.0)	77 (25.3)	193 (21.1)
American Indian or Alaskan Native	3 (0.5)	1 (0.3)	4 (0.4)
Asian	7 (1.1)	9 (3.0)	16 (1.8)
Black or African American	89 (14.6)	57 (18.8)	146 (16.0)
Multiracial	16 (2.6)	9 (3.0)	25 (2.7)
Native Hawaiian or Other Pacific Islander	1 (0.2)	1 (0.3)	2 (0.2)
Ethnicity (n,%)			
Hispanic or Latino	60 (9.8)	19 (6.3)	79 (8.6)
Not Hispanic or Latino	550 (90.2)	285 (93.8)	835 (91.4)
Age (yrs)			
Mean (SD)	40.7 (12.6)	42.3 (12.2)	41.2 (12.5)
Median	41.0	42.0	41.0
Range	18 - 85	18 - 76	18 - 85
Age (n,%)			
< 50	466 (76.4)	214 (70.4)	680 (74.4)
50 or Older	144 (23.6)	90 (29.6)	234 (25.6)
Asthma Status (n,%)			
No	501 (82.1)	250 (82.2)	751 (82.2)
Yes	109 (17.9)	54 (17.8)	163 (17.8)
ICS# Use for Asthma Treatment Among the Asthmatic subjects	28 (25.7)	11 (20.4)	39 (23.9)
Percent Predicted FEV_1 for Asthmatics (%)			
Mean (SD)	91.00 (12.11)	92.78 (19.47)	91.59 (14.91)
Median	90.70	91.16	90.70
Range	63.6 - 131.6	65.8 - 176.4	63.6 - 176.4

From original BLA STN 125478/000; Module 5, CSR P05751, Page 59-61 of 7193

Subjects in the placebo and study drug groups were also similar with respect to height and weight.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population Protocol P05751

Approximately 18% of each study group had mild intermittent asthma. Asthmatics were equally distributed among the study drug and placebo groups; Percent predicted FEV_1 was also similar between the two study groups.

6.3.10.1.3 Subject Disposition Protocol P05751

One subject (subject number 100703, site 149) was randomized in error (site made the IVRS call by mistake) and the study drug was not dispensed to this subject. This subject's status was assessed as "did not meet protocol eligibility."

Two other subjects also did not meet protocol eligibility due to not meeting the skin test requirements. A total of 609 subjects received 12 Amb a 1-U ragweed AIT and 304 subjects received placebo. Of the 914 randomized subjects, 873 (95.5%) subjects completed the protocol specified, double-blind treatment period, while 41 subjects (4.5%) discontinued the investigational treatment early. The primary reasons for study discontinuation was AEs (24 subjects, 2.6% overall). A list identifying the individual subjects who discontinued treatment early and the reasons for discontinuation appears in [16.4]. A summary of the disposition of subjects is presented in [14.1.3].

Table 32. **Disposition of Subjects, Study P05751**

	12 Amb a 1-U n (%)	Placebo n (%)	Total N (%)
Randomized	610 (100)	304 (100)	914 (100)
Treated	609 (99.8)	304 (100)	913 (99.9)
Discontinued Treatment Phase	35 (5.7)	6 (2.0)	41 (4.5)
-Adverse Event	21 (3.4)	3 (1.0)	24 (2.6)
-Lost To Follow-Up	3 (0.5)	0	3 (0.3)
-Subject Withdrew Consent	4 (0.7)	1 (0.3)	5 (0.5)
-Non-Compliance With Protocol	4 (0.7)	2 (0.7)	6 (0.7)
-Did Not Meet Protocol Eligibility	3 (0.5)	0	3 (0.3)
Completed Study	575(94.3)	298 (98.0)	873 (95.5)

Extracted from original BLA STN 125478/000; Module 5, CSR P05751, Page 52 of 1971

6.3.11 Efficacy Analyses Protocol P05751

This is a safety study; there are no efficacy data.

6.3.12 Safety Analyses Protocol P05751

6.3.12.1 Methods Protocol P05751

The safety variables assessed included: AEs, vital signs, physical examinations, an ECG at screening, and safety laboratory assessments. Symptoms were recorded daily by the subject (or parent/guardian) on a daily diary card. Diary cards were collected at each study visit. The Study Schedule for survey of AE of Protocol p05239 is essentially identical to that of Protocol P05238.

There was no Data Safety Monitoring Committee (DSMC).

6.3.12.2 Overview of Adverse Events Protocol P05751

AEs were reported by 54.0% in the MK- 3641 group and 45.7% in the placebo group. The occurrence of AEs was slightly higher in the MK-3641 group.

Table 33. Summary of AE Protocol P05751

	12 Amb a 1-U n (%)	Placebo n (%)	Total N (%)
Total	609	304	913
Number of Subjects Reporting at Least One Adverse Event	329 (54.0)	139 (45.7)	468 (51.3)
Number of Subjects Reporting TEAEs	321 (52.7)	130 (42.8)	451 (49.4)
Number of Subjects Reporting Treatment-Related TEAEs	240 (39.4)	64 (21.1)	304 (33.3)
Number of Subjects Reporting Serious TEAEs	1 (0.2)	3 (1.0)	4 (0.4)
Number of Subjects Reporting Serious Treatment-Related TEAEs	0 (0.0)	1 (0.3)	1 (0.1)
Number of Subjects Reporting TEAEs Leading to Study Discontinuation	21 (3.4)	3 (1.0)	24 (2.6)
Number of Subjects Reporting Treatment-Related TEAEs Leasing to Study Number of Discontinuation	17 (2.8)	2 (0.7)	19 (2.1)

Extracted from original BLA STN 125478/000; Module 5, CSR P05751, Page 66 of 1971

Fewer than half of the subjects (304/913, or 33.2%) reported AEs that were considered by the investigator as related to study treatment. Slightly more subjects in the active group (39.4%) reported treatment-related AEs compared to the placebo group (33.3%). The most commonly reported treatment-related AEs were local application site reactions in the mouth, throat, and ear. The statistical inferences (p-values and 95% confidence intervals) were performed on the expected AE.

Table 34. Pre-specified TEAE for Protocol P05751

	Proportion n/N (%)	Difference from placebo (%)	95% CI for Difference from Placebo (%)	p-Value
Any TEAE				
12 Amb a 1-U	321/609 (52.7)	9.95	(3.1,16.7)	0.005
Placebo	130/304 (42.8)			
Study Discontinuation Due to TEAE				
12 Amb a 1-U	21/609 (3.4)	2.46	(0.3, 4.4)	0.029
Placebo	3/304 (1.0)			
ORAL PRURITUS				
12 Amb a 1-U	44/609 (7.2)	5.58	(2.9, 8.2)	<.001
Placebo	5/304 (1.6)			
EAR PRURITUS				
12 Amb a 1-U	52/609 (8.5)	7.88	(5.5,10.5)	<.001
Placebo	2/304 (0.7)			
THROAT IRRITATION				
12 Amb a 1-U	82/609 (13.5)	10.17	(6.6,13.6)	<.001
Placebo	10/304 (3.3)			
EDEMA MOUTH				
12 Amb a 1-U	34/609 (5.6)	5.25	(3.3, 7.4)	<.001
Placebo	1/304 (0.3)			
EYE PRURITUS				
12 Amb a 1-U	11/609 (1.8)	0.17	(-2.1, 1.9)	0.861
Placebo	5/304 (1.6)			
NASAL PASSAGE IRRITATION				
12 Amb a 1-U	21/609 (3.4)	1.15	(-1.5, 3.3)	0.344
Placebo	7/304 (2.3)			
SKIN PRURITUS				
12 Amb a 1-U	18/609 (3.0)	0.99	(-1.5, 3.0)	0.382
Placebo	6/304 (2.0)			

Extracted from original BLA STN 125478/000; Module 5, CSR P05751, Page 67-68 of 1971

In addition, these TEAE more frequently in the RAGWITEK than Placebo group.

Table 35. Additional TEAE in Protocol P05751

	12 Amb a 1-U N=609	Placebo n = 304	Total N = 913
LIP SWELLING	18 (3.0)	0	18 (2.0)
NAUSEA	10 (1.6)	6 (2.0)	16 (1.8)
ORAL PRURITUS	44 (7.2)	5 (1.6)	49 (5.4)
PARAESTHESIA ORAL	70 (11.5)	16 (5.3)	86 (9.4)
TONGUE PRURITUS	29 (4.8)	1 (0.3)	30 (3.3)
FATIGUE	4 (0.7)	8 (2.6)	12 (1.3)
THROAT IRRITATION	81 (13.3)	10 (3.3)	91 (1.0)

From original BLA STN 125478/000; Module 5, CSR P05751, Page 70 of 1971

6.3.12.3 Deaths Protocol P05751

There were no deaths.

6.3.12.4 Nonfatal Serious Adverse Events Protocol P05751

There were nine SAE that occurred during the clinical trial. Four of these SAE were in the RAGWITEK group: ankle fracture, fibula fracture, tibia fracture, and hemorrhagic anemia; none of these were related RAGWITEK. The five SAE in the Placebo group were thrombophlebitis, bacterial arthritis accompanied by Henoch-Schonlein purpura and gastrointestinal hemorrhage. The fourth SAE in the placebo group was an anaphylactic reaction in a latex allergic subject.

The reviewer concurs that none of the SAE were related to study drug.

6.3.12.5 Adverse Events of Special Interest (AESI) Protocol P05751

AESI are severe local reactions, systemic reactions and administration of epinephrine, either self-administered or administered by a health care provider.

There was one episode of anaphylaxis that occurred in response to the RAGWITEK on Day 6 of therapy. The subject was having worsening local allergic reactions and took this dose under medical supervision. The episode resolved without hospitalization and the subject was discontinued from the trial.

The second episode of anaphylaxis was in a subject in the placebo group. The subject is latex allergic, and presumably she was exposed to latex during the first administration of placebo. The episode resolved and the subject was discontinued from the trial.

In addition, there were two episodes of “throat tightness” among RAGWITEK subjects that precipitated discontinuation from the trial. One on Day 1 (considered moderate) and one on Day 14, considered severe.

All AESI including these two events are discussed in Section 8.4.8.

6.3.12.6 Clinical Test Results Protocol P05751

No clinically relevant test results were reported.

6.3.12.7 Dropouts and/or Discontinuations Protocol P05751

Table 36. Dropouts and Discontinuations, 12 Amb a 1-U Study Group Protocol P05751

Sex/Age/ Race	Preferred Term	Begin@ Day/ Date	End@ Day/ Date	Severity	Rel.
F/58/W	ASTHMA	18	Ongoing	MOD	UNL
F/22/W	DYSPHAGIA	3	7	MOD	PROB
	OEDEMA MOUTH	3	7	MOD	PROB
M/34/W	ANAPHYLACTIC REACTION	6	6	SEV	PROB
F/41/W	OEDEMA MOUTH	8	10(1)	MILD	PROB
F/39/W	ERYTHEMA	2	3(1)	MILD	POSS
	NASAL CONGESTION	2	3(1)	MILD	POSS
	SNEEZING	2	3(1)	MILD	POSS
F/58/W	ANKLE FRACTURE	15(1)	Ongoing	SEV	UNL
	FIBULA FRACTURE	15(1)	Ongoing	SEV	UNL
	TIBIA FRACTURE	15(1)	Ongoing	SEV	UNL
	HAEMORRHAGIC ANAEMIA	17(3)	20(6)	LT	UNL
F/52/W	PALPITATIONS	1	1	MILD	UNL
M/45/W	OEDEMA MOUTH	13	15	MOD	PROB
F/27/W	OEDEMA MOUTH	9	19	MILD	PROB
F/34/W	ASTHMA	3	13(9)	MOD	POSS
F/25/A	URTICARIA	2	3(1)	SEV	PROB
F/68/W	PRURITUS GENERALISED	2	3(1)	SEV	POSS
	URTICARIA	2	3(1)	MOD	PROB
M/65/M	BRONCHITIS	10	15(5)	MOD	UNL
M/62/W	LIP SWELLING	1	3(2)	MOD	POSS
F/39/W	ORAL PRURITUS	1	1	MOD	PROB
	THROAT TIGHTNESS	1	1	MOD	PROB
M/38/W	COUGH	6	16(2)	MILD	POSS
	PRURITUS GENERALISED	6	16(2)	MILD	PROB
	RASH	6	16(2)	MILD	UNL
F/58/W	OEDEMA MOUTH	13	16	MILD	PROB
M/38/B	ORAL MUCOSAL BLISTERING	12	26(13)	MILD	POSS
F/42/N	PRURITUS	3	10(3)	MOD	PROB
	FACE OEDEMA	9(2)	24(17)	MOD	UNL
	POST PROCEDURAL OEDEMA	9(2)	24(17)	MOD	UNL
	PROCEDURAL PAIN	9(2)/	24(17)	MOD	UNL
M/41/M	THROAT TIGHTNESS	14	14	SEV	PROB
F/50/W	OEDEMA MOUTH	8	12(2)	MOD	PROB

Extracted from original BLA STN 125478/000; Module 5, CSR P05751, Page 80-81 of 1971

Table 37. Dropouts and Discontinuations, Placebo Group Protocol P05751

Sex/Age/ Race	Preferred Term	Begin@ Day/ Date	End@ Day/ Date	Severity	Rel.
F/43/W	THROMBOPHLEBITIS SUPERFICIAL	11(1)	13(3)	SEV	UNL
	PROCEDURAL PAIN	9(2)	24(17)	MOD	UNL
F/42/W	DRY THROAT	1	2(1)	MILD	PROB
	PARAESTHESIA ORAL	1	1	MILD	PROB
	PHARYNGEAL OEDEMA	1	2(1)	MILD	PROB
F/45/W	ANAPHYLACTIC REACTION	1	2(1)	LT	PROB

Extracted from original BLA STN 125478/000; Module 5, CSR P05751, Page 81 of 1971

6.3.13 Study Summary and Conclusions Protocol P05751

In Study P05751, RAGWITEK was associated with treatment related AE that are predominantly mild or moderate, and that did not precipitate withdrawal from the study. There was one episode of anaphylaxis that occurred in response to the RAGWITEK on Day 6 of therapy. The subject was having worsening local allergic reactions and took this dose under medical supervision; the episode resolved in the physician's office.

The safety profile of RAGWITEK observed in Protocol P05751 is consistent with data from P05233 and P05234, and with other trials of tablets for sublingual immunotherapy recently evaluated by this reviewer.

6.4 Trial #4: Protocol P06081

A 28-day study evaluating the safety of ragweed (Ambrosia artemisiifolia) sublingual tablet (SCH 39641) in adult subjects 50 years of age and older with ragweed-induced rhinoconjunctivitis

6.4.1 Objectives (Primary, Secondary, etc) Protocol P06081

See Protocol P05751 for Primary and Key secondary objectives of Protocol P06081.

6.4.2 Design Overview Protocol P06081

This was a multicenter, double-blind, randomized, placebo-controlled, parallel group study in subjects 50 years of age or older, of either gender, and of any race with a history of ragweed-induced rhinoconjunctivitis with or without asthma. The subjects were treated once daily with MK-3641 (SCH39641) at either 6 or 12 Amb a 1-U daily, or with placebo for approximately 28 days.

This study design was identical to that of P05751 with these exceptions:

1. Inclusion of an additional MK-3641 group at a dose of 6 Amb a 1-U
2. Age 50 years of age or greater (no upper age limit)
3. Subjects taking any dose of inhaled corticosteroids were excluded.

6.4.3 Population Protocol P06081

Key Inclusion and Exclusion criteria were identical to P05751 except:

1. Age 50 years of age or greater (no upper age limit)
2. Subjects taking any dose of inhaled corticosteroids were excluded

6.4.4 Study Treatments or Agents Mandated by Protocol P06081

Table 388. Batch numbers of Study Drug and Placebo Protocol P06081

Drug	MK-3641	MK-3641	Placebo
Strength	6 Amb a 1-U	12 Amb a 1-U	Not Applicable
Batch Numbers	(b) (4)		

From original BLA STN 125478/000; Module 5, CSR P06081, Page 40 of 1054

6.4.5 Directions for Use Protocol P06081

One tablet sublingually, daily.

6.4.6 Sites and Centers Protocol P06081

There were 30 sites, all of which were in the US

6.4.7 Surveillance/Monitoring Protocol P06081

All Independent Ethics Committees (IECs) reviewed and approved the protocol and applicable amendments. All IECs, also referred to as an Ethical Review Committees (ERCs) or Institutional Review Boards (IRBs) used for this study meet the following definition of an "IEC" consistent with the definition outlined in the Food and Drug Administration Code of Federal Regulations (CFR) Title 21, Part 312.3. An IEC is a review panel responsible for ensuring the protection of the rights, safety, and well-being of human subjects/patients involved in this clinical investigation. All IECs used for this study were adequately constituted in accordance with local regulations to provide assurance of human subject/patient protection.

There was no DSMB for this study.

6.4.8 Endpoints and Criteria for Study Success Protocol P06081

The primary safety endpoint for this study was the proportion of subjects reporting treatment-emergent AEs.

The secondary endpoints were the proportion of subjects reporting local AEs that occur with application of this type of therapy, including oral pruritus, ear pruritus, throat irritation, edema mouth, eye pruritus, nasal passage irritation, and skin pruritus, and the frequency of discontinuations due to treatment-emergent AEs.

6.4.9 Statistical Considerations & Statistical Analysis Plan Protocol P06081

The sample size for this trial was based on clinical considerations, as there were no inferential analyses planned for this study. Approximately 300 subjects were to be screened, assuming a screen failure rate of approximately 33%. Approximately 200 subjects were to receive randomized treatment assignment in the trial with approximately 65 subjects assigned to each of the active treatment arms (total o**f** 130 subjects) and approximately 65 subjects assigned to placebo.

A total of approximately 65 subjects in each active treatment group and 65 subjects in the placebo group would provide a half width of 95% confidence interval (CI) of 14.9% for a difference in proportion of subjects who reported AEs of 31%, assuming the proportion on the active treatment and placebo was 85% and 54%, respectively (based on the incidence of overall AEs in Study RT-01).
Extracted from original BLA STN 125478/000; Module 5, CSR P06081, Page 49 of 1054

6.4.10 Study Population and Disposition Protocol P06081

6.4.10.1 Populations Enrolled/Analyzed Protocol P06081

All subjects who were randomized and took at least one dose of placebo or Amb a 1-tablets at any dose are included in the analysis with the exception of subjects form Site 31 of the study.

On 05 August 2010, the sponsor notified the Food and Drug Administration Division of Scientific Investigations (FDA DSI) and the Center for Biologics Evaluation and Research (CBER) that Site 31 in this study had been closed due to observed misconduct and significant departures from GCP (i.e., fictitious subject names and dates of birth for two subjects). The data from Site 31 have been excluded from all safety analyses.

6.4.10.1.1 Demographics Protocol P06081

Table 39. Demographics of subjects in Protocol P05751

	6 Amb a 1-U Short Ragweed Tablet n=66	12 Amb a 1-U Short Ragweed Tablet n=65	Total Short Ragweed Tablet n=131	Placebo n=65
Sex (n,%)				
Female	43 (65)	40 (62)	83 (63)	38 (58)
Male	23 (35)	25 (38)	48 (37)	27 (42)
Race (n, %)				
White	56 (85)	55 (85)	111 (85)	54 (83)
Non-White	10 (15)	10 (15)	20 (15)	11 (17)
American Indian or Alaskan Native	0	0	0	1 (2)
Asian	0	1 (2)	1 (1)	0
Black or African American	9 (14)	9 (14)	18 (14)	10 (15)
Native Hawaiian or Other Pacific Islander	1 (2)	0	1 (1)	0
Ethnicity (n, %)				
Hispanic or Latino	3 (5)	4 (6)	7 (5)	2 (3)
Not Hispanic or Latino	63 (95)	61 (94)	124 (95)	63 (97)
Age (yrs)				
Mean (SD)	56.4 (5.4)	56.2 (5.7)	56.3 (5.6)	56.4 (4.7)
Median	55.0	55.0	55.0	55.0
Range	50-73	50-78	50-78	50-67
Age (n, %)				
50 ≤ 60	52 (79)	52 (80)	104 (79)	49 (75)
61 or older	14 (21)	13 (20)	27 (21)	16 (25)
Asthma Status (n, %)				
Asthmatics	9 (14)	6 (9)	15 (11)	7 (11)
Non-Asthmatics	57 (86)	59 (91)	116 (89)	58 (89)
Percent Predicted FEV1 for Asthmatics (%)				
Mean (SD)	91.80 (11.15)	92.32 (11.48)	92.01 (10.87)	84.64 (15.20)
Median	91.50	91.45	91.50	79.72
Range	74.9-107.0	75.0-108.5	74.9-108.5	72.7-116.3

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6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population Protocol P06081

The percentage of subjects in each study group with asthma is shown above in Table 37 (above).

6.4.10.1.3 Subject Disposition Protocol P06081

Of the 66 subjects in the 6 Amb a 1-U study group, two subjects discontinued due to AE, and one discontinued because of noncompliance with the protocol.

Of the 65 subjects in the 12 Amb a 1-U study group, five subjects discontinued due to AE, and one discontinued because of withdrawal of consent.

Of the 65 subjects in the Placebo group, 1 subject discontinued due to an AE.

6.4.11 Efficacy Analyses Protocol P06081

This is a safety study; there are no efficacy data.

6.4.12 Safety Analyses Protocol P06081

6.4.12.2 Overview of Adverse Events Protocol P06081

None of the differences in the occurrence of TEAEs between the pooled active (6 and 12 Amb a 1-U short ragweed tablet) groups versus placebo and each of the 6 and 12 Amb a 1-U short ragweed tablet groups versus placebo were statistically significant—probably due to the small sample size of this study. The most frequently reported TEAEs were:

- Oral pruritus (16.7% in the 6 Amb a 1-U short ragweed tablet group; 16.9% in the 12 Amb a 1-U short ragweed tablet group; 1.5% in the placebo group);
- Throat irritation (12.1% in the 6 Amb a 1-U short ragweed tablet group; 9.2% in the 12 Amb a 1-U short ragweed tablet group; 3.1% in the placebo group);
- Ear pruritus (6.1% in the 6 Amb a 1-U short ragweed tablet group; 7.7% in the 12 Amb a 1-U short ragweed tablet group; 0 subjects in the placebo group);
- Paresthesia oral (4.5% in the 6 Amb a 1-U short ragweed tablet group; 6.2% in the 12 Amb a 1-U short ragweed tablet group; 4.6% in the placebo group);
- Eye pruritus (3.0% in the 6 Amb a 1-U short ragweed tablet group; 6.2% in the 12 Amb a 1-U short ragweed tablet group; 6.2% in the placebo group).

6.4.12.3 Deaths Protocol P06081

There were no deaths.

6.4.12.4 Nonfatal Serious Adverse Events Protocol P06081

Two SAEs (acute cholecystitis and post procedural bile leak) were reported by one subject in the 12 Amb a 1-U short ragweed tablet group. The two SAEs were considered unlikely related to study medication.

The reviewer concurs that none of the SAE were related to study drug.

6.4.12.5 Adverse Events of Special Interest (AESI) Protocol P06081

AESI are severe local reactions, systemic reactions and administration of epinephrine, either self-administered or administered by a health care provider. All AESI including these two events are discussed in Section 8.4.8.

6.4.12.6 Clinical Test Results Protocol P06081

No clinically relevant test results were reported.

6.4.12.7 Dropouts and/or Discontinuations Protocol P06081

Two subjects in the 6 Amb a 1-U study group withdrew from the study—both because of a tooth extraction. Six subjects in the 12 Amb a 1-U discontinued the study due to AE. Three of these SAE were unrelated to the study drug—diarrhea and vomiting, cholecystitis (the SAE described above) and back pain. Three subjects in the 12 Amb a-1-U study group discontinued due to AE that were related to the study drug:

A 50 year old male who had a swollen tongue and throat tightness on Day 14; these were judged to be severe.
A 58 year old male who had a swollen tongue; this was judged to be severe
A 54 year old female with severe nasal congestion, moderate eye pruritus, lacrimation, rhinitis, and erythematous rash, and mild sneezing and pruritus

6.4.13 Study Summary and Conclusions Protocol P06081

In Study P06081, RAGWITEK was associated with treatment related AE that are predominantly mild or moderate, and that did not precipitate withdrawal from the study. There were no SAE that were related to study drug, but three subjects in the 12 Amb a 1 study group withdrew due to AE, two of whom had severe tongue swelling.

The safety profile of RAGWITEK observed in Protocol P06081 is consistent with data from P05233, P05234, and P05751, and with other trials of tablets for sublingual immunotherapy recently evaluated by this reviewer. There is no indication from this study that the AE profile of severity in otherwise healthy adults 50-65 years of age is any different from younger otherwise healthy adults. Safety with regard to subjects older than 65 will be discussed in Section 8.

7. Integrated Overview of Efficacy

7.1 Indication #1: "RAGWITEK is an allergen extract indicated as immunotherapy for 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 adults 18 through 65 years of age.

RAGWITEK is not indicated for the immediate relief of allergic symptoms."

7.1.1 Methods of Integration

P05233 and P05234 were the two efficacy studies conducted in support of RAGWITEK. These studies were conducted simultaneously; Their results were not integrated.

7.1.2 Demographics and Baseline Characteristics

Adapted from original BLA 125478/000; summary of clinical efficacy, Pages 152-156

Efficacy data on adults have been provided from two Phase 3 efficacy and safety studies with MK-3641 (P05233 and P05234) with identical selection criteria.

In all of the studies, subjects were required to have a positive SPT to *Ambrosia artemisiifolia*. The characteristics (sex, age, and weight) of the recruited subjects were similar among the two adult studies. The history, in years, of ragweed pollen-induced rhinoconjunctivitis was also comparable, as was the prevalence of asthma (~20%).

There are no pediatric studies in the BLA submission, and children and adolescents have not been treated with RAGWITEK.

7.1.3 Subject Disposition

Subject disposition for each study is outlined in Section 6.

7.1.4 Analysis of Primary and Key Secondary Endpoint(s)

The primary endpoint is difference of the TCS for peak ragweed pollen season. The key secondary endpoints are The DSS and DMS for peak ragweed season, and the TCS, DSS, and DMS for the entire ragweed season. The data for each of the two efficacy trials are similar, indicating ~25% point estimate improvement in peak and total ragweed pollen season ARC symptoms.

Table 40. Study P05233 primary and key secondary endpoints

	N	Adjusted Mean	Treatment Difference (RAGWITEK – Placebo) (95% CI)[a]	% difference relative to Placebo (95% CI)[b]	P-Value
TCS peak ragweed season (primary endpoint)					
12 Amb a 1-U	159	6.22	-2.24 (-3.41, -1.07)	-26.49 (-38.74, -14.59)	0.0002
Placebo	164	8.46	---	---	---
TCS entire ragweed season					
12 Amb a 1-U	160	5.21	-1.80 (-2.78, -0.82)	-25.66 (-37.55, -13.48)	0.0003
Placebo	166	7.01	---	---	---
DSS peak ragweed season					
12 Amb a 1-U	159	4.65	-0.94 (-1.70, -0.19)	-16.87 (-28.64, -4.62)	0.0144
Placebo	164	5.59	---	---	---
DSS entire ragweed season					
12 Amb a 1-U	160	4.05	-0.82 (-1.46, -0.18)	-16.85 (-28.47, -4.54)	0.0125
Placebo	166	4.87	---	---	---
DMS peak ragweed season					
12 Amb a 1-U	159	1.57	-1.30 (-1.95, -0.64)	-45.28 (-65.39, -26.99)	0.0001
Placebo	164	2.87	---	---	---
DMS entire ragweed season					
12 Amb a 1-U	160	1.16	-0.98 (-1.53, -0.44)	-45.86 (-65.53, -24.02)	0.0004
Placebo	166	2.15	---	---	---

Table 41. Study P05234 primary and key secondary endpoints

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

7.1.5 Analysis of Secondary Endpoint(s)

Discussed above

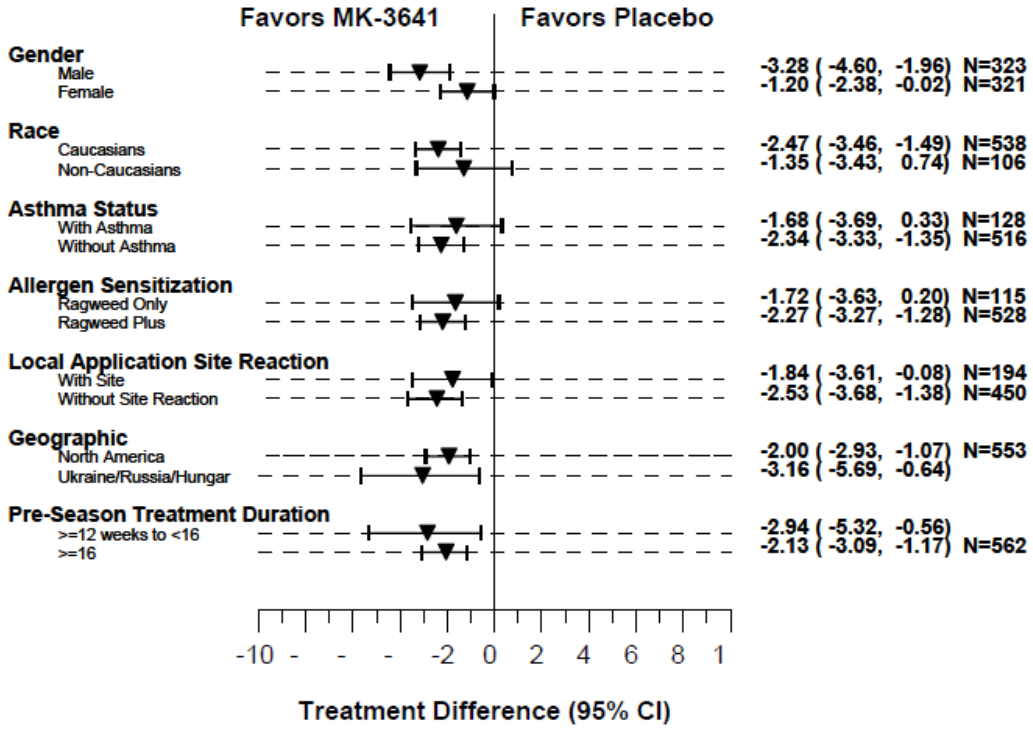
7.1.6 Other Endpoints

No other endpoints will be discussed in this section.

7.1.7 Subpopulations

Figure 3 shows efficacy on subpopulations of adult participants in P05233 and P05234.

Figure 3. Efficacy on subpopulations of RAGWITEK treated subjects



Extracted from original BLA STN 125478/000; Module 5, Summary of Clinical Efficacy; Page 98 of 179

Reviewer's note: The differences between Caucasians and non-Caucasians are difficult to interpret because of differences in sample sizes, and differences in scores among the placebo groups.

7.1.8 Persistence of Efficacy

There are no studies of persistence of efficacy with RAGWITEK.

7.1.9 Product-Product Interactions

None

7.1.10 Additional Efficacy Issues/Analyses

None

7.1.11 Efficacy Conclusions

RAGWITEK is effective for the treatment of AR with or without conjunctivitis in adults 18-65 years of age. The expected treatment effect is approximately an improvement of 25% of symptoms and medication score.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

AE were collected on open-ended paper daily diary comment cards (specific adverse events were not solicited) that were collected at each study visit.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Data were analyzed across four clinical trials for safety during the first 28 days of treatment, and across two safety and efficacy trials for 52 weeks of treatment.

Table 42. Safety studies of RAGWITEK

Safety					
Study #	Location	Years conducted	Age Range	# Subjects RAGWITEK	# Subjects Placebo
P06081	US	2009-2010	50-78	67	67
P05751	US, Canada	2011-2012	18-85	609	304
Efficacy and safety					
Study #	Location	Years conducted	Age Range	# Subjects RAGWITEK	# Subjects Placebo
P05233	US Canada	2009-2011	18-50	187	188
P05234	US, Canada, Hungary, Ukraine, Russia	2009-2011	18-50	194	198

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

These pooled analyses included 1,707 adults randomized to receive RAGWITEK at any dose: Of these, 196 adults received 1.5 Amb a 1-U, 454 adults received 6 Amb a 1-U, and 1057 adults received Amb a 1-U. There were 757 placebo subjects.

The age distribution of the subjects is shown in Table 42:

Table 43. Age distribution of safety data base of RAGWITEK

Age (years)	RAGWITEK Any dose N = 1707	RAGWITEK 12 Amb a 1-U N = 1057	Placebo N = 757
18-49	1405 (80%)	841 (80%)	590 (78%)
50-85	302 (20%)	216 (20%)	167 (22%)
50-64	274 (91%)	194 (90%)	153 (92%)
65-74	23 (7%)	17 (8%)	12 (7%)
75-85	5 (2%)	5 (2%)	2 (1%)

8.2.3 Categorization of Adverse Events

Safety was monitored by observation in the physician's office for 30 minutes following the first dose (also after the second and third doses in two studies), phone calls to capture adverse events over the first 2-4 days of home administration in some studies, safety assessments at study visits, paper diary comment cards and electronic diaries

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

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

A serious adverse event was any event that:

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

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

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

None

8.4 Safety Results

Table 44. Adverse events: number (%) of subjects, from the two 28-day efficacy

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

Table 45. Adverse events: number (%) of subjects, from the two 52-week efficacy

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

8.4.1 Deaths

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

8.4.2 Nonfatal Serious Adverse Events

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

- In the 12 Amb a 1-U treatment group, there was one subject who experienced "hypersensitivity," who was hospitalized and recovered. This event followed ingestion of propolis, a bee product; the subject continued the study medication without additional treatment-related adverse events.
- One subject was hospitalized prior to randomization for hypoxia due to lobar pneumonia.
- Life-threatening adverse events through Week 52 in two 1.5 Amb a 1-U recipients: one who had a spontaneous abortion and one who developed breast cancer.
- Life-threatening adverse events were reported for two subjects through Day 28: hemorrhagic anemia in a 12 Amb a 1-U recipient following a leg fracture; and an anaphylactic reaction in a placebo recipient on Day 1 which is reviewed further, below.

In addition, there was one episode of anaphylaxis in a placebo subject with a history of latex allergy, within five minutes of taking the first dose of placebo. The subject required two doses of epinephrine and was transferred to an emergency facility. Since the subject took placebo, it is assumed that the event was due to inadvertent latex exposure.

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

8.4.3 Study Dropouts/Discontinuations

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

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

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

Figure 4 shows the rate of discontinuation due to treatment-related AE during the first 28 days.

Figure 4. Rate of discontinuation due to treatment related AE during the first 28 days of treatment.

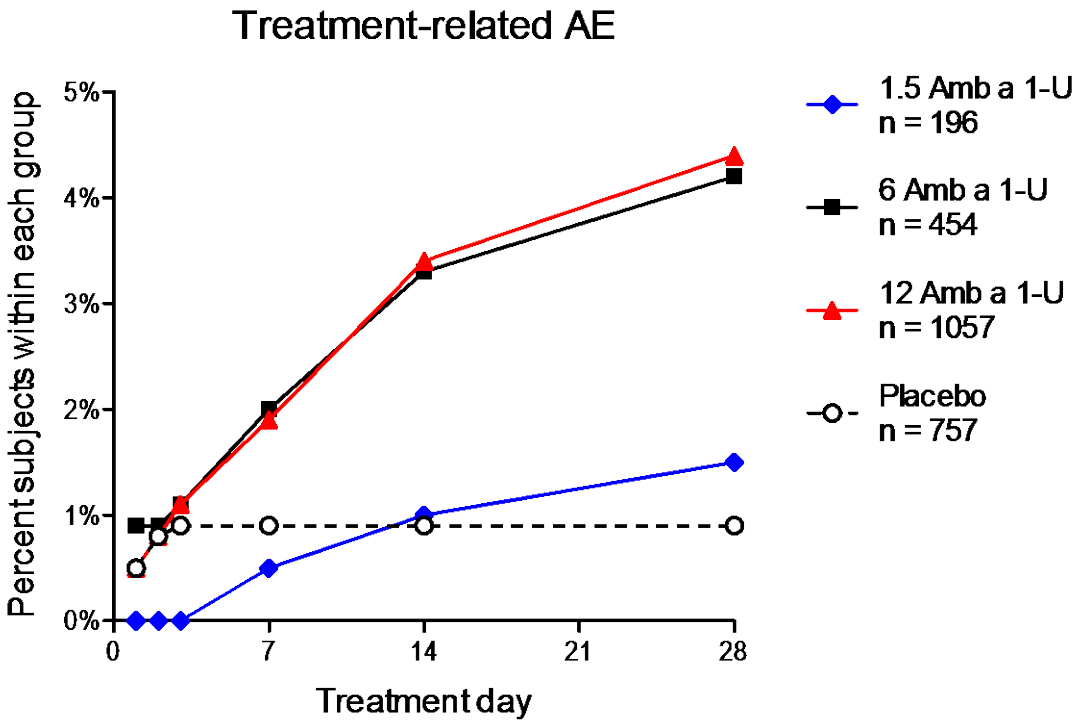
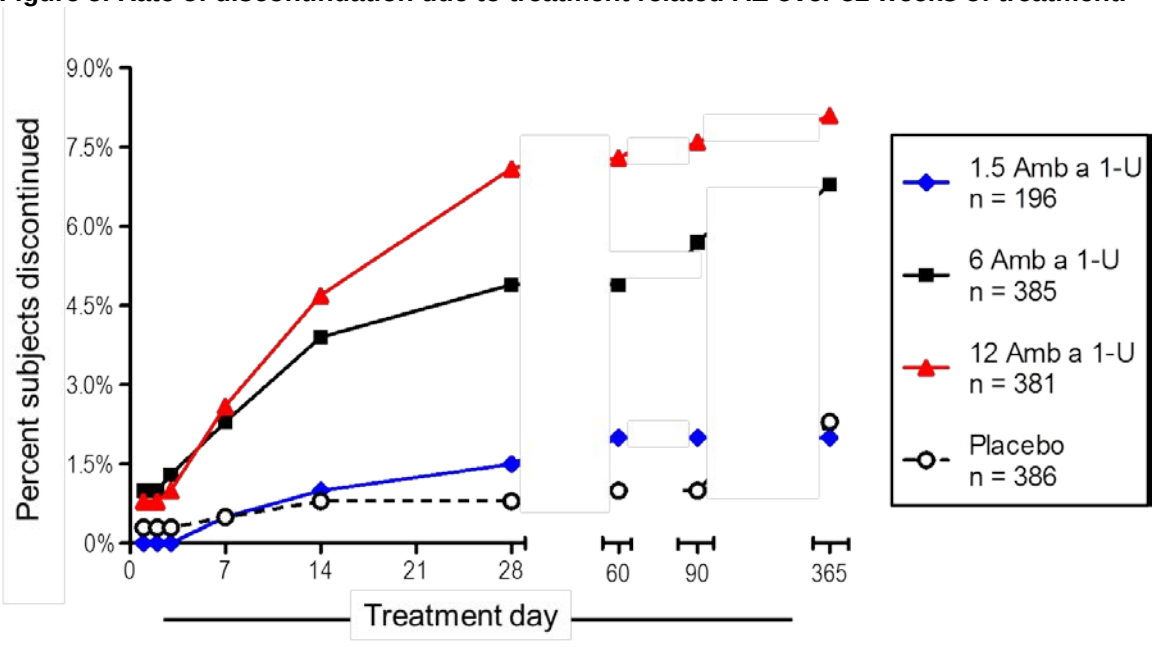


Figure 5 shows treatment discontinuation due to treatment related AE during 52 weeks.

Figure 5. Rate of discontinuation due to treatment related AE over 52 weeks of treatment.



8.4.4 Common Adverse Events

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

Treatment-related adverse events were reported at a higher frequency among the 1707 subjects treated over 28 days with RAGWITEK 12 Amb a 1-U compared to the 757 placebo subjects (56.5% RAGWITEK, 37.6% placebo). The most commonly reported treatment-related adverse events in the 28 day safety data base are shown in Table 45.

Table 46. Most common TEAE in 28 day safety data base

	RAGWITEK n=1057	Placebo n=757
Any	45.6%	20.5%
Oral pruritus	10.9%	2.0%
Oral paresthesia	10.0%	4.0%
Throat irritation	16.6%	3.3%
Ear pruritus	10.4%	1.1%
Mouth edema	6.1%	0.5%

TEAE reported in ≥ 2.5% of RAGWITEK recipients and at higher frequency than Placebo recipients were lip swelling, swollen tongue, tongue pruritus

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

Treatment-related adverse events were reported at a higher frequency among the 381 subjects treated over 52 weeks with RAGWITEK compared to the 386 placebo subjects (80.6% RAGWITEK, 68.4% placebo). The most commonly reported treatment-related adverse events in the 52-week safety data base are shown in Table 46.

Table 47. Most common TEAE in 52-week safety data base

	RAGWITEK N=381	Placebo N=386
Any	61.2%	25.4%
Oral pruritus	17.3%	2.6%
Oral paresthesia	8.4%	2.8%
Throat irritation	24.9%	4.4%
Ear pruritus	13.9%	1.6%
Mouth edema	9.2%	0.5%

TEAE reported in ≥ 2.5% of RAGWITEK recipients and at higher frequency than Placebo recipients: swollen tongue, tongue pruritus, lip swelling or edema, oropharyngeal pain

8.4.5 Clinical Test Results

There are no clinical laboratory tests that reflect the safety profile of RAGWITEK.

8.4.6 Systemic Adverse Events

Serious Adverse Events

- At least one serious adverse event was reported in 20 of 1707 (1.5%) RAGWITEK recipients, and in 8 of 757 (1.1%) placebo recipients. Of note:
- In the 12 Amb a 1-U treatment group, there was one subject who experienced "hypersensitivity," who was hospitalized and recovered. This event followed ingestion of propolis, a bee product; the subject continued the study medication without additional treatment-related adverse events.
- One subject was hospitalized prior to randomization for hypoxia due to lobar pneumonia.
- Life-threatening adverse events through Week 52 in two 1.5 Amb a 1-U recipients: one who had a spontaneous abortion and one who developed breast cancer.
- Life-threatening adverse events were reported for two subjects through Day 28: hemorrhagic anemia in a 12 Amb a 1-U recipient following a leg fracture; and an anaphylactic reaction in a placebo recipient on Day 1 which is reviewed further, below.
- There was one episode of anaphylaxis in the placebo subject discussed above with a history of latex allergy, within five minutes of taking the first dose of placebo. The subject required two doses of epinephrine and was transferred to an emergency facility. Since the subject took placebo, it is assumed that the event was due to inadvertent latex exposure.

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

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

8.4.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no potential for drug abuse with this product. Increasing the dose will increase the possibility of adverse reactions, including swelling of the upper airways and anaphylaxis.

8.4.8 Adverse Events of Special Interest

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

Subjects who received RAGWITEK 12 Amb a 1-U:

1. Lip swelling, abdominal pain and diarrhea on Day 7 of treatment; all were considered mild in severity, but the abdominal pain and diarrhea persisted for subsequent days. No treatment was required, but the subject was discontinued from the trial.
2. Mild swollen tongue and dyspnea on Day 24 of treatment; the dyspnea was treated with albuterol and the subject was discontinued from the trial.
3. Mild wheezing and dyspnea on Day 162 of the trial; the events persisted for a few days and resolved. The subject continued in the trial and tolerated study medication.
4. Palatal edema and flushing on Day 1; no treatment was required. The subject developed palatal edema on subsequent administrations and ultimately discontinued from the trial.
5. Palatal edema and mild urticaria on Day 2; the subject did not require treatment and continued in the trial with resolution of the events.
6. Anaphylaxis on Day 41 in a subject who is allergic to almonds and ingested almonds shortly prior to the event.
7. Anaphylaxis in a 34 year-old male who developed local application site reactions starting at Day 1. The events persisted with subsequent tablet administrations and on Day 6, the subject developed local symptoms within 5 minutes of tablet administration followed by significant swelling in the throat, shortness of breath, nausea, and light-headedness 30 minutes after dosing. The subject self-administered epinephrine and proceeded to an emergency department where he received antihistamine therapy and corticosteroids. The relationship between the AE and RAGWITEK was considered probably related by the investigator. The subject fully recovered following treatment and was discontinued from the trial.
8. Severe throat tightness on Day 14 of treatment that resulted in self-injection of epinephrine by a 41 year old male. There was no history of respiratory compromise. The subject administered epinephrine approximately 2 hours following the event. The investigator assessed the event as a severe local reaction but did not assess epinephrine as necessary for treatment. This was judged by the investigator as probably related to RAGWITEK. The subject was discontinued from the trial.
9. Self-injection of epinephrine by a 71 year old male in response to persistent gastrointestinal symptoms (including abdominal pain, diarrhea, and vomiting) 26 hours after the second administration of study drug; the subject was evaluated by the site following the epinephrine administration. The events were assessed by the investigator as moderate in severity and unlikely related to study medication. This subject was discontinued from the trial.
10. Administration of epinephrine in a health care setting to a 22 year old female who developed local application events that began on Day 3 of treatment. Due to worsening of the events on Day 4, treatment was interrupted for two days so that the next dose of study drug could be administered under supervision in the investigator's office. Within 5 minutes of taking 12 Amb a 1-U, the subject developed mouth swelling and dysphagia. The subject was treated with epinephrine, albuterol and an antihistamine. This was judged by the investigator as probably related to study medication. The subject fully recovered following in-office treatment and discontinued from the trial.
11. Anaphylaxis in a peanut allergic subject with inadvertent exposure to peanut on Day 95.

Subjects who received RAGWITEK 6 Amb a 1-U

1. Syncope and urticaria on Day 121 of study drug administration. These symptoms were not considered severe, and were assessed by the investigator as unlikely related to the study drug. The subject completed the trial with local application side effects that were tolerated.
2. Administration of epinephrine in a health care setting to a 21 year old female in response to pharyngeal edema following administration of the study drug on Day 22. There were no signs of respiratory distress and the subject discontinued from the trial following the event.

Subjects in the Placebo group

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

Systemic Allergic Reactions

For an analysis of systemic allergic reactions, the sponsor searched the database for: anaphylaxis, anaphylactic reactions, and hypersensitivity reactions using specified MedDRA terms; events that could indicate possible systemic allergic reactions when applying criteria proposed by the Food Allergy and Anaphylaxis Network (FAAN); and administrations of epinephrine.

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

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

Epinephrine use during RAGWITEK clinical trials

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

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

Asthma related events

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

Eosinophilic Esophagitis
There is a post-marketing safety report of development of eosinophilic esophagitis in a 23 year-old male. The patient was undergoing sublingual immunotherapy for allergy to house dust mites for a year when he began concomitant treatment with GRAZAX. One month after initiating therapy with GRAZAX, the patient developed severe dysphagia and retrosternal chest pain. The symptoms subsided after GRAZAX was discontinued. Upon re-challenge with GRAZAX, the symptoms recurred and the patient underwent endoscopy. Mucosal biopsy established the diagnosis of eosinophilic esophagitis. The complete report is published in the *Journal of Allergy and Clinical Immunology* (Pubmed ID: 24636095).

In addition to the above report, there are three additional reports to the Adverse Events Reporting System (AERS) of eosinophilic esophagitis associated with GRASTEK, including an 8 year old female who lost 5 Kg prior to discontinuing GRAZAX. In two of these reports, GRAZAX was discontinued and the symptoms resolved. One patient continued GRAZAX treatment with medical treatment of the eosinophilic esophagitis.

> *Clinical Reviewer comment: Eosinophilic esophagitis has been reported in the context of oral immunotherapy for food allergy. These are the first reports of eosinophilic esophagitis with tablets used for SLIT. Although this report was associated with GRAZAX (grass pollen extract), it is likely that RAGWITEK may also cause eosinophilic esophatitis.*

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Not applicable.

8.5.2 Time Dependency for Adverse Events

The TEAE are allergic responses, which may divided into early (within minutes) and late (within hours) phase, relative to the time of allergen exposure (treatment). The local and systemic TEAE that are associated with this product are early phase events and occur within minutes of exposure.

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

8.5.3 Product-Demographic Interactions

None

8.5.4 Product-Disease Interactions

None

8.5.5 Product-Product Interactions

None

8.5.6 Human Carcinogenicity

None

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is limited potential for an allergic subject to harm him/herself by taking multiple tablets. This would require opening multiple blister packs and simultaneous sublingual administration of multiple tablets. There is no potential for abuse or withdrawal effects.

8.5.8 Immunogenicity (Safety)

Not applicable.

8.5.9 Person-to-Person Transmission, Shedding

Not applicable.

8.6 Safety Conclusions

For the majority of subjects who participated in the clinical trials and the post-marketing studies, RAGWITEK was well tolerated and safe. There were no episodes of anaphylaxis in the clinical studies, and there were no treatment-associated deaths in the clinical studies.

RAGWITEK causes local application reactions that may be severe or serious; most but not all of these occurred on Day 1 of treatment, which takes place in the health care setting. Therefore, the clinical reviewer recommends that patients who are prescribed RAGWITEK should be co-prescribed auto-injectable epinephrine. The potential for severe or serious local reactions and anaphylaxis should be stated in the package insert as a boxed warning. In addition, a Medication Guide should be distributed with the prescription to insure that patients are aware of the risk of these reactions at home, and are educated towards the self-administration of epinephrine with an auto-injectable device.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There are no data regarding human reproduction or pregnancy. Based on animal toxicity data, the product will be placed in Pregnancy Category B.

9.1.2 Use During Lactation

Nursing mothers were excluded from the study, and the product was discontinued if a female who became pregnant chose to carry the fetus to term. Therefore, the effect of the product during lactation is unknown.

9.1.3 Pediatric Use and PREA Considerations

The product was presented to PeRC on March 19, 2014. PREA requirements were waived for children below five years of age, as studies are highly impractical because seasonal environmental allergies are unusual in this age group. PeRC agreed to the sponsor's proposed PMR study, discussed below.

9.1.4 Immunocompromised Patients

Efficacy of the product requires a competent immune system. Immunocompromised subjects were excluded from the studies. The product is not expected to be used in immunocompromised subjects, and should be contraindicated in the absence of a competent immune system.

9.1.5 Geriatric Use

The product has not been studied in subjects greater than 65 years of age. Very few subjects greater than 65 years of age have been exposed to RAGWITEK. Consequently the indications for adults must be limited to those who are 18-65 years of age.

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

None

10. Conclusions

RAGWITEK, 12 Amb a 1-U per dose, is safe and effective for immunotherapy of allergic rhinoconjunctivitis due to sensitivity to ragweed for patients 18-65 years of age for subjects who are allergic to short ragweed pollen. There are too few subjects above 65 years of age to evaluate safety in that age group.

The first tablet must be taken in the office of a health care provider who is experienced in the treatment of life threatening allergic reactions, including those that may occlude the upper airway and systemic anaphylaxis.

The dosage for adults is 12 Amb a 1-U per day. Patients should be educated as to the potential risk of life-threatening laryngopharyngeal application site reactions, and be educated in the use of an epinephrine administration device. The risk of SAE and severe AE may decrease with longer treatment times (such as > 6-12 months), but this must be confirmed with a safety data base much larger than currently available.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Table 48. Risk/Benefit analysis of RAGWITEK

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The symptoms of ARC are runny or stuffy nose, excessive tearing, itchy or scratchy throat • Seasonal ARC is caused by allergic sensitivity to seasonal environmental allergens, such as ragweed pollens • ARC is common in US pediatric and adult populations • ARC impacts on quality life including lost work and school days • ARC in children may resolve, or it may progress to include allergic asthma	• ARC is highly prevalent in US populations • ARC impacts on quality of life • In a subset of patients, ARC precedes and contributes to allergic asthma
Unmet Medical Need	• ARC may be treated with pharmacologic therapy, such as nasal steroids, or topical or systemic antihistamines • Pharmacologic therapy is sufficient for a subset of mildly affected ARC patients • When pharmacologic therapy is insufficient, immunotherapy may improve quality of life • Subcutaneous immunotherapy (SCIT) is the current mode of Immunotherapy in the US. • SCIT must be administered in a health care setting, and requires frequent visits (every 2-4 months); many patients who may benefit from immunotherapy opt out of SCIT • For a substantial majority of patients, SLIT may be safely self-administered at home	• Because of the convenience of SLIT administration, its availability is expected to increase the use of immunotherapy to treat ARC • RAGWITEK may increase the use of immunotherapy in ragweed pollen allergic US patients, and significantly impact on overall quality of life in this population
Clinical Benefit	• The data suggests that RAGWITEK improves ragweed-pollen induced ARC symptoms and medication use by about 25%, which is above the threshold that impacts upon quality of life • While the totality of data supports the conclusion of efficacy of RAGWITEK , at least one individual study failed to demonstrate improvement. • It is uncertain whether the treatment effect of RAGWITEK is maintained beyond one or multiple courses of treatment.	• The totality evidence for clinical benefit of RAGWITEK suggests ~25% improvement in symptoms, medication use, or both.

Risk	• The most substantial risks of RAGWITEK are life threatening local or systemic allergic reactions. These are most common, but may not be restricted to the first day of treatment, which should be administered in a health care setting. • Risk of severe and serious adverse events may decrease in the second and subsequent treatment years. • The most common risks are mild to moderate application site reactions, including itching or swelling to the back of the throat, tongue, or mouth • The clinical study population had substantially less morbidity than patients who will be prescribed RAGWITEK. In particular, this includes patients with moderate to severe asthma, and those with underlying cardiac and non-asthmatic pulmonary disease. • Based on clinical reports with GRASTEK, eosinophilic esophagitis may be a risk associated with RAGWITEK • RAGWITEK has not been studied in a limited number of adults > 65 years of age	• Overall, the benefit of RAGWITEK outweigh the risks • The first tablet must be taken in the office of a health care provider who is experienced in at treating life threatening allergic reactions, including upper airway edema and systemic anaphylaxis. • Patients should be educated as to the potential risk of life-threatening laryngopharyngeal application site reactions, and be educated in the technique of epinephrine self-administration; the device should be co-prescribed with RAGWITEK. • If RAGWITEK is approved, it will be indicated for patients 18-65 years of age.
Risk Management	• RAGWITEK may result in severe or serious laryngopharyngeal reactions or systemic allergic reactions. Most often, these will occur on Day 1 of therapy.	• If RAGWITEK is approved for patients 18-65 years of age, the package insert should include a boxed warning of the potential of serious local or systemic reactions, and a medicine guide would have to be distributed to all patients. • The first dose is taken in the office of a health care provider who is experienced in the treatment of allergic reactions

11.2 Risk-Benefit Summary and Assessment

Data submitted to the BLA establish that treatment of patients 18-65 years of age with RAGWITEK may decrease the symptoms of ARC and significantly improve quality of life in patients with ARC.

Clinical data indicate that the overwhelming majority of patients will tolerate RAGWITEK with mild or moderate AE due to local application reactions. A subset of patients who experience mild to moderate local application reactions will discontinue treatment because of discomfort rather than risk. Based on clinical studies and post-marketing analysis, the data indicate that 0.1-0.5% of subjects will experience severe or serious laryngopharyngeal or systemic reactions. Most, but not all of these will be associated with the first treatment exposure to RAGWITEK.

11.3 Discussion of Regulatory Options

The clinical reviewer recommends that the RAGWITEK 12 Amb a 1-U be approved for the treatment of ARC with or without mild asthma.

11.4 Recommendations on Regulatory Actions

1. I recommend approval of RAGWITEK for adults 18-65 years of age for treatment of ARC with or without mild asthma.
2. The first dose of RAGWITEK should be taken in the health care setting.
3. The package insert should include a boxed warning of the potential of serious local or systemic reactions, and a medicine guide would have to be distributed to all patients.

11.5 Labeling Review and Recommendations

1. The trade name is RAGWITEK®. The Product Proper Name is Short Ragweed Pollen Allergen Extract.
2. RAGWITEK is an allergen extract indicated as immunotherapy for 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 adults 18 through 65 years of age. RAGWITEK is not indicated for the immediate relief of allergic symptoms.
3. The dose of the sublingual tablets is 12 Amb a 1-U per day for adults.
4. The Package Insert should include a boxed warning of the potential of serious local or systemic reactions, and a medicine guide to be distributed to all patients.
5. A Medication Guide should be provided to all patients.
6. Patients who are prescribed RAGWITEK should also be prescribed auto-injectable epinephrine.

11.6 Recommendations on Postmarketing Actions

Based upon the submitted information and current clinical knowledge, routine pharmacovigilance as proposed by the sponsor is appropriate.

<u>PREA requirements: Post-marketing requirement studies in children and adolescents</u>
The sponsor proposes two studies to satisfy PREA:

1. A natural exposure field placebo-controlled safety and efficacy trial in which children 5-17 years of age will be randomized RAGWITEK to placebo (1:1) to demonstrate efficacy over a single ragweed pollen season. The study will be

performed similarly to the adult studies P05233 and P05234. Because the sponsors intend to enroll 1000 subjects, however, they assert that it will take 2 or 3 years to complete the study.

2. A safety trial in which subjects 5-17 years of age will be treated with RAGWITEK for 28 days outside of ragweed pollen season. This study will be conducted similar to P05751 and P06081. After completion of the 28 days, subjects will be enrolled into an open-label study of efficacy of RAGWITEK.

CBER concurs with the study proposals to satisfy PREA requirements.

Postmarketing commitment for surveillance of safety

The sponsor proposes to routine Pharmacovigilance in accordance with ICH Guidance E2E. Expedited AE and periodic safety reports will be submitted to FDA. These events are subject to enhanced surveillance: allergic reactions including severe laryngopharyngeal disorders, autoimmune disease, and anaphylaxis. CBER agrees with the proposed plan. In addition, enhanced pharmacovigilance through questionnaires sent to healthcare professionals will be collected to supplement information on health outcomes of interest reported with early dose exposure

In addition, the sponsor has agreed to two postmarketing studies. The first will be a post-market claims-based study to further describe the safety profile of RAGWITEK in marketed use in the United States. Outcomes of interest in this study will include serious allergic reactions and eosinophilic esophagitis. The study will enroll all new users of RAGWITEK identified through claims data from a large US health insurance database for a period of at least three years from launch of RAGWITEK. The study observation period will be for at least 3 years and until at least 10,000 patients are accrued between both post-market studies. Outcomes of interest identified through claims data will be verified using medical record review.

To capture events within the first seven days of RAGWITEK therapy, the sponsor commits to conduct a post-market electronic medical record study to further describe the safety profile of RAGWITEK in marketed use in the United States. Outcomes of interest in this study will include serious allergic reactions and eosinophilic esophagitis. The study will enroll all new users of RAGWITEK identified through electronic medical records in a large US integrated health system for a period of at least three years from launch of RAGWITEK. The study observation period will be for at least 3 years and until at least 10,000 patients are accrued between both post-market studies. This study will include early exposures to RAGWITEK, including administration through starter packs provided in physician offices as well as all subsequent exposures.

CBER agrees with the proposed plan.

Risk Management / Risk Evaluation and Mitigation Strategy (REMS)

No REMS or similar non-US action has been undertaken for this product; none is contemplated following US licensure.

CBER agrees that REMS is not necessary for RAGWITEK