Application Type	Original BLA
STN	125473
CBER Received Date	January 25, 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	Allergenic Extract, Timothy Grass (*Phleum pratense*) sublingual tablet for oral use
(Proposed) Trade Name	GRASTEK
Pharmacologic Class	Allergenic extract
Formulation	Tablet
Dosage Form and Route of Administration	Sub-lingual (placed beneath the tongue until dissolved)
Dosing Regimen	2800 BAU (Biological Allergenic Units), once per day
Indication and Intended Population	GRASTEK is an allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis or conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass and cross-reactive grass pollens. GRASTEK is approved for use in persons 5 through 65 years of age. GRASTEK 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
ANOVA	Analysis of Variance
AR/ARC	Allergic Rhinitis/Allergic Rhinoconjunctivitis
BAU	Bioequivalent Allergy Unit
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
GPS	Grass 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
Phl p 5	*Phleum pratense* major allergen 5
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
SQ-T	Standardized quality tablet
SQ-U	Standardized quality unit
TCS	Total Combined Score
WAO	World Allergy Organization

1. EXECUTIVE SUMMARY

Background

MK-7243 (also referred to in IND documents as SCH 697243) is a fast-dissolving--less than 10 seconds--sublingual tablet for oromucosal delivery. The active substance is a natural grass pollen extract which is partially purified and standardized from Timothy grass. Timothy grass is a member of the Pooideae subfamily that may be cross-reactive with other Pooideae members such as rye (*lolium*), meadow fescue (*festuca*), bluegrass (*poa*), orchard/cocksfoot (*dactylis*), sweet vernal (*anthoxanthum*), redtop/bent/velvet (*agrostis*), and Johnson grass, all of which are major aeroallergens in North America. The tablet is standardized according to potency units proscribed by CBER; each tablet has a potency of 2800 BAU (Bioequivalent Allergy Unit).

MK-7243 is currently marketed in Europe under the trade name GRAZAX®. A Marketing Authorization Application for GRAZAX® was filed by the Mutual Recognition Procedure in the European Union (EU) and ALK received its first approval in 2006. Subsequently, ALK has received marketing authorizations in 30 countries. According to the sponsor, as of 30 September 2012, GRAZAX® has an estimated 112,981 patient years of post-marketing use in Europe. GRAZAX® is indicated in the EU for the disease-modifying treatment of grass pollen-induced rhinitis and conjunctivitis in adults and children (5 years or older) with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen.

The submitted BLA is for licensure of this product in the United States with the indication "The disease modifying treatment of diagnosed Timothy and related grass (*Phleum pratense*) pollen induced allergic rhinitis, with or without conjunctivitis, in adults and children 5 years of age and older." The sponsor asserts that they have demonstrated safety and efficacy for this proposed indication. GRASTEK is the proposed U.S. proprietary name, which is acceptable to the Agency.

Upon approval of GRASTEK, adults and children will take 75 SQ-T per tablet, 1 tablet sublingually, daily for a time period prior to the grass pollen season (GPS, which runs from May through September in the mid-Atlantic region of the United States), and then throughout the GPS. The time period prior to the GPS proposed by the sponsor is "at least 8-12 weeks prior to GPS," but CBER will require that the instructions for drug administration are consistent with the most successful US Phase 3 study, P08067, in which subjects took the drug "for at least 12 weeks prior to the anticipated GPS." 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 six RDBPC Phase 3 studies, four of which are comprehensively reviewed in this document. Two of the Phase 3 efficacy trials were conducted in Europe; neither was under IND.

- Protocol GT-08 was a five-year study of adults, 18-65 years of age that ran from September, 2004 through September, 2009. Subjects were treated for three consecutive years for approximately 6 months each year—16 weeks prior to the anticipated start of GPS and throughout the GPS. In order to demonstrate that efficacy was sustained beyond these three years, subjects were observed but not treated for the last two years. The data demonstrate that efficacy was sustained for those two years.

- Protocol GT-12 was a 12 month study conducted in Germany that demonstrated efficacy in children 5-16 years of age. This protocol is not comprehensively reviewed in this document because the North American pediatric trial P05239 met its clinical endpoints and is sufficient to support approval for children 5-17 years of age.

Four Phase 3 RDBPC studies were conducted in North America.

- Protocol GT-14 was a 12 month study of adults 18-65 years of age that was conducted in the U.S. in 2006 and failed to demonstrate efficacy, and is not comprehensively reviewed in this document.
- Protocol P05238 was a 12 month study of adults 18-65 years of age conducted in the U.S. and Canada in 2009. While the point estimate of the treatment and placebo groups suggested that the product was effective, the variance (95% Confidence Intervals) was unacceptable. The study is considered supportive, but did not meet its primary endpoint.
- Protocol P05239 was a 12 month study of children 5-17 years that ran concurrent with P05238 in the U.S. and Canada, and that demonstrated efficacy.
- Protocol P08067 was a 12 month study conducted in the U.S. and Canada in 2012 in children and adults 5-65 years of age. The data demonstrated efficacy among all subjects and in the subsets of children 5-17 years of age, and adults 18-65 years of age.

In addition, the BLA includes CSR of five Phase 1 trials, two Phase 2 trials, four Phase 3 trials that were not designed to demonstrate efficacy, and one post-marketing Phase 4 study designed to demonstrate subject compliance. Data from each of these studies are included in the integrated summary of safety, but will not be addressed in the context of efficacy in this document.

Finally, European post-marketing safety data are discussed in the context of overall product safety, the package insert, and post-marketing requirements.

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 GPS. 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 TCD, difference and 95% CI (in percentage) and statistical significance between the treatment and placebo groups in the North American studies.

Table 1. Primary efficacy endpoint data from the three North American studies that demonstrated efficacy of GRASTEK

Protocol	TCD* GRASTEK	TCD* Placebo	Difference (%)	95% CI (%)	P-value
P08067	3.24	4.22			
P05238	5.08	6.39	-20%	-33.0%, -6.0%	=0.005
P05239^	4.62	6.25	-26%	-38.0%, -10.0%	=0.001

Adapted from original BLA submission 125473, Module 5: CSR P08067 Volume 1, p84; CSR P05238 p95; CSR P05239 p99 * Values of the TCD for P08067 are the median values; for P05238 and P05239 are adjusted means.
^ P05239 is a pediatric study of children 5-17 years of age

CBER considers the improvement in the TCS between 20-26% over placebo as clinically significant, and the lower 95% CI of 10% as statistically acceptable. Therefore, Protocols P08067 and P05239 met their primary endpoints, while Protocol P05238 did not.

In addition to the studies conducted in North America, the European protocol GT-08 demonstrated a statistically significant decrease in the TCS during the three years of treatment. These differences remained statistically significant at the end of the following two post-treatment (observation) years.

Table 2. Difference in TCS for each year of the European protocol GT-08.

	Treatment Year 1	Treatment Year 2	Treatment Year 3	Post-treatment Year 4	Post-treatment Year 5
Difference relative to Placebo (%)	-34.2	-40.9%	-34.0%	-27.2%	-22.7%
P value	<0.0010	<0.0001	=0.0001	=0.0014	=0.0128

Adapted from original BLA submission 125473, Module 5: CSR datasets gt08\legacy\datasets\yr1, legacy\datasets\yr2, legacy\datasets\yr3, legacy\datasets\yr4, legacy\datasets\yr5

Assessment of Safety

The North American and European safety data base includes 4465 subjects ≤ 65 years of age who have been randomized into GRASTEK, including 481 adolescents 12-17 years of age, and 397 children 5-11 years old. Duration of exposure in these trials ranges from a single dose up to 1072 consecutive doses (1 dose per day). The submission includes safety results from six post-EU-submission market-support clinical studies in 1666 subjects, and safety data from European post-approval studies that total approximately 11,000 subjects. Since approval of MK-7243 in Europe in 2006 through September 30, 2012, the sponsors estimate an exposure of 112,981 patient treatment years.

Data from clinical trials demonstrate that GRASTEK may cause allergic reactions, which are associated with sublingual administration of natural grass 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, GRASTEK, 2800 BAU 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 GRASTEK.

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 grass pollen allergy.

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 postmarketing study will enroll all new users of GRASTEK based on dispensing claims for three years. This study will also capture exposures to other immunotherapies (e.g. beta-agonist or steroid inhalers). The primary outcome for this study will be local and systemic allergic reactions and eosinophilic esophagitis resulting in hospitalization, emergency department care, or ambulatory visits that are associated with epinephrine injections (hereafter referred to as "serious allergic reactions"). These data will be ascertained through diagnosis codes for anaphylaxis, anaphylactic reaction, anaphylactic shock, systemic allergic reaction, or upper airway obstruction. Outcomes will also be identified through codes for procedures to treat these conditions, such as emergency endotracheal intubation or surgical airway. Each outcome identified through automated data will be adjudicated by a panel of clinicians who are experts in the field using medical chart review. Because this study is based on dispensing claims, it may not capture events within the first seven days of GRASTEK therapy.

To capture events within the first seven days of GRASTEK therapy, the sponsor proposes to conduct a second postmarketing study that uses an integrated healthcare system with access to electronic medical record (EMR) data. The integrated healthcare system will pick up the events that are associated with the early exposures based on use of the starter-packs as well as events that might occur during longer term therapy exposure including serious allergic reactions and eosinophilic esophagitis.

CBER agrees with the proposed plan.

Proposed Package Insert
The proposed indication in the original BLA submission is phrased:

> "The disease modifying treatment of diagnosed Timothy and related grass pollen induced allergic rhinitis, with or without conjunctivitis, in adults and children 5 years of age and older."

The final version of the package insert will read:

> "GRASTEK is an allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis or conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass and cross-reactive grass pollens. GRASTEK is approved for use in persons 5 through 65 years of age.
>
> GRASTEK is not indicated for the immediate relief of allergic symptoms".

The amendments reflect CBER's rejection of the phrase "disease modifying," which implies permanency, which has not been demonstrated, and limiting the indications in adults to those 65 years of age or younger, as safety and efficacy have not been demonstrated in the elderly.

Reviewer's Conclusions
The sponsor has demonstrated that GRASTEK is safe and effective for the treatment of ARC due to Timothy grass pollen allergy in children and adults ages 5-65. The agency accepts the sponsor's assertion that those sensitive to related grass pollens such as Red top, June (Kentucky blue), Perennial rye, Orchard, meadow fescue and sweet vernal grasses will also benefit from this product.

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. Grass 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 grass 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. 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-7243 in tablet form. MK-7243 is a fast-dissolving (e.g., less than 10 seconds), sublingual tablet for oromucosal delivery. MK-7243 is currently marketed in Europe under the trade-name GRAZAX®. A Marketing authorization application for GRAZAX® was filed by the Mutual Recognition Procedure in the European Union (EU) and ALK received its first approval in 2006. Subsequently, ALK has received marketing authorizations in 30 countries. According to the sponsor, as of 30 Sep 2012, GRAZAX® has an estimated 112,981 patient years of post-marketing use in Europe. GRAZAX® is indicated in the EU for the disease-modifying treatment of grass pollen-induced rhinitis and conjunctivitis in adults and children (5 years or older) with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen.

The dose is 2,800 BAU 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 grass pollen season (GPS), which in runs from May through September 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
The table below 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 3. 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)

General summary of European experience with GRAZAX® MK-7243 is currently marketed in Europe under the trade-name GRAZAX®. A Marketing Authorization Application for GRAZAX® was filed by the Mutual Recognition Procedure in the European Union (EU) and ALK received its first approval in 2006. Subsequently, ALK has received marketing authorizations in 30 countries. The sponsor asserts that as of 30 Sep 2012, GRAZAX® has an estimated 112,981 patient years of post-marketing use in Europe. GRAZAX® is indicated in the EU for the disease-modifying treatment of grass pollen-induced rhinitis and conjunctivitis in adults and children (5 years or older) with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen.

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

CMC Issue 1: Use of different form of unitage (SQ-T) for the drug product batches to be used during phase III trial

<u>September 15, 2006 (IND 13143 Original Submission)</u>
The sponsor proposed a phase III study of GRASTEK tablet for treatment of grass pollen allergy. The unitage indicated on the product was 75,000 SQ-T per tablet. Since Timothy grass pollen extract is a standardized extract and has reference standard which is defined as BAU/mL, CBER specified that the unitage of the product will need to be

according to CBER unitage for standardized Timothy grass extract. CBER also pointed out that the final lot release must be with the FDA/CBER standard in establishing the potency of the final drug product. In addition at the time of licensure product label must reflect potency in BAU.

November 11, 2006 (13143 Amendment 5)
The sponsor accepted the suggestion and indicated potency of 2800 BAU in addition to 75,000 SQ-T on phase III trial batch. The sponsor also agreed to determine the potency of each lot of licensed product in BAU using FDA Competition ELISA. The sponsor submitted the protocol essentially identical to FDA ELISA and also provided certificate of analysis of investigational product indicating relative potency as 2800 BAU. The Agency found the response acceptable.

CMC Issue 2: Exclusion of (b) (4) *units at release.*

July 31, 2009 (13143 Amendment 72)
The sponsor requested for exclusion of (b)(4) units. They proposed that the (b)(4) units to be monitored throughout the manufacturing process by (b)(4)

October 29, 2009 (CBER comment on 13143 Amendment 72)
The Agency issued letter to the sponsor agreeing to their proposal of excluding (b)(4) units test in accordance with (b)(4) .

January 25, 2013 (STN 125473 BLA Original Submission)
During the primary review process of this BLA, the reviewer noticed that the sponsor has not performed (b)(4) units test on the final drug product and justifications for exclusion were that the tablet is a freeze dried true solution and (b) (4) are performed throughout the manufacturing process (b)(4) . They also referred to CBER's letter dated October 29, 2009 which stated that the proposal was acceptable.

The issue was internally discussed within the division, and with the Agency's tablet expert from CDER. It was determined that this tablet is non-official product (non-compendial without a monograph in USP) and contains (b)(4) of active ingredient and is applicable for (b)(4) testing as per (b)(4) . The sponsor must define the (b)(4) across batches.

June 18, 2013 (Letter from the Agency)
Through this letter the sponsor was notified that tablets do not meet the requirements of the Compliance Policy Guide (CPG) Sec (b)(4) or the current (b)(4) threshold for use of a (b)(4) Test instead of a (b)(4) The sponsor was asked to perform (b)(4) test as a final drug product release test and to provide release specifications and qualification data in support of the test.

July 19, 2013 (STN 125473 supplement 06)
In response to the Agency's suggestion for performing (b)(4) test as final drug product release testing, the sponsor reiterated that the drug product consisting of highly soluble allergenic extract and excipients is a (b) (4) and therefore (b)(4) is the only factor that causes difference in (b)(4) . The sponsor also indicated that

the (b)(4) can only be determined by (b)(4) In support of (b)(4) test sponsor also included a simulation analysis and asked for CBER's concurrence.

August 8, 2013 (Informal Teleconference)
During this teleconference the need for (b)(4) testing on the final drug product was discussed with the sponsor. CBER stated that the proposed use of (b)(4) to test for (b)(4) units is not sufficient; (b)(4) testing is required according to (b)(4) . It was explained that there is not enough evidence to confirm that the product is a(b) (4) prior to freeze drying and testing (b)(4) on the product in the final blister pack is not sufficient to show (b)(4) . Although the flow diagram explains the manufacturing process, there are multiple stages throughout manufacture where the loss of (b)(4) may occur. CBER requested that the sponsor implement a (b)(4) test and it may be acceptable to broaden the (b)(4) to meet the needs of this product. The Agency requested the sponsor for a proposal for method to determine (b)(4) and release specification for review.

September 20, 2013 (STN 125473 Supplement 08)
In this supplement to BLA 125473, the firm proposed (b)(4) method will be used for (b)(4) testing. (b)(4) is the most appropriate method. The sponsor developed acceptance criteria for the (b)(4) units-(b)(4) test for the tablet. (b)(4) presented the modified values for CBER concurrence. The suggested value for(b)(4) . CBER concurred with the sponsor s proposal.

Clinical Issues
December 3, 2001
Representatives from ALK-Abello (ALK-Abello A/S) met with CBER representatives for a Pre-IND Meeting to discuss, "Manufacture and pre-clinical testing requirements of Timothy Grass (*Phleum pratense*), Allergenic Extract, Tablet Form." While ALK did not provide any details nor ask any questions regarding their clinical plans, CBER provided general comments regarding initial study of dose escalation and safety monitoring.

August 23, 2005 Advice Information
An advice Information Letter was sent to the sponsor, (ALK-Abello A/S, Denmark), with comments regarding the Master File (b)(4) that was submitted on April 14 2005, for "Manufacture and Control of Timothy Grass (*Phleum pratense*), Allergenic Extract, Tablet Form." CBER provided advice to the sponsor concerning product characterization, final product specifications and related assays pertinent to U.S. licensure requirements.

September 15, 2006
The original investigational new drug application, IND 13143 for Timothy Grass (*Phleum pratense*), Allergenic Extract, Tablet Form, submitted to CBER with a proposed Phase 3 clinical trial entitled "GT-14: A phase III trial assessing the efficacy and safety of GRAZAX in subjects with seasonal grass pollen induced rhinoconjunctivitis with or

without asthma." A clinical study report (CSR) for each of the five previously conducted trials and one ongoing clinical trial in Europe were later submitted to the IND file. Included in these reports was Protocol GT-08, a multi-year Phase 3 trial in Northern Europe that met its clinical efficacy and safety endpoints, and demonstrated statistically significant differences in efficacy between the treatment and placebo groups during a two year observation period that followed three sequential years of treatment. Protocol GT-08 is reviewed in Section 6.

~September 26, 2006
This first marketing authorization for GRAZAX sublingual tablet was granted in Sweden and then throughout Europe.

October 13, 2006
Protocol GT-14 was placed on Clinical Hold due to lack of a relationship between the potency units SQ-U and BAU and lack of individual and study stopping criteria.

December 6, 2006
Clinical Hold deficiencies were appropriately addressed by the sponsor. CBER allowed Protocol GT-14 to commence.

November 13 and 21, 2007
The sponsor submitted Amendment 20 (Protocol P05239) and Amendment 22 (Protocol P05238), Phase 3 protocols intended to prove safety and efficacy for children and adults respectively. In addition, GT-14 had failed to meet its primary efficacy endpoint.

- Study GT-14 did not show differences in efficacy endpoints between the study drug and placebo groups. The sponsors asserted that GT-14 failed because the intensity of pollen seasons widely vary in North America and that CBER should accept post-hoc analyses of high pollen regions as together, data from these regions demonstrate efficacy. CBER rejected the assertion that the post-hoc analysis may satisfy requirements for submission of a BLA.
- Protocol P05239, a Phase 3 trial of children 5-17 years of age was placed on Clinical Hold because it lacked Study Stopping criteria and because CBER disagreed with the sponsor's clinical scoring system.
- Protocol P05238, a Phase 3 trial of adults 18-65 years of age was placed on Clinical Hold because it lacked Study Stopping criteria, inadequate monitoring during the initial period of administration of the study drug, the necessity of distribution of an Epipen (or similar epinephrine self-injection device) , and questions about the upper age limit of subjects in the study.

The sponsor appropriately addressed the Clinical Hold issues and CBER allowed the studies to proceed on or about January 17, 2008.

July 29, 2009
The sponsors submitted Amendment 74 to revise the clinical study endpoint of P05238 to the combined sum of the DSS and DMS averaged over the entire GPS. These revised endpoints were acceptable.

April 30, 2010
The agency requested a detailed SAP for Protocols P05238 and P05239; these must be submitted prior to data lock.

June 25, 2010
Advice Information Letter regarding the submissions through May 13, 2010, to IND 13143. The pre-BLA Meeting request submitted on May 13, 2010, was cancelled because the content of the Meeting Briefing Package did not include any data from the clinical studies performed in the U.S.

December 17, 2010
Advice Information Letter regarding review of data submitted on October 15, 2010, which contained clinical safety and efficacy data of the pivotal North America studies (GT-14, P05238 and P05239). CBER informed the sponsor that the efficacy data from the adult study were insufficient to support a BLA because GT-14 failed to demonstrate a difference between the placebo and study drug groups, and for the adult study P05238, the 95% CI LL of the mean difference was unacceptably low.

February 14, 2011 (Amendment 123)
The sponsor submitted a proposed protocol for, "A Multicenter, Double-Blind, Randomized, Placebo Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of Grass (Phleum pratense)Sublingual Tablet (SCH 697243) in Subjects at Least 5 Years of Age, with a History of Grass Pollen-Induced Rhinoconjunctivitis, With or Without Asthma (Protocol P08067)."The protocol was approved by CBER shortly thereafter.

May 12, 2011; Informational APAC meeting to discuss chamber studies to support effectiveness

CBER Biostatistician Tammy Massie, PhD presented to APAC on May 12, 2011 a presentation entitled "Statistical Criteria for Establishing Safety and Efficacy of Allergenic Products," in which the lower bound of the 95% CI as a pre-specified threshold in this type of clinical trial was discussed.

As a consequence of discussion and public comments in response to APAC presentation by Dr. Massie on May 12, 2011 (available for review in the meeting transcript), CBER began a process of defining its statistical criteria to prove efficacy of allergenic products for immunotherapy. Ultimately CBER defined these criteria such that a 95% LL greater than 10% of the combined score of the placebo group was considered acceptable.

July 21, 2011 (Sponsor presentation)
Dr. Hendrik Nolte, MD, PhD, Senior Director, Respiratory & Immunology; Schering Plough, Inc./Merck presented "Considerations and Implications of using a Lower Bound for the 95% CI to Determine Efficacy of Immunotherapy Products." The speaker asserted that according to the sponsor's statistical analysis, the compiled data from the European trial GT-08 and the US trial P05238 are sufficient to support a BLA. CBER reviewers did not concur with the sponsor's assertion, and requested either an additional field trial or a trial performed in an environmental exposure chamber.

May 1, 2012 (Amendment 154)
Submission of Amendment 154, which informed CBER of sponsor merger: "As of May 1, 2012, Schering Corporation and Merck Sharp & Dohme [Corporation have] merged."

November 9, 2012 (Amendment 162)
The sponsors submitted a draft report of the study synopsis of Protocol P08067, which met its clinical endpoints.

January 10, 2013: Type B Pre-BLA Meeting

January 25, 2013: CBER Receipt of BLA 125473.0

March 19, 2013: BLA 125473.0 was filed.

December 12, 2013: BLA presented to APAC.

2.6 Other Relevant Background Information

None

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

3.2 Compliance With Good Clinical Practices And Submission Integrity

Bioresearch monitoring (BIMO) data audit inspections were issued for 6 clinical investigator sites for Protocol 08067 (Site #11, 18, 55, 116, 127, and 308). NAI letters were issued to three sites. To the fourth site, a VAI (voluntary action indicated) letter was issued the site study coordinator, performed physical examinations early termination physical exams on three subjects, but was not authorized to do so. No FDA 483 forms were issued to any of the sites. The inspections do not indicate that there are issues of data integrity or misconduct during the clinical trial.

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

The proper name of the drug substance (DS) is Allergenic Extract, Standardized Grass Pollen Extract, Timothy Grass (*Phleum pratense)*, (b)(4) for Further Manufacture. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., has designated the laboratory code name for the *Phleum pratense* Pollen Allergenic Extract as SCH 697243/MK-7243 Drug Substance.). The sponsor's proposed nomenclature of the drug substance is shown in Table 4.

Table 4. Sponsor's proposed nomenclature of Drug Substance

Proper Name:	Allergenic Extract, Standardized Grass Pollen Extract, Timothy Grass (*Phleum pratense)*, (b)(4) for Further Manufacture
Laboratory Code Names	SCH 697243/MK-7243
Other Non-Proprietary Names	Timothy Grass Pollen Allergenic Extract *Phleum pratense* Pollen Allergenic Extract

Extracted from the original BLA STN 125473/000; Module 3.2.S.1.1, Page 1

The drug substance is a (b)(4)

The drug product (DP) is a tablet that contains the drug substance, which is standardized in SQ-T to the In House Reference Standard. The product substance is measured for potency using the competition ELISA for lot release testing of grass pollen allergenic extracts (SOP 000152, using reference reagents provided by CBER.

The DP is a tablet, packaged in 10-tablet blister packs. 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 697243 Tablet, 2800 BAU

Ingredient	Quality Standard	Function	Amount per Tablet
SCH 697243 Drug Substance	Standardized in SQ-T to In House Reference Standard	Active ingredient	2800 BAU
Gelatin (Fish, (b)(4) Molecular Weight)	(b) (4)	(b)(4)	
(b) (4)	(b) (4)	(b)(4)	
Mannitol	(b) (4)	(b)(4)	
Sodium Hydroxide	(b) (4)	(b)(4)	
Purified Water			(b)(4)
(b)(4)			

(b)(4)

4.2 Assay Validation

The drug product (DP) is a tablet that contains the drug substance, which is standardized in SQ-T to the In House Reference Standard. The product substance is measured for potency using the competition ELISA for lot release testing of grass pollen allergenic extracts (The Standard Operating Procedure may be found in Laboratory of Immunobiochemistry Document ID: 000152. The method uses two reference reagents, Timothy grass extract and pooled human sera from highly grass-allergic donors reference provided to this manufacturer by CBER. In January, 2014, Merck submitted to CBER samples from 10 lots of GRASTEK for validation of potency testing. CBER tested the samples in February 2014; Table 6 shows the results of testing three of these lots. The complete set of data may be found in the CMC review.

Table 6. Potency validation of samples from ten lots of GRASTEK.

Lot number	Sponsor's potency measurement	CBER's potency measurement	Potency Validated by CBER
(b)(4)	1.01	1.06	Yes
(b)(4)	1.00	1.14	Yes
(b)(4)	1.00	1.00	Yes

4.3 Nonclinical Pharmacology/Toxicology

The nonclinical toxicity of GRASTEK® Phleum pratense allergens was evaluated in repeat-dose studies in mice for 4, 15, and 26 weeks and dogs for 4 and 52 weeks. Reproductive and developmental toxicity was evaluated in mice for fertility, embryo-fetal and post natal toxicity. Genetic toxicity was evaluated in the in vitro bacterial reversion assay and in vivo mouse lymphoma assay.

The toxicology studies in mice and dogs with GRASTEK® Phleum pratense allergens demonstrated no overt toxicity at doses up to 500,000 SQ-U/T (corresponding to approximately 7-fold greater than the clinical dose of 2,800 BAU). No treatment-related reproductive and developmental toxicities were observed at doses up to 500,000 SQ-U/T (corresponding to approximately 7-fold greater than the clinical dose of 2,800 BAU) Genetic toxicology assays were not positive. Nonclinical toxicology findings do not demonstrate toxicity prohibitive to the clinical application.

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 grass immunotherapy product.

4.6 Pharmacovigilance

The PV plan was submitted and reviewed in a document submitted to the file on January 25, 2014 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..

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 13143.

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 125473.

The BLA includes a total of 13 clinical trials that comprise the MK-7243 Clinical Program conducted to evaluate the efficacy and safety of MK-7243*:

- Five Phase 1 trials (GT-01, GT-03 and GT-04 in adults; GT-09 and GT-11 in children);
- One Phase 2 safety and efficacy trial in adults with AR and asthma (GT-07);
- One dose-finding Phase 2/3 efficacy and safety trial in adults (GT-02);
- Six Phase 3 efficacy and safety trials: trials of adults were GT-08 in Europe, GT-14 in the US, and P05238 in North America; trials of children were GT-12 and P05239 in children in Germany and North America, respectively; trial P08067 included children and adults and was conducted in North America

* For consistency throughout this report, Arabic numerals are used to define the study phase; e.g. "Phase 3" rather than "Phase III."

The Phase 3 European GT-08 trial is a study of three years of treatment and to demonstrate long term efficacy, two years of follow-up. The data from the three treatment years and the two follow-up years are reviewed in this application.

P08067 and P05239 are the pivotal U.S. trials that demonstrated efficacy of the product in adults 18-65 and children 5-17 years of age respectively. Both these trials are comprehensively reviewed in this document.

The US study GT-14 failed to demonstrate efficacy, and the study will only be considered in the context of integrated safety data. Similarly, the P05238 did not meet its endpoints because the lower bound of the 95% CI of the study drug group TCS was within 10% of the placebo group TCS, but because the point estimate of efficacy did meet its endpoints, Protocol P05238 is discussed in Section 6..

The sponsor also submitted, under the heading "Other Study Reports," data on six additional studies that the sponsor does not consider as pertinent to the clamed indication. While safety data from these studies will be included in the overall safety analysis, these studies will be discussed in this review. These studies are:

- GT-10, P05440, an open-label Phase 3 trial to assess treatment compliance with GRAZAX (in adults with grass-induced ARC)
- GT-15, P07022; Observational national clinical trial of safety and tolerance in patients suffering of an allergic grass pollen rhinitis and treated by GRAZAX® in real life settings
- GT-16, P06990; A randomized, double-blind, placebo-controlled Phase 3b study investigating changes in immunological parameters and cutaneous reactivity induced by a short course immunotherapy with ALK grass tablets
- GT-17, P06991; A randomized, parallel-group, Phase 4, open trial evaluating compliance to the treatment with GRAZAX tablets in patients with seasonal grass pollen rhinoconjunctivitis
- GT-18, P06744; A Phase 3 trial assessing the pharmacodynamic effect and the tolerability of GRAZAX treatment initiated in the grass pollen season in subjects with seasonal grass pollen induced rhinoconjunctivitis

Because these five trials minimally impact the assessment of efficacy and the package insert they will not be addressed individually in this review. Data from these trials will be included in the integrated summary of safety.

In addition to the original submission, there are five amendments to the BLA. BLA 125473/5 was received 27 June 2013, and is a Safety Update Summary of European post-marketing experience from 01 Oct 2012 through 30 Apr 2013. In this amendment, the sponsor reports SAE from observational, non-interventional studies after the European cut-off date of 30Sept2012. The sponsor also includes 14 SAE that were not included in an IND Annual Report or the original BLA.

Overlapping the clinical data submitted in the BLA are four publications from the sponsor:

- Nolte H, Hébert J, Berman G, Gawchik S, White M, Kaur A, Liu N, Lumry W, Maloney J. Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults. Ann Allergy Asthma Immunol. 2013 Jun;110(6):450-456.e4. PMID 23706715
- Nelson H, Blaiss M, Nolte H, Würtz SØ, Andersen JS, Durham SR. Efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet in mono- and poly-sensitized subjects. Allergy. 2013 Feb;68(2):252-5. PMID: 23205670

- Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. J Allergy Clin Immunol. 2011 Jan;127(1):72-80, 80.e1-2. PMID: 21211643
- Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. J Allergy Clin Immunol. 2011 Jan;127(1):64-71, 71.e1-4. PMID: 21211642

5.3 Table of Studies/Clinical Trials

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

Phase	Study/ Protocol #	# Sites/ Countries Location	Objective	Subjects (Study Drug/Placebo)	Tx* Duration	Study Dates
Phase 1	GT-01 P06431	1/1 Denmark	Safety	Adults 18-65y Period 1: (39/8) Periods 2, 3, 4: 36/12	Period 1: 1 dose Period 2: 8 wks Period 3: 15 wks Period 4: None (F'U)	Nov 2001 to Sept 2002
Phase 1	GT-03 P06543	1/1 Germany	Safety	Adults 18-65y (63/21)	28 days	Nov 2002 to May 2003
Phase 1	GT-04 P06544	1/1 Ireland	Safety	Adults 18-65y (32/11)	28 days	Mar 2004 to May 2004
Phase 1	GT-09 P06546	1/1 Spain	Safety	Children 5-12y (23/7)	28 days	Mar 2006 to May 2006
Phase 1	GT-11 P06547	3/1 Germany	Safety	Children 5-12y (22/8)	28 days	Feb 2006 to Apr 2006
Phase 2	GT-02 P06542	55/8 EU	Safety, Efficacy (Dosing)	Adults 18-65y (569/286)	8 wks	Feb 2002 to Aug 2003
Phase 2	GT-07 P06545	15/2 Denmark Sweden	Safety, Efficacy	Adults 18-65y (74/40)	22-24 wks	Feb 2004 to Sept 2004

Phase	**Study/ Protocol #**	**# Sites/ Countries Location**	**Objective**	**Subjects (Study Drug/Placebo)**	**Tx* Duration**	**Study Dates**
Phase 3 Randomized trials for efficacy	GT-08	51/8 Europe	Efficacy	Adults 18-65y 316/318**	10-34 months**	Sept 2004 to Sept 2009
Phase 3 Randomized trials for efficacy	P08067	145 U.S. Canada 28	Efficacy and Safety	Children and Adults Ages 5-65 (752/749)	12 weeks prior to, and during 2012 GPS	2012
Phase 3 Randomized trials for efficacy	GT-14	21/1 U.S.	Efficacy and Safety	Adults 18-65y 166/163	24-36 wks	Dec 2006 to Aug 2007
Phase 3 Randomized trials for efficacy	P05238	69/2 U.S. (59) Canada (10)	Efficacy	Adults 18-65y 166/163	36 wks	Jan 2008 to Sept 2009
Phase 3 Randomized trials for efficacy	GT-12	26/1 Germany	Efficacy and Safety	Children 5-16y 126/127	36 wks	Nov 2006 to Nov 2007
Phase 3 Randomized trials for efficacy	P05239	62/2 U.S. (52) Canada (10)	Efficacy and Safety	Children 5-18y 175/169	36 wks	Jan 2008 to Sept 2009
Phase 3 other than efficacy	GT-10 P06550		Safety, Compliance	Adults 18-65y 460 subjects all active; Follow on 264 subjects	6-12 wks; follow on for ~ 1 yr	2006
Phase 3 other than efficacy	GT-16 P06990		"Phase 3b" Immune parameters, cutaneous reactivity	Adults 18-65y (52/26)	2-4 months prior to, and during 2007 GPS	2007
Phase 3 other than efficacy	GT-18 P06744		PD effect and tolerability	Adults 18-65y (219/57)		
Phase 3 other than efficacy	GT-19 P07021		Safety in combination with desloratadine	Adults 18-65 46 subjects, all received single doses	Single doses	???
Phase 4 (post marketing)	GT-15 P07022		Observational Safety, Tolerance	Adults 18-???? 628 subjects, all active	4 months prior to and during 2008 GPS	2008

Phase	Study/ Protocol #	# Sites/ Countries Location	Objective	Subjects (Study Drug/Placebo)	Tx* Duration	Study Dates
Phase 4 (post marketing)	GT-17 P06991		Compliance	Adults 18-65y 261 subjects, all active	48 weeks of tx	???

* GT-07 and all Phase 3 studies treated for a defined pre-GPS duration and then during the GPS. For the purpose of this table, GPS = 20 weeks.
**GT-08 was a 5 year study in which subjects who elected to continue past the first year were treated for a total of three years, and observed for the last two.

5.4 Consultations

None

5.4.1 Advisory Committee Meeting

This BLA was presented before the Allergic Products Advisory Committee on December12, 2013. The committee voted unanimously that the available data are adequate to support the safety of GRASTEK when administered to persons 5-65 years of age with the understanding that auto-injectable epinephrine will be available to patients at home.

APAC then addressed the question of sustained efficacy and "disease modifying activity." There was no vote, but the discussion indicates that the committee was not persuaded that GRASTEK has "disease modifying activity." There was general agreement that the data support sustained efficacy for an additional fourth year and perhaps a fifth year after three years of GRASTEK.

APAC had reservations regarding safety, including the following:

1. APAC was concerned about life-threatening local and systemic allergic reactions, and therefore recommended that patients who are prescribed GRASTEK also must be prescribed auto-injectable epinephrine.
3. APAC was of the opinion that data on subjects >65 years of age were lacking. During this discussion, the sponsors agreed to a limit of upper age of 65 years of age in the product indications.
4. APAC suggested the post-marketing studies in the following sets of subjects to define more clearly safety and/or efficacy:
    a. Adults > 65 years of age (primarily safety)
    c. Children and adults with moderate to severe asthma
    d. Children and adults with food allergy
    e. Racial or ethnic subpopulations (e.g. African-American, Hispanic)
    f. Monitor patients who have gastrointestinal symptoms for eosinophilic esophagitis and related diseases.
    g. Efficacy on subjects who are sensitive to additional environmental allergens (e.g. ragweed, trees)
    h. Safety for those receiving concomitant SCIT.
    i. Longer duration of treatment to test for disease modifying effect.

5.4.2 External Consults/Collaborations

None

5.5 Literature Reviewed (if applicable)

The clinical reviewer consulted the literature for background and context and refers in the text to the following reports:

1. Radulovic S., Calderon M. A., Wilson D., Durham S. Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev. 2010;12:CD002893
2. Bousquet J, Schunemann HJ et al. Allergic Rhinitis and its Impact on Asthma (ARIA): Achievements in 10 years and future needs. *J Allergy Clin Immunol* 130:1049; 2012
3. Greiner N and Hellings PW et al. *The Lancet* 178:2112; 2012
4. Cox L and Jacobsen L, *Ann Allergy Asthma Immunol* 103:451; 2009
5. Cox L and Nelson H et al. Immunotherapy practice parameters of the American Academy of Allergy, Asthma, and Immunology [AAAAI] *J Allergy Clin Immunol* 127:S1; 2011
6. Burks, WA, Calderon MA et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immuology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol* 131:1288; 2013
7. Passalacqua, G. Baena-Cagnani, CE et al. Grading local side effects of sublingual immunotherapy for respiratory allergy: Speaking the same language. *J Allergy Clin Immunol* 132:93; 2013

The following reports specific to this BLA were consulted:

8. Nolte H, Hébert J, Berman G, Gawchik S, White M, Kaur A, Liu N, Lumry W, Maloney J. Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults. Ann Allergy Asthma Immunol. 2013 Jun;110(6):450-456.e4. PMID 23706715
9. Nelson H, Blaiss M, Nolte H, Würtz SØ, Andersen JS, Durham SR. Efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet in mono- and poly-sensitized subjects. Allergy. 2013 Feb;68(2):252-5. PMID: 23205670
10. Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. J Allergy Clin Immunol. 2011 Jan;127(1):72-80, 80.e1-2. PMID: 21211643
11. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. J Allergy Clin Immunol. 2011 Jan;127(1):64-71, 71.e1-4. PMID: 21211642

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 GRASTEK.

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, grass 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 grass pollen season (GPS).

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 syrup 1 mg/mL – 5 mL QD (5 to □6 yr)	6 (per 5 mL)	6
1a	Loratadine RediTabs tablet 10 mg – 1 tablet QD ≥ 18 yr); Claritin syrup 1 mg/mL – 10 mL QD (□	6 (per tablet or 10 mL)	6
1b	Olopatadine hydrochloride 0.1% ophthalmic solution -1 drop in the affected eye BID	1.5 (per drop)	6
2	Mometasone furoate monohydrate nasal spray 50 mcg – 1 spray in each nostril QD (5 to □12 yr)	4 (per spray)	8
2	Mometasone furoate monohydrate nasal spray 50 mcg - 2 sprays in each nostril QD (□12 yr	2 (per spray)	8
3	Prednisone tablet 5 mg (Day 1 - 1 mg/kg/day, Max 50 mg/day)	1.6 (per tablet)	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 GT-08

A randomized, parallel-group, double-blind, placebo-controlled Phase III trial assessing the efficacy and safety of ALK Grass tablet Phleum pratense in subjects with seasonal grass pollen induced rhinoconjunctivitis

6.1.1 Objectives (Primary, Secondary, etc) Protocol GT-08

The primary objective of Protocol GT-08 was to evaluate the efficacy of specific immunotherapy with the 75,000 SQ-T ALK Grass tablet compared to placebo in subjects with grass pollen induced rhinoconjunctivitis, based on the rhinoconjunctivitis symptom score as well as the rhinoconjunctivitis medication score during the grass pollen season 2005. (The Total Combined Score (TCS) was a post-hoc analysis)

Secondary Objectives (key to evaluation of BLA)

1. To evaluate the efficacy of 2 and 3 years of treatment with the 75,000 SQ-T ALK Grass tablet compared to placebo in subjects with grass pollen induced rhinoconjunctivitis
2. To evaluate the persistent efficacy after 3 years of treatment with the 75,000 SQ-T ALK Grass tablet compared to placebo in subjects with grass pollen induced rhinoconjunctivitis. Persistent efficacy will be evaluated at 4 and 5 years after initiation of treatment (end of each grass pollen season 2008 and 2009) based on the secondary efficacy endpoints.

6.1.2 Design Overview Protocol GT-08

Study GT-08 was performed at 51 sites in eight EU countries (Austria, Germany, Denmark, Spain, Italy, Netherlands, Sweden, and UK). GT-08 was a randomized, double-blind placebo controlled trial of GRASTEK 2800 BAU compared to Placebo.

Subjects were treated with 75,000 SQ-T ALK or Placebo, one tablet sublingual each day year around until the end of Year 3.

- Treatment began before the estimated start of the grass pollen season
- At initiation of treatment, rescue medication, an electronic diary to record symptoms and medication usage, and an record card to record AE were dispensed. AE were recorded in response to an open-ended query; specific AE were not listed.
- Subjects return at various points prior to grass pollen season, at peak season
- Years 4 and 5 were observation years in which subjects were monitored of sustained efficacy of GRASAX.

Efficacy was monitored through an electronic diary of symptoms kept by the subject. Safety data were kept through a paper diary that surveyed for AE with an open-ended question (rather than specific queries for AE).

Study visits for Year 1 are shown in Table 9; schedule of visits for Years 2 and 3 were similar to Year 1.

Table 9. Schedule of study visits Year 1, GT-08

Visit	**1** ***Screen-ing***	**2** ***Random-isation***	**3** ***Off-season***	**4** ***Off-season***	**5** ***Pre-season***	**6** ***season***	**7** ***End of treat-ment[9]***	**Phone Follow- up** ***Post-season[10]***	**Un-scheduled[3]**
Time		*1 week after visit 1 ± 1 Week*	*Approx. weeks after 1 visit 2*	*Approx. 16 weeks after visit 2[1]*	*Approx. 2 weeks before anticipa-ted start of GPS[1]*	*In Peak Grass Pollen 2 Season*	*Approx. 1 week after GPS ± 1 week*	*1 week after visit 7 ± 1 week*	
Informed consent[4]	x								
Demography	x								
Medical history	x								
Allergy and asthma medication history	x								
In-/exclusion criteria	x	x							
Randomisation		x							
Physical examination	x						x		x[5]
Vital signs	x						x		x[5]
FEV_1	x						x		x[5]
Skin prick test	x								
Urine pregnancy test[6]	x						x		
Safety laboratory	x						x		x[5]
Specific IgE against *Phleum pratense*	x								
Issued and instructed to electronic diaries[7]					x				
Review of diary Recordings						x	x		x
Global Evaluation[8]	x						x		
Recorded concomitant Medication	x	x	x	x	x	x	x		x
AEs assessed		x	x	x	x	x	x	x	x
Dispensed IMP		x	x	x	x	x			x[5]
Dispensed rescue Medication					x	x			x[5]
Collection of trial IMP – compliance checked, drug accountability			x	x	x	x	x		
Blood sampling for immunological markers[11]	x		x	x	x	x	x		

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6.1.3 Population Protocol GT-08

The population comprised adult subjects with grass pollen induced allergic rhinoconjunctivitis and with no other significant allergic or respiratory disease coinciding with the grass pollen season.

Key Inclusion Criteria

1. Age between 18 and 65 years (study dependent)
2. ARC ± asthma, treated during previous grass pollen season
3. Evidence of allergy to Timothy grass (Phleum pratense) pollen
4. Positive skin prick test and specific IgE (≥ 0.70 kIU/L, Class 2)
5. FEV1 ≥70% of predicted value

Key Exclusion Criteria

1. Sensitivity to an unrelated seasonal allergen that overlaps grass pollen season, or to a perennial allergen
2. History of severe asthma or asthma requiring chronic treatment (e.g. inhaled corticosteroids, long-acting β-agonists)

For Year 1, 634 subjects were enrolled; 351 of these subjects participated in Year 4, and 258 subjects entered the trial period, Of those, 241 delivered diary data during the grass pollen season 2009, and 238 completed the trial.

6.1.4 Study Treatments or Agents Mandated by Protocol GT-08

The study drug was provided by ALK-Abelló. The daily dose of the study drug was 1 tablet, which preferably was taken in the morning. The tablet was placed under the tongue and swallowing should be avoided for 1 minute. Eating and drinking was not allowed within 5 minutes after IMP intake.

The first dose was taken in the clinic and the subject should stay in the clinic for 60 minutes for observation, and the following doses were taken at home.

The study drug was supplied in blister cards containing 10 tablets each. The blister cards were packed in visit specific boxes. The dosage form was an oral lyophilisate for sublingual use.

Active treatment:
Active ingredients: Phleum pratense grass pollen extract
Dosage form: Oral lyophilisate for oromucosal use (sublingually)
Strength: 75,000 SQ-T tablets (15 µg phl p5 major allergen; equivalent to 2800 BAU)
Lot numbers used for Year 1, 2 and 3 are shown in Tables 10-12 below.

Table 10. Lot numbers of GRAZAX and Placebo used for Year 1 of GT-08

Tablets	Batch Numbers	Expiry Dates
ALK Grass tablets, 75,000 SQ-T	141292/141302	14 December 2005
	141293/141308	19 December 2005
	141295/141326	20 December 2005
	141296/141327	22 December 2005
ALK Grass tablets, Placebo	141329/141333	2 December 2005
	141331/141335	11 December 2005
	141330/141334	9 December 2005

Table 11. Lot numbers of GRAZAX and Placebo used for Year 2 of GT-08

Tablets	Batch Numbers	Expiry Date
Grazax	141308	19 December 2005
	141326	20 June 2006
	271014	28 Marts 2007
Placebo	141332	1 June 2006
	271013	29 April 2007

Table 12. Lot numbers of GRAZAX and Placebo used for Year 3 of GT-08

Tablets	Batch Numbers	Expiry Date
Grazax	276862	29 September 2007
	370228	04 December 2007
	370225	06 December 2007
Placebo	271013	29 April 2007
	370233	03 January 2008

Comment [RLR1]: need third year batch

6.1.5 Directions for Use Protocol GT-08

One tablet sublingual per day.

6.1.6 Sites and Centers Protocol GT-08

The study was designed to be performed at 51 sites in eight EU countries (Austria, Germany, Denmark, Spain, Italy, Netherlands, Sweden, and UK). Eight sites closed during Year 1 resulting in the dropout of 68 subjects, and 127 subjects from the other sites withdrew consent.

6.1.7 Surveillance/Monitoring Protocol GT-08

This trial was conducted in compliance with the principles of *Good Clinical Practice* (2). The trial was monitored according to ALK-Abelló standard operating procedures for the monitoring of clinical trials and other trial-specific procedures.

The trial was monitored by the sponsor or its delegate by means of on-site visits, telephone calls, and regular inspection of the case record form (CRF) with sufficient frequency to verify the following: subject enrolment; compliance with the protocol; the completeness and accuracy of data entered in the CRFs by verification against original source documents; compliance in the use of IMP; compliance with diary; drug accountability; and recording of AEs. Ten site audits were performed during the first year of the GT-08 trial. Each country had at least one audit. No audits were performed during the second year of the trial.

6.1.8 Endpoints and Criteria for Study Success Protocol GT-08

The primary efficacy endpoints were the average daily rhinoconjunctivitis symptom score (DSS) and the average daily rhinoconjunctivitis medication score (RMS). These two scores were calculated for each subject as the average of the observed total daily scores throughout the entire grass pollen season 2006.

For the two primary efficacy endpoints the ranking of the null hypotheses were as follows:

1. GRAZAX versus placebo on rhinoconjunctivitis symptom score
2. GRAZAX versus placebo on rhinoconjunctivitis medication score

From the Clinical Study Report: "If the first null hypothesis was rejected the trial had succeeded to confirm an effect on rhinoconjunctivitis symptoms disregarding the outcome of second ranked test on rhinoconjunctivitis medication score. If both null hypotheses were rejected, effect on both symptoms and medication were confirmed." Criteria for success included a point-estimate significance without limits on variability or confidence limits.

6.1.9 Statistical Considerations & Statistical Analysis Plan Protocol GT-08

The primary investigation of the comparison of the 2 treatment groups was done via an analysis of variance (ANOVA) with the average rhinoconjunctivitis symptom score or the average rhinoconjunctivitis medication score as response variable and treatment group as a fixed effect and pollen region as random effect, as well as adjusting for different error variation for each treatment group. Analysis includes 2-sided 95%-confidence interval for the difference in adjusted means between the two groups in addition to the coherent p-value. The difference in adjusted means between the two treatment groups relative to the adjusted mean of the placebo group is presented as a percentage.

A reduction of at least 25% in symptoms could be discovered with a 5% significance level and a power of 95% if the sample size without drop-outs was 268 subjects in each arm. With a 10% dropout 300 subjects were to be included in each treatment arm.

6.1.10 Study Population and Disposition Protocol GT-08

6.1.10.1 Populations Enrolled/Analyzed Protocol GT-08

Analysis sets used for GT-08

Full-Analysis Set (FAS) – consisting of all subjects randomized following the Intent to Treat (ITT) ICH principle. The FAS was the primary set for analysis.

Per-Protocol Set (PP) – comprising subjects without major protocol deviations. The PP analysis set comprised subjects who:

1. Did not take prohibited medication
2. Had sufficient IMP compliance defined as a drug compliance of at least 80%, i.e. number of tablets used compared to number of treatment days
3. Provided sufficient diary data defined as at least 50% of diary data in the grass pollen season

6.1.10.1.1 Demographics Protocol GT-08

Table 13 shows that subjects were distributed similarly between study drug and placebo groups for sex, age, and severity and length of time of grass pollen allergy.

Table 13. Key Demographics for Protocol GT-08

Treatment Group	75,000 SQ-T N	75,000 SQ-T (%)	Placebo N	Placebo (%)	Overall N	Overall (%)
Number of Subjects	316		318		634	
Sex						
N	316		318		634	
Men	179	(57)	193	(61)	372	(59)
Women	137	(43)	125	(39)	262	(41)
Age (Years)						
N	316		318		634	
Mean (SD)	33.8	(9.6)	34.5	(10.0)	34.2	(9.8)
Median	33.0		33.0		33.0	
Q5% - Q95%	21	- 53	20	- 54	20	- 53
Grass Pollen Allergy (Severity):						
N	316		318		634	
Moderate	137	(43)	144	(45)	281	(44)
Severe	179	(57)	174	(55)	353	(56)
Grass Pollen Allergy (Years):						
N	313		316		629	
Mean (SD)	15.9	(9.8)	15.7	(10.4)	15.8	(10.1)
Median	14.0		14.5		14.0	
Q5% - Q95%	3	- 34	2	- 36	2	- 35

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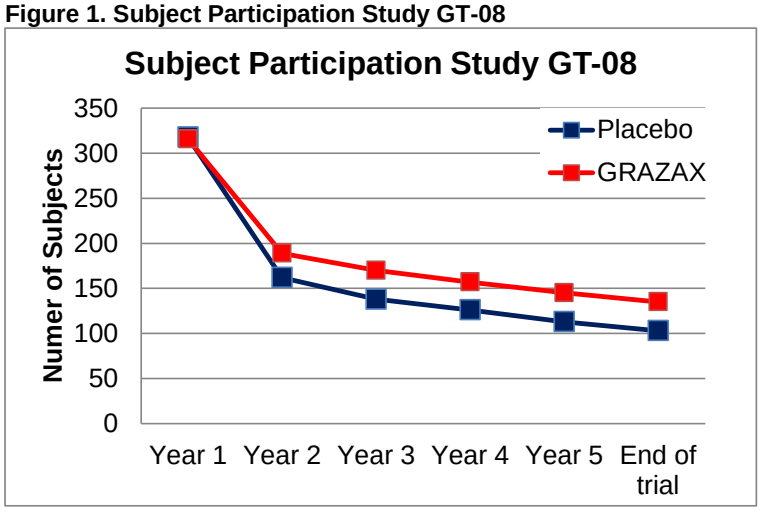
6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population GT-08
There are no other considerations of the medical/behavioral characterizations other than severity of pollen allergy (above).

6.1.10.1.3 Subject Disposition Protocol GT-08
Figure 1 shows participation rates of subjects during all five years of GT-08. Note that after Year 1, dropout rates from the study drug and placebo groups were equivalent.

Figure 1. Subject Participation Study GT-08



Adapted from Original BLA 125473/000; Module 5, CSR GT08Yr5; Page 65 of 6373

6.1.11 Efficacy Analyses Protocol GT-08

6.1.11.1 Analyses of Primary and Secondary Endpoints Protocol GT-08
The primary efficacy endpoint was a difference in the DSS between the GRAZAX and placebo study groups during the entire pollen season. The start date of the grass pollen season was for each pollen region defined as first day of three consecutive days with (non-missing) pollen counts larger than or equal to 10 grains/m^3. The stop date of the season was for each pollen region defined as the last day before three consecutive days with (non-missing) pollen count less than 10 grains per m^3.

The criterion for success was a statistical difference in the point estimates of the DSS. For purposes of evaluation within the US, however, the ad hoc analysis of the TCS is considered the primary endpoint. These values are shown in Table 14.

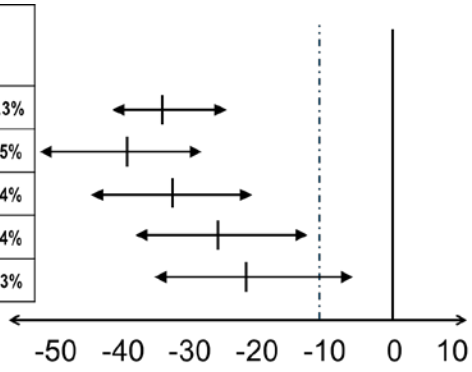
Table 14. TCS of GRAZAX and placebo groups in Study GT-08

	Treatment Group	Number of Subjects	TCS (adjusted mean)	Percent difference in average scores (95% CI)	Percent difference in average scores (95% CI)
Treatment Year 1	GRASTEK	282	4.46	-34.2%	-42.0% -26.3%
Treatment Year 1	Placebo	286	6.78	-34.2%	-42.0% -26.3%
Treatment Year 2	GRASTEK	172	4.10	-40.9%	-51.8%, -29.5%
Treatment Year 2	Placebo	144	6.94	-40.9%	-51.8%, -29.5%
Treatment Year 3	GRASTEK	160	4.39	-34.0%	-45.5%, -21.4%
Treatment Year 3	Placebo	127	6.64	-34.0%	-45.5%, -21.4%
Observation Year 4	GRASTEK	142	4.96	-27.2%	-39.9%, -12.4%
Observation Year 4	Placebo	115	6.81	-27.2%	-39.9%, -12.4%
Observation Year 5	GRASTEK	137	4.96	-22.7%	-37.1%, -6.3%
Observation Year 5	Placebo	104	6.42	-22.7%	-37.1%, -6.3%

Adapted from sponsor's Briefing Document to the Allergenic Products Advisory Committee, December 12, 2013

Figure 2. Graphic comparison of difference in TCS with 95% confidence limits, Study GT-08

Year	2800 BAU	Placebo	% difference	95% CI
1	282	286	-34.2%	-42.0%, -26.3%
2	172	144	-40.9%	-51.8%, -29.5%
3	160	127	-34.0%	-45.5%, -21.4%
4	142	115	-27.2%	-39.9%, -12.4%
5	137	104	-22.7%	-37.1%, - 6.3%



Adapted from sponsor's Briefing Document to the Allergenic Products Advisory Committee, December 12, 2013

The TCS is the sum of the daily symptom score (DSS) and the daily medication score (DMS). The difference in these scores between placebo and GRAZAX study drug groups are shown in Table 15.

Table 15. Percent change in DSS and DMS between GRAZAX and placebo study groups.

Study GT-08 Year	Number of subjects GRASTEK	Number of subjects Placebo	% change in DSS (95% CI)	% change in DMS (95% CI)
1 (2005 season)	282	286	-31.2 % (-38.3, -23.4)	-38.4% (-49.8, -26.5)
2 (2006 season)	172	144	-36.2% (-46.5, -26.2)	-45.5% (-60.4, -28.2)
3 (2007 season)	160	127	-29.0% (-40.3, -16.3)	-40.1% (-55.4, -21.2)
4 (2008 season) [no treatment]	142	115	-26.2% (-37.6, -12.2)	-28.6% (-46.3 , -6.0)
5 (2009 season) [no treatment]	137	104	-24.7% (-37.7, -9.7)	-20.4% (-39.8, +4.3)

Adapted from sponsor's Briefing Document to the Allergenic Products Advisory Committee, December 12, 2013

6.1.11.2 Analyses of Secondary Endpoints Protocol GT-08
Secondary endpoint analyses are included in Section 6.1.10.1 above.

6.1.11.3 Subpopulation Analyses Protocol GT-08
There are no subpopulation analyses essential for this review.

6.1.11.4 Dropouts and/or Discontinuations Protocol GT-08
In the efficacy analyses no imputation of data was carried out in case of missing data, but all available data was used to its full extent. This implied that subjects who withdrew prior to the start of the 2009 grass pollen season (and therefore not provided any diary data) were not part of the efficacy analysis.

6.1.11.5 Exploratory and Post Hoc Analyses Protocol GT-08
No exploratory or post-hoc analyses are considered for this review.

6.1.12 Safety Analyses Protocol GT-08

6.1.12.1 Methods Protocol GT-08
Subjects were observed in the physician's office for 30 minutes after taking the first dose of study medication. Thereafter, AE were recorded on an open-ended diary card that was collected at study visits.

6.1.12.2 Overview of Adverse Events Protocol GT-08
Overall, AE were limited to local swelling and application reactions. Most were mild to moderate in severity.

The five most common AEs reported during the trial were (in MedDRA PTs) oral pruritus, ear pruritus, mouth edema, and throat irritation. The severity and assessed causality for all events of oral pruritus, ear pruritus, mouth edema, and throat irritation in safety analysis set for all five years of the trial are summarized in Table 16.

Table 16. Incidence and assessed causality of all Adverse Events in GT-08

	Placebo N=113	**Placebo N=113**	**Placebo N=113**	**Grazax N=145**	**Grazax N=145**	**Grazax N=145**	**Overall N=258**	**Overall N=258**	**Overall N=258**
	N	**(%)**	**E**	**N**	**(%)**	**E**	**N**	**(%)**	**E**
All AEs	100	(100%)	745	139	(100%)	1027	239	(100%)	1772
Causality									
Possible	29	(29%)	58	45	(32%)	70	74	(31%)	128
Probable	15	(15%)	22	104	(75%)	210	119	(50%)	232
Unlikely	100	(100%)	665	124	(89%)	747	224	(94%)	1412
Severity									
Mild	97	(97%)	415	133	(96%)	649	230	(96%)	1064
Moderate	73	(73%)	299	97	(70%)	346	170	(71%)	645
Severe	20	(20%)	31	22	(16%)	31	42	(18%)	62
Unknown/NA	-	-	-	1	(<1%)	1	1	(<1%)	1
Seriousness									
Non-serious	100	(100%)	728	139	(100%)	1013	239	(100%)	1741
Serious	14	(14%)	17	11	(8%)	14	25	(10%)	31

6.1.12.3 Deaths Protocol GT-08
One subject from the placebo group, diagnosed with a subarachnoid hematoma/subarachnoid hemorrhage, died during Study GT-08.

6.1.12.4 Nonfatal Serious Adverse Events Protocol GT-08
No study drug-related fatalities or other IMP-related SAEs occurred during the trial.

During the five years of the trial 42 SAEs were reported (in 40 reports), all assessed as unlikely related to the study drug.

> *The Clinical Reviewer agrees with the sponsor's assertion that none of the SAE reported during Study GT-08 were related to the study drug.*

6.1.12.5 Adverse Events of Special Interest (AESI) Protocol GT-08
There were no reports of anaphylaxis in any subjects who participated in Study GT-08.

6.1.12.6 Clinical Test Results Protocol GT-08
There were clinically significant changes in laboratory or pulmonary function test results during the study.

6.1.12.7 Dropouts and/or Discontinuations Protocol GT-08
Over the 5 years of the trial, 41 AEs led to withdrawals of a total of 29 subjects (including one death). Eighteen of the AE withdrawals belonged to the GRAZAX group and 11 to the placebo group. Twenty-four of the AE withdrawals occurred during the 1st year of the trial, while the remaining 5 occurred in the extension (during the 2nd or 3rd year of the trial). During the 4th and 5th year of the trial, no subjects withdrew due to AEs.

Four of the AEs leading to withdrawal were severe (unlikely related subarachnoid hemorrhage leading to death in the placebo group, unlikely related brain neoplasm in the placebo group and probable related oral pruritus and pharyngeal edema in the same subject in the GRAZAX group), while the rest were mild (N=15) or moderate (N=21). For one AE (pregnancy leading to caesarean section), the severity was listed as NA.

There were 12 withdrawals due to pregnancy.

6.1.13 Study Summary and Conclusions Protocol GT-08

The point estimate of TCS and the DSS in the GRAZAX study drug group was improved during the treatment years by 30-40% compared to placebo group. The point estimate of the change in TCS was improved by 27% during the first observation year (Year 4 of the study), and 22% during the second observation year. For treatment years 1-3 and the first year of post-treatment observation, the 95% CI UL of the difference of TCS was less than -10%. For Years 1-4, GT-08 met the clinical endpoints considered by CBER as most critical for defining efficacy—TCS difference of -15% with a 95% CI UL <10%.

6.2 Trial #2: Protocol GT-12

A phase III trial investigating the efficacy and safety of GRAZAX® in children aged 5-16 years with grass pollen induced rhinoconjunctivitis with or without asthma

6.2.1 Objectives (Primary, Secondary, etc) Protocol GT-12

Primary Objective

To evaluate the efficacy of GRAZAX, 75,000 SQ-T compared to placebo in children aged 5-16 years with grass pollen-induced rhinoconjunctivitis (with or without asthma), based on the rhinoconjunctivitis symptom and medication scores during the entire grass pollen season. The Total Combined Score (TCS) was a post-hoc analysis.

Secondary Objectives

1. To evaluate the efficacy of GRAZAX, 75,000 SQ-T compared to placebo in children aged 5-16 years with grass pollen-induced rhinoconjunctivitis (with or without asthma), based on secondary endpoints, including asthma endpoints.
2. To evaluate the safety and tolerability of GRAZAX, 75,000 SQ-T compared to placebo in children aged 5-16 years with grass pollen-induced rhinoconjunctivitis (with or without asthma).

6.2.2 Design Overview Protocol GT-12

See Study GT-08. The study schedule was essentially identical to GT-08, except there was one off-season visit (the visit between randomization and the visit that was approximately 2 weeks before the anticipated start of GPS) in GT-12.

6.2.3 Population Protocol GT-12

With the exception of age, the inclusion and exclusion criteria were similar to those of GT-08. GT-12 included children and adolescents 5-16 years of age. Children with asthma were included only if the asthma was intermittent and there was no requirement for daily inhaled corticosteroid therapy. Children were also excluded if atopic dermatitis was considered severe.

6.2.4 Study Treatments or Agents Mandated by Protocol GT-12
Grazax 75,000 SQ-T (*Phleum pratense*, approximately 15 µg Phl p 5), blisters of 10 tablets.

Table 17. Lot numbers of GRAZAX and Placebo used for Year 1 of GT-12

Tablets	Batch Numbers	Expiry Dates
Grazax 75,000 SQ-T	370228	4 June 2008
	276862	29 September 2007
	271014	28 September 2007
Placebo	271013	29 October 2007

From original BLA 125473, Module 5, CSR GT12; Page 29 of 1315

6.2.5 Directions for Use Protocol GT-12
Oral lyophilosate for sublingual administration once daily.

6.2.6 Sites and Centers Protocol GT-12
There were 26 investigators in Germany. The signatory investigator was Prof. Albrecht Bufe, MD, Director of the Experimental Pneumology Department, Medical Faculty of Ruhr-Universität Bochum, Bürkle-de-la-Camp-Platz 1, 44789 - Bochum, Germany

6.2.7 Surveillance/Monitoring Protocol GT12
The safety variables assessed included: AEs, vital signs, physical examinations, ECGs (screening only), and safety laboratory assessments, and they were to be summarized by treatment groups. A Data Safety Monitoring Committee (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.

6.2.8 Endpoints and Criteria for Study Success Protocol GT12
Primary Efficacy Endpoints:
1. Average rhinoconjunctivitis symptom score, entire grass pollen season 2007
2. Average rhinoconjunctivitis medication score, entire grass pollen season 2007

Key Secondary Efficacy Endpoints:
1. Average rhinoconjunctivitis symptom score, peak grass pollen season
2. Average rhinoconjunctivitis medication score, peak grass pollen season
3. The percentage of rhinoconjunctivitis “well days”, entire grass pollen season 2007

6.2.9 Statistical Considerations & Statistical Analysis Plan Protocol GT12
Similar to GT-08 (Section 6.1.9)

6.2.10 Study Population and Disposition Protocol GT12

6.2.10.1 Populations Enrolled/Analyzed Protocol GT12
The Full Analysis Set (FAS and Per-Protocol Set (PP) are identical to those defined for GT-08.

6.2.10.1.1 Demographics Protocol GT-12

Table 18. Key Demographics for Protocol GT-12

Treatment Group	75,000 SQ-T (n)	75,000 SQ-T %	Placebo (n)	Placebo %	Overall N	Overall %
Sex						
Male	83	(66)	83	(65)	166	(66)
Female	43	(34)	44	(35)	87	(34)
Ethnic origin						
Caucasian	123	(98)	123	(97)	246	(97)
Asian	1	(<1)	0	(0)	1	(<1)
African	1	(<1)	2	(2)	3	(1)
Other	1	(<1)	2	(2)	3	(1)
Age (years)						
Mean (SD)	10.1	(2.9)	10.1	(3.1)	10.1	(3.0)
Median	10.0		9.0		10.0	
Q25% - Q75%	8.0	- 12.0	8.0	- 13.0	8.0	- 13.0
Min – Max	5.0	- 16.0	5.0	- 16.0	5.0	- 16.0
Years with grass pollen allergy						
Mean (SD)	3.5	(2.6)	3.4	(2.4)	3.5	(2.5)
Median	2.9		2.7		2.8	
Q25% - Q75%	1.5	- 4.7	1.6	- 4.6	1.6	- 4.6
Min – Max	0.5	- 12.6	0.3	- 11.5	0.3	- 12.6
Asthma						
Yes	53	(42)	50	(39)	103	(41)
No	73	(58)	77	(61)	150	(59)
Any other relevant medical history						
Yes	72	(57)	80	(63)	152	(60)
No	54	(43)	47	(37)	101	(40)

From original BLA 125473/000, Module 5 CSR GT12, Pages 61-62 of 1315

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population Protocol GT12
As shown in Table 17 (above), approximately 40% of subjects had asthma. Subjects with asthma were equally distributed between study drug and placebo groups.

6.2.10.1.3 Subject Disposition Protocol GT12
Of the 307 subjects who were screened, 54 were screening failures; 253 subjects were randomized and exposed to the IMP. These 253 subjects were included in the FAS, and out of this analysis set, 234 subjects (92%) completed the trial, with 90% of the GRAZAX group and 94% of the placebo group completing the trial. The withdrawal rate was 8%, which was less than the 20% assumed in the power calculation

The PP set comprised 191 subjects (75% of the FAS) which were evenly distributed between the two treatment groups, with 91 subjects (72%) and 100 subjects (79%) in the GRAZAX and placebo groups respectively. Subjects were classified into the PP analysis data set prior to unblinding of the data.

Table 19. Subject Disposition GT-12

Treatment Group	N	Grazax (%)	N	Placebo (%)	N	Total (%)
Screened					307	
Full Analysis Set	126	(100)	127	(100)	253	(100)
Per Protocol Set (PP)	91	(72)	100	(79)	191	(75)
Subjects withdrawn	12	(10)	7	(6)	19	(8)
Reason for withdrawal						
Adverse event	4	(3)	2	(2)	6	(2)
Lost to follow-up	2	(2)	0	(0)	2	(<1)
Subject non-compliance	3	(2)	2	(2)	5	(2)
Withdrawal of consent	0	(0)	1	(<1)	1	(<1)
Other	3	(2)	2	(2)	5	(2)
Withdrawal initiated by						
Investigator	5	(4)	1	(<1)	6	(2)
Sponsor	3	(2)	1	(<1)	4	(2)
Subject	4	(3)	5	(4)	9	(4)

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6.2.11 Efficacy Analyses Protocol GT12

6.2.11.1 Analyses of Primary Endpoint and Key Secondary Endpoints Protocol GT12
The primary efficacy endpoints were the average DSS and the DMS. These two average scores were calculated as the sum of the individual daily scores (TCS) for each subject during the entire grass pollen season 2007 divided by the number of subject diary recordings of that score during the entire grass pollen season. Tables 20-22 show the TCS for the treatment and placebo groups and the change in the TCS for the treatment relative to placebo.

Table 20. TCS of treatment and placebo groups GT-12

Treatment	Number of Subjects	Total Combined Score (adjusted mean)	Percent change in TCS relative to placebo Point estimate	Percent change in TCS relative to placebo 95% CI
Grastek	117	3.70	-24.2 %	-41.3%, -4.5%
Placebo	121	4.87		

From Merck Briefing Document (Advisory Committee Background Package); Page 62 of 163

Table 21. DSS of treatment and placebo groups GT-12

Treatment	Number of Subjects	Daily Symptom Score (adjusted mean)	Percent change in DSS relative to placebo Point estimate	Percent change in DSS relative to placebo 95% CI
Grastek	117	2.18	-22.2 %	-37.6%, -3.7%
Placebo	121	2.80		

From original BLA 125473/000, Module 5 CSR GT12, Page 68 of 1315

Table 22. DMS of treatment and placebo groups GT-12

Treatment	Number of Subjects	Daily Medication Score (median)	Percent change in DMS relative to placebo Point estimate	Percent change in DMS relative to placebo 95% CI
Grastek	117	0.78	-34.3 %	-57.1%, -0.8%
Placebo	121	1.19		

From original BLA 125473/000, Module 5 CSR GT12, Page 70 of 1315

6.2.11.2 Analyses of Secondary Endpoints Protocol GT12
The key secondary endpoints of the DSS and the DMS are discussed above.

6.2.11.3 Subpopulation Analyses Protocol GT-12

6.2.11.4 Dropouts and/or Discontinuations Protocol GT-12
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 grass pollen season did not contribute to the efficacy analyses. Thus, 117 out of 126 subjects on GRAZAX and 121 out of 127 subjects on placebo contributed with diary data in the efficacy analyses.

6.2.11.5 Exploratory and Post Hoc Analyses Protocol GT12
None

6.2.12 Safety Analyses Protocol GT12

6.2.12.1 Methods Protocol GT12
Methods of analysis of safety are identical to those in GT-12.

6.2.12.2 Overview of Adverse Events Protocol GT12
The severity and assessed causality for all events of oral pruritus, ear pruritus, mouth edema, and throat irritation in safety analysis set for all five years of the trial are summarized in Table 23. Note that out of the few severe AEs observed, the majority were reported by the GRAZAX group.

Table 23. Incidence and assessed causality of all Adverse Events in GT-08

	Placebo N=113 N	**Placebo N=113 (%)**	**Placebo N=113 E**	**Grazax N=145 N**	**Grazax N=145 (%)**	**Grazax N=145 E**	**Overall N=258 N**	**Overall N=258 (%)**	**Overall N=258 E**
All AEs	109	(87)	426	106	(83)	278	215	(85)	704
Mild	100	(79)	288	87	(69)	171	187	(74)	459
Moderate	65	(52)	126	65	(51)	103	130	(51)	229
Severe	7	(6)	11	4	(3)	4	11	(4)	15
Unknown	1	(<1)	1	0	(0)	0	1	(<1)	1
Severity of IMP-related AEs									
All adverse events	67	(53)	151	37	(29)	48	104	(41)	199
Mild	63	(50)	116	27	(21)	35	90	(36)	15
Moderate	15	(12)	32	12	(9)	13	27	(11)	45
Severe	1	(<1)	3	0	(0)	0	1	(<1)	3
Seriousness of all AEs									
All adverse events	109	(87)	426	106	(83)	278	215	(85)	704
Serious [a]	2	(2)	3	2	(2)	2	4	(2)	5
Not serious	109	(87)	423	106	(83)	276	215	(85)	699
IMP-relation									
All adverse events	109	(87)	426	106	(83)	278	215	(85)	704
Probable	53	(42)	104	16	(13)	18	69	(27)	122
Possible	27	(21)	47	22	(17)	30	49	(19)	77
Unlikely	94	(75)	275	95	(75)	230	189	(75)	505
Action									
All adverse events	109	(87)	426	106	(83)	278	215	(85)	704
Dose not changed	108	(86)	394	103	(81)	261	211	(83)	655
Temporarily interrupted	5	(4)	6	2	(2)	2	7	(3)	8
IMP discontinued	4	(3)	14	3	(2)	3	7	(3)	17
Not exposed to IMP [b]	10	(8)	10	10	(8)	10	20	(8)	20
Unknown	2	(2)	2	2	(2)	2	4	(2)	4
Outcome									
All adverse events	109	(87)	426	106	(83)	278	215	(85)	704
Recovered	109	(87)	406	103	(81)	262	212	(84)	668
Recovering	7	(6)	9	3	(2)	4	10	(4)	13
Not recovered	7	(6)	9	8	(6)	8	15	(6)	17
Unknown	2	(2)	2	4	(3)	4	6	(2)	6

From original BLA 125473/000, Module 5 CSR GT12, Page 93 of 1315

Subjects in the GRAZAX group experienced 3.4 AEs on average, 1.2 of which were assessed as treatment-related; the corresponding figures for the placebo group are 2.2 and 0.4 respectively.

Four types of adverse events had a treatment-related incidence ≥ 5%: Oral pruritus, throat irritation swelling face and cough. The three most frequent of these most commonly reported IMP-related AEs were local reactions at or near the application site. Oral pruritus was the most frequent reaction, reported by 32% of the subjects in the GRAZAX group compared to 2% of the placebo-treated subjects. "Abdominal pain" was observed with an overall incidence below 5% and with similar incidence for the two treatment groups; the only incidence of abdominal pain that was assessed as treatment-related was in a subject in the placebo group.

6.4.12.3 Deaths Protocol GT12
There were no deaths.

6.2.12.4 Nonfatal Serious Adverse Events Protocol GT12
Five SAE were reported, two were in the placebo group. All three SAE that occurred in subjects in the GRAZAX group were episodes of asthma:

1. A 16 yo female who had an exacerbation of asthma on Day 52 of treatment, and was hospitalized five days later, and discharged two days after that. She continued to take GRAZAX throughout the episode.
2. The same 16 yo female experienced an asthma exacerbation on Day 199 of GRAZAX therapy; she was hospitalized on that day and discharged two days later.
3. A 9 yo male who experienced a severe, life-threatening asthmatic reaction on Day 62 of GRAZAX therapy 10 minutes after ingestion of an herbal mixture for cough. The subject was hospitalized for one day. Therapy was discontinued.

These three events were considered by the investigator as unlikely to have been caused by GRAZAX.

Reviewer's note: The clinical reviewer agrees with this assessment.

6.2.12.5 Adverse Events of Special Interest (AESI) Protocol GT-12
There were no episodes of anaphylaxis associated with the study drug. Nine subjects in the study drug group reported at least one AE that was graded as severe, of which the AE in only one subject were considered probably related to the study drug, a subject who experienced oral pruritus, dyspnea, and "tongue disorder) on Day 17 of GRAZAX; treatment and was was discontinued. All other treatment-emergent AE, including those that affected four placebo subjects, were considered unlikely to be related to treatment.

6.2.12.6 Clinical Test Results Protocol GT12
There were no clinical test results that impact on evaluation of the study drug or immunotherapy.

6.2.12.7 Dropouts and/or Discontinuations Protocol GT-12
Nineteen subjects withdrew from the study; Two subjects in the GRAZAX group were lost to follow-u, and five subjects (three in GRAZAX group, two in the Placebo group) were non-compliant. One placebo subject withdrew consent. Three subjects chose not to participate, and two failed study criteria at randomization.

Six subjects, two in the placebo group and four in the study drug group, withdrew from the study due to AE. Only the asthma episode in Subject 351 was considered serious.

Table 24. Dropouts and Discontinuations Protocol GT-12

Subject	Allocation	Preferred Term	Duration (days)	Onset (days)	IMP-relation	Outcome	Severity
179	Placebo	Rhinitis allergic	N/A	47	Unlikely	Recovered	Moderate
348	Placebo	Gastroenteritis	8	20	Unlikely	Unknown	Moderate
274	Grazax	Lip blister	12	3	Probable	Recovered	Mild
		Swollen tongue	1	15	Probable	Recovered	Moderate
		Chest discomfort	1	15	Probable	Recovered	Moderate
		Dyspnoea	1	15	Probable	Recovered	Moderate
		Swollen tongue	1	15	Probable	Recovered	Moderate
		Oral pruritus	1	17	Probable	Recovered	Severe
		Dyspnoea	1	17	Probable	Recovered	Severe
		Tongue disorder	1	17	Probable	Recovered	Severe
347	Grazax	Swelling face	1	17	Probable	Recovered	Mild
351	Grazax	Asthma	1	93	Unlikely	Recovered	Severe
412	Grazax	Oral pruritus	1	34	Probable	Recovered	Moderate
		Throat irritation, headache	1 3	34 34	Probable Possible	Recovered Recovered	Moderate Recovered

From original BLA 125473/000, Module 5, CSR GT12; Page 98 of 1315

6.2.13 Study Summary and Conclusions Protocol GT12

Study GT-12 was well designed to meet its clinical endpoint, an improvement in the DSS in the GRASAX study drug group. The point estimate of that improvement was better than the minimal 15% considered acceptable by CBER. The 95% CI were not criteria for success of this European study (that was not conducted under IND), and did not meet CBER's requirements for proof of efficacy.

The results of this study are considered supportive for efficacy and safety of treatment with GRAZAX (GRASTEK) in children of ARC.

6.3 Trial #3: Protocol P05238

Protocol P05238: A multicenter, double-blind, randomized, placebo-controlled parallel-group study evaluating the efficacy and safety of grass (Phleum Pratense) Sublingual Tablet (SCH 697243) in adult subjects with a history of grass pollen

6.3.1 Objectives (Primary, Secondary, etc) Protocol P05238

Primary Objective:

To evaluate the efficacy of grass sublingual tablet (SCH 697243) versus placebo in the treatment of grass pollen-induced rhinoconjunctivitis based on the Total Combined Score, the sum of rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS) averaged over the entire grass pollen season (GPS).

Key Secondary Objectives:

1. The safety and to compare the following between the SCH 697243 and placebo groups:
2. The average rhinoconjunctivitis DSS for the entire GPS.
3. The average rhinoconjunctivitis DMS for the entire GPS

6.3.2 Design Overview Protocol P05238

Protocol P05238 is a pivotal Phase 3 multicenter double blind, randomized, placebo-controlled parallel group study evaluating the efficacy and safety of grass (*Phleum pratense*) sublingual tablet (SCH 697243) in adults age 18-65 with a history of grass pollen induced ARC with or without asthma.

This study was an approximately 19-month study including an observational period during Year 1 2008 Grass Pollen Season (GPS), with no administration of investigational medicinal product (IMP), and a treatment period during Year 2 2009 GPS, with randomization to either SCH 697243 or placebo.

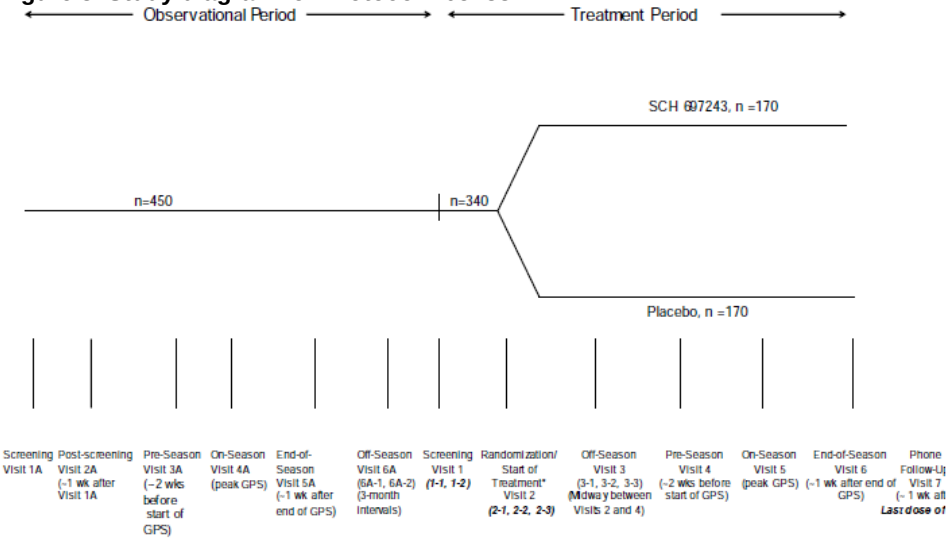
The purpose of the observation period was to characterize the subjects to allow for exclusion of subjects who do not present a clear increase in symptoms and need for rescue medication during pollen exposure. However, participation in the in the observational period was not a prerequisite for randomization into the treatment period.

In the treatment period, subjects were treated once daily with either SCH 697243 or placebo for approximately 16 weeks prior to the GPS and during the GPS.

Approximately 450 subjects were recruited during the observation period. In the treatment period, subjects were to be randomized in a 1:1 ratio to receive either SCH 697243 or placebo once daily for approximately 16 weeks before and during the entire GPS. Approximately 8 to 30 subjects per site were to be randomized. Assuming a dropout rate of 25% in the observational period, up to 450 subjects could be enrolled in the observational period in order to ensure a total of approximately 340 randomized subjects in the treatment period.

Subjects visited the study site for at least nine visits during the treatment period. 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 3. Study diagram for Protocol P05238.



Extracted from original BLA STN 125473/000; Module 5, CSR p05238, Vol 1, Page 35

Reviewer's comment: The study was well designed to determine efficacy and safety of the product, and was consistent with the pre-IND proposal.

The schedule of study visits is shown in Table 25.

Table 25. Study Schedule including survey for AE of Protocol P05238

Visit Name[a]	**1A**	**2A**	**3A**	**4A**	**5A**	**6A (6A-1, 6A-2)**	**1-1**	**1-2**	**2-1**	**2-2**	**2-3**	**3 (3-1, 3-2, 3-3)**[a]	**4**	**5**	**6**	**7**	
Visit Description	**Scr**	**Post-Scr**	**Pre**	**On**	**End**	**Off**	**Scr**	**Scr**	**Ran**			**Off**	**Pre**	**On**	**End**	**Tel**	**Uns**[b]
Time Point		**~1 wk After Scr**	**~2 wk Before Anticipa-ted Start of GPS**	**In Peak GPS**[c]	**~1 wk After End of GPS**	**~3-month inter-vals**			**1 wk After Visit 1-1 or 1-2**			**Midway Be- tween Visit 2-3 and 4**	**~2 wk Before Anticipa-ted Start of GPS**	**In Peak GPS**[c]	**~1 wk After End of GPS**	**~1 wk After last dose of IMP**	
Period	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treatment**	**Treatme-nt**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treat-ment**
Week[d]	**-2 to -4**	**-1 to -3**	**Day 0**	**6 to 7**	**13 to 14**	**25 to 26**	**-1 to -40 wks**	**-1 to -40 wks**	**Day 1**	**Day 2**	**Day 3**	**5 to 7**	**10 to 14**	**19 to 20**	**26 to 27**	**27 to 28**	
Informed Consent[e]	X						X[f]										
Inclusion/Exclusion Criteria	X	X					X	X[f]	X								
Demography	X						X[f]										
Body Height/Weight	X						X										
Medical History	X						X										
Assess/Record Concomitant Medication	X	X	X	X	X	X	X	X[f]	X	X	X	X	X	X	X		X
Physical Examination	X				X		X								X		X
Vital Signs	X		X	X	X	X	X	X[f]	X	X	X	X	X	X	X		X
Electrocardiogram							X										
Pulmonary Function Tests	X		X	X	X		X						X	X	X		X
Safety Laboratory Assessments	X	rev					X	rev[f]	rev						X		X
Urine Pregnancy Test (Female subjects of Childbearing Potential)	X		X	X	X	X	X	X[f]	X			X	X	X	X		X
Skin Prick Test	X						Xf										

Visit Name[a]	**1A**	**2A**	**3A**	**4A**	**5A**	**6A (6A-1, 6A-2)**	**1-1**	**1-2**	**2-1**	**2-2**	**2-3**	**3 (3-1, 3-2, 3-3)**[a]	**4**	**5**	**6**	**7**	
Visit Description	**Scr**	**Post-Scr**	**Pre**	**On**	**End**	**Off**	**Scr**	**Scr**	**Ran**			**Off**	**Pre**	**On**	**End**	**Tel**	**Uns**[b]
Time Point		**~1 wk After Scr**	**~2 wk Before Anticipa-ted Start of GPS**	**In Peak GPS**[c]	**~1 wk After End of GPS**	**~3-month inter-vals**			**1 wk After Visit 1-1 or 1-2**			**Midway Be- tween Visit 2-3 and 4**	**~2 wk Before Anticipa-ted Start of GPS**	**In Peak GPS**[c]	**~1 wk After End of GPS**	**~1 wk After last dose of IMP**	
Period	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treatment**	**Treatme-nt**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treat-ment**
Week[d]	**-2 to -4**	**-1 to -3**	**Day 0**	**6 to 7**	**13 to 14**	**25 to 26**	**-1 to -40 wks**	**-1 to -40 wks**	**Day 1**	**Day 2**	**Day 3**	**5 to 7**	**10 to 14**	**19 to 20**	**26 to 27**	**27 to 28**	
Specific IgE	X						Xf										
Other Immunological Assessments	X		X	X	X		X							X	X		
IVRS	X						Xf		X			X	X	X		X	X
Issue/Review Paper Subject Diary Comments Card	X	X	X	X	X	X	X	Xf	X	X	X	X	X	X	X		X
Issue and Instruct in the Use of Electronic Diariesg		X							X								
Discuss Electronic Diary Recordings and Compliance			X	X	X					X	X	X	X	X	X		X
Discontinue Electronic Diary					X										X		X
Assess AEs		X	X	X	X	X	X	Xf	X	X	X	X	X	X	X	X	X
Dispense Self-Injectable Epinephrine, Instruct in its Use, Provide Educational Information and written Anaphylaxis Emergency Action Plan									X								X

Visit Name[a]	**1A**	**2A**	**3A**	**4A**	**5A**	**6A (6A-1, 6A-2)**	**1-1**	**1-2**	**2-1**	**2-2**	**2-3**	**3 (3-1, 3-2, 3-3)**[a]	**4**	**5**	**6**	**7**	
Visit Description	**Scr**	**Post-Scr**	**Pre**	**On**	**End**	**Off**	**Scr**	**Scr**	**Ran**			**Off**	**Pre**	**On**	**End**	**Tel**	**Uns**[b]
Time Point		**~1 wk After Scr**	**~2 wk Before Anticipa-ted Start of GPS**	**In Peak GPS**[c]	**~1 wk After End of GPS**	**~3-month inter-vals**			**1 wk After Visit 1-1 or 1-2**			**Midway Be- tween Visit 2-3 and 4**	**~2 wk Before Anticipa-ted Start of GPS**	**In Peak GPS**[c]	**~1 wk After End of GPS**	**~1 wk After last dose of IMP**	
Period	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treatment**	**Treatme-nt**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treat-ment**
Week[d]	**-2 to -4**	**-1 to -3**	**Day 0**	**6 to 7**	**13 to 14**	**25 to 26**	**-1 to -40 wks**	**-1 to -40 wks**	**Day 1**	**Day 2**	**Day 3**	**5 to 7**	**10 to 14**	**19 to 20**	**26 to 27**	**27 to 28**	
Verify That Subject has Self-Injectable Epinephrine and Instruct in Its Use										X	X	X	X	X			X
Examination of oral cavity									X	X	X	X	X	X	X		X
On-site dosing of IMP									X	X	X						
Dispense IMP[h]											X	X	X	X			X
Check/Collect IMP												X	X	X	X		X
Dispense Rescue Medication			X	X									X	X			X
Check/Collect Rescue Medication				X	X									X	X		X
Collect Self-Injectable Epinephrine															X		
Compliance and Drug Accountability				X	X		X		X	X	X	X	X	X	X		X
Collect Pharmacogenetic Sample[i]																	

Visit Name[a]	**1A**	**2A**	**3A**	**4A**	**5A**	**6A (6A-1, 6A-2)**	**1-1**	**1-2**	**2-1**	**2-2**	**2-3**	**3 (3-1, 3-2, 3-3)**[a]	**4**	**5**	**6**	**7**	
Visit Description	**Scr**	**Post-Scr**	**Pre**	**On**	**End**	**Off**	**Scr**	**Scr**	**Ran**			**Off**	**Pre**	**On**	**End**	**Tel**	**Uns**[b]
Time Point		**~1 wk After Scr**	**~2 wk Before Anticipa-ted Start of GPS**	**In Peak GPS**[c]	**~1 wk After End of GPS**	**~3-month inter-vals**			**1 wk After Visit 1-1 or 1-2**			**Midway Be- tween Visit 2-3 and 4**	**~2 wk Before Anticipa-ted Start of GPS**	**In Peak GPS**[c]	**~1 wk After End of GPS**	**~1 wk After last dose of IMP**	
Period	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Observa-tional**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treatment**	**Treatme-nt**	**Treat-ment**	**Treat-ment**	**Treat-ment**	**Treat-ment**
Week[d]	**-2 to -4**	**-1 to -3**	**Day 0**	**6 to 7**	**13 to 14**	**25 to 26**	**-1 to -40 wks**	**-1 to -40 wks**	**Day 1**	**Day 2**	**Day 3**	**5 to 7**	**10 to 14**	**19 to 20**	**26 to 27**	**27 to 28**	
Dispense PEF Meter, Train/Perform Measurements, Review Results (asthmatic subjects in countries where required)									X	X	X	X	X	X	X		X

a: All subjects were to complete a minimum of one Visit 3 (ie, Visit 3-1) approximately 4 to 6 weeks following Visit 2-3. However, if the time between Visit 3-1 and Visit 4 was estimated to be beyond a 4 to 6 week interval, then the subject was to return to the site for Visit 3-2 and possibly Visit 3-3 (if the interval between Visit 3-2 and Visit 4 was estimated to be beyond a 4 to 6 week interval). A maximum of 3 'Visit 3' could be completed for each subject.
b: Unscheduled Visits occurred as necessary. A telephone contact between the investigator/designee and the subject was to occur 2 to 4 days after the visit to ensure that asthma symptoms were improving and to schedule a follow-up visit 7 to 10 days after the unscheduled visit. Study procedures were to be performed as deemed necessary by the investigator/designee.
c: The visit was required to take place in the anticipated peak grass pollen season.
d: The weeks were estimates, and may have varied for each site depending on the presumed duration of each site's GPS.
e: Informed consent was to be obtained before any trial related procedures were performed.
f: All Visit 1-2 procedures were to be performed for new subjects only.
g: Rhinoconjunctivitis and asthma symptoms scores, and VAS were to be recorded in the electronic diary by the subject on a daily basis from Visits 2A to 5A and from Visits 2-1 to 6. Use of rescue medication was to be recorded in the electronic diary by the subject on a daily basis from Visits 3A to 5A and from Visits 4 to 6. IMP compliance was to be recorded daily by the subject from Visits 2-1 to 6. Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities (RQLQ(S)) was to be completed at Visit 2A, 3A, 4A, and 5A, 2-1, and then weekly from Visits 4 to 6. Baseline subject pharmacoeconomic assessment was to be completed at Visits 2A and 2-1. Work Productivity and Activity Impairment-Allergy Specific Questionnaire (WPAI-AS) was to be completed at Visits 2A, 4A, 5A, 2-1, 5, and 6. Overall Treatment Effect (OTE) Global Questionnaire was to be completed at Visits 3A, 4A, 5A, 4, 5, and 6.
h: A telephone contact between the investigator/designee and the subject was to occur daily for the first 4 days of at-home administration of IMP for AE

assessment. IMP supply was to be checked and re-dispensed as necessary.
i: Informed consent for pharmacogenetic samples was required to be obtained before the DNA sample.
Abbreviations: Visit Description: Scr = Screening Visit, Ran = Randomization Visit, Off = Off-season Visit, Pre = Pre-season Visit, On = On-season Visit, End = End-of-season Visit, Uns = Unscheduled Visit; GPS = grass pollen season; IMP = investigational medicinal product; AE = adverse event; IVRS = interactive voice response system; PEF = peak expiratory flow, Tel = telephone, wk = week, rev = review.
Extracted from original BLA 125473/000, Module 5, CSR P05238; Pages 36-39 of 2569

6.3.3 Population Protocol P05238

Key Inclusion Criteria:

1. Subject was 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 grass (with or without asthma) diagnosed by a physician and received treatment for their disease during the previous GPS.
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 *Phleum pratense* at the Screening Visit.
4. Subject must have been positive for specific IgE against *Phleum pratense* (≥ IgE Class 2) at the Screening Visit.
5. Subject must have had an FEV1 ≥70% of predicted value at the Screening Visit.
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 GPS.
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. Subject with sufficient pre-seasonal data in the observational period was not eligible to continue in the treatment period if the subject:
    a. did not experience an increase in rhinoconjunctivitis symptom score of equal to or greater than 4 above the pre-seasonal average symptom score for at least 2 days
    b. did not use allergy rescue medication for at least 2 days, during the observational period Year 1 2008 GPS. (applied only to the treatment period and for those subjects who had participated in the observation period.)

6.3.4 Study Treatments or Agents Mandated by Protocol P05238

Table 26. Study treatments in Protocol 05238

Treatment	Active Ingredients	Dosage Form	Dose/Strength
SCH 697243[a]	*Phleum pratense* grass pollen allergen extract	Rapidly dissolving tablet administered sublingually once daily	2800 BAU (*Phleum pratense* extract)
Placebo	None	Rapidly dissolving tablet administered sublingually once daily	NA

BAU = Bioequivalent Allergy Unit; NA = Not applicable
Extracted from the original BLA STN 125473/000; Module 5, CSR p05238, Vol 1, Page 47

The lot numbers of the study drug and placebo were not provided.

6.3.5 Directions for Use Protocol P05238

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

6.3.6 Sites and Centers Protocol P05238
This study was performed at 59 sites in the United States and 10 sites in Canada.

6.3.7 Surveillance/Monitoring Protocol P05238
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.

6.3.8 Endpoints and Criteria for Study Success Protocol P05238
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 entire grass pollen season (GPS).

The key secondary endpoints were:
1. The average rhinoconjunctivitis DSS for the entire GPS
2. The average rhinoconjunctivitis DMS for the entire GPS
3. The average weekly rhinoconjunctivitis quality of life total score for the entire GPS.

6.3.9 Statistical Considerations & Statistical Analysis Plan Protocol P05238
For the treatment period, the primary efficacy endpoint of the combined (sum of) rhinoconjunctivitis DSS and DMS averaged over the entire GPS was to be evaluated using a linear model with asthma status, study site, and treatment group as fixed effects. This model was to allow for heterogeneous variance estimates for each treatment group.

In the observational period, up to 450 subjects were to be enrolled. Assuming a 25% dropout from the observational period, approximately 340 subjects were to be enrolled in the treatment period. New subjects were also to be enrolled after the start of the Year 1 2008 observational period GPS if needed to meet the targeted sample size. In the treatment period, the subjects were to be randomized in a 1:1 ratio to either SCH 697243 or placebo. With approximately 170 subjects per group, the study was able to detect the following difference from placebo in the primary endpoint with 88% power at a 5% level of significance (2-sided test):

For the primary analysis, there was no imputation of missing data. The combined average score was based on the available number of days of data. The primary analysis was supplemented by sensitivity analyses using various imputation techniques, which were specified in the statistical analysis plan. However, for rhinoconjunctivitis DMS, if rescue medication use was missing on any single day of the diary card, it was assumed to be “no use” and a score of zero was assigned in such cases as a convention.

For each of the primary and key secondary endpoints of TCS, DSS, and DMS, 11.54% (24/208) of subjects in the SCH 697243 group and 8.00% (18/225) of subjects in the placebo group had no data during GPS.

Please refer to the Statistical Review for more information.

6.3.10 Study Population and Disposition Protocol P05238

6.3.10.1 Populations Enrolled/Analyzed Protocol P05238
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 Harmonisation (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 IMP.

6.3.10.1.1 Demographics Protocol P05238
Table 27 shows key demographic data from Study P05238. Subjects were equally distributed between the study drug and placebo groups for each of these variables, as well as weight, height, BMI, and duration of ARC (not shown).

Table 27. Key Demographics Study P05238

	SCH 697243 2800 BAU n=213	Placebo n=225	Total N=438
Sex (n,%)			
Female	109 (51)	112 (50)	221 (50)
Male	104 (49)	113 (50)	217 (50)
Race (n,%)			
White	182 (85)	187 (83)	369 (84)
Non-White	31 (15)	38 (17)	69 (16)
Asian	4 (2)	9 (4)	13 (3)
Black or African American	21 (10)	21 (9)	42 (10)
Multiracial	6 (3)	5 (2)	11 (3)
Native Hawaiian or Other Pacific Islander	0	3 (1)	3 (1)
Age (yrs)			
Mean (SD)	35.9 (11.1)	35.9 (9.8)	35.9 (10.5)
Median	36.0	36.0	36.0
Range	18-63	18-61	18-63
Age (n,%)			
18 - <50	189 (89)	208 (92)	397 (91)
50 - <65	24 (11)	17 (8)	41 (9)
Pre-Seasonal Duration of Treatment (days)			
Mean (SD)	118.88 (17.75)	119.52 (17.57)	119.21 (17.64)
Median	118.0	119.0	119.0
Range Missing[b]	53.0-158.0 0	51.0-166.0 1	51.0-166.0 1

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6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population Protocol P05238

Of the 438 subjects, 45 (21%) subjects in the treatment group and 59 (26%) subjects in the Placebo group had asthma.

6.3.10.1.3 Subject Disposition Protocol P05238

Table 28. Disposition of randomized study subjects Protocol P05238

Disposition of Subjects	SCH 697243 (2800 BAU)	Placebo Number (%) of Subjects	Total Number (%) of Subjects
Treated	213 (100)	225 (100)	438 (100)
Discontinued Treatment Period	38 (18)	33 (15)	71 (16)
Adverse Event	11 (5)	8 (4)	19 (4)
Lost to follow-up	5 (2)	4 (2)	9 (2)
Subject did not wish to continue for unrelated to assigned study treatment	9 (4)	8 (4)	17 (4)
Noncompliance with protocol	12 (6)	12 (5)	24 (5)
Did not meet protocol eligibility	1 (<1)	1 (<1)	2 (<1)
Completed Treatment Period	175 (82)	192 (85)	367 (84)

Extracted from the original BLA STN 125473/000; Module 5, CSR p05238, Vol 1, Page 83

6.3.11 Efficacy Analyses Protocol P05238

6.3.11.1 Analyses of Primary Endpoint(s) Protocol P05238
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 entire grass pollen season 2007, divided by the number of subject diary recordings of that score during the entire grass pollen season. The TCS is shown in Table 29 shows the TCS for the treatment and placebo groups and the change in the TCS for the treatment relative to placebo.

Table 29. TCS of treatment and placebo groups P05238

Treatment	Number of Subjects	Total Combined Score (adjusted mean)	Percent change in TCS relative to placebo Point estimate	Percent change in TCS relative to placebo 95% CI
Grastek	184	5.08	-20.0 %	-33%, -6%
Placebo	207	6.39		

Extracted from the original BLA STN 125473/000; Module 5, CSR p05238, Vol 1, Page 99

6.3.11.2 Analyses of Secondary Endpoints Protocol P05238
The two key secondary endpoints are the DSS and DMS, which are added together to calculate the TCS. Tables 30 and 31 show that the DSS and RMS of the FAS during the entire GPS. Similar to the TCS, the point estimates of these two secondary variables were acceptable evidence of efficacy, but the 95% lower CI of -6% and +5% were not.

Table 30. DSS of treatment and placebo groups P05238

Treatment	Number of Subjects	Daily Symptom Score (adjusted mean)	Percent change in DSS relative to placebo Point estimate	Percent change in DSS relative to placebo 95% CI
Grastek	184	3.83	-18.0%	-19%, -6%
Placebo	207	4.69		

Extracted from the original BLA STN 125473/000; Module 5, CSR p05238, Vol 1, Page 99

Table 31. DMS of treatment and placebo groups P05238

Treatment	Number of Subjects	Daily Medication Score (median)	Percent change in DMS relative to placebo Point estimate	Percent change in DMS relative to placebo 95% CI
Grastek	184	1.25	-26 %	-49%, +5%
Placebo	207	1.70		

Extracted from the original BLA STN 125473/000; Module 5, CSR p05238, Vol 1, Page 103

6.3.11.3 Subpopulation Analyses Protocol P05238
There were 22 and 30 asthmatics (~12% and 14.5%, respectively) in the treatment and placebo groups, respectively. All had mild asthma. Use of asthma medications was scored; the study drug group use of rescue medication was decreased by 46% compared to the control group; the lower 95% CI interval was 12.4%.

6.3.11.4 Dropouts and/or Discontinuations Protocol P05238
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 grass pollen season did not contribute to the efficacy analyses.

6.3.11.5 Exploratory and Post Hoc Analyses Protocol P05238
None

6.3.12 Safety Analyses Protocol P05238

6.3.12.1 Methods Protocol P05238
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 25 (above).

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.

6.3.12.2 Overview of Adverse Events Protocol P05238
A total of 76.9% of subjects reported an AE during the treatment period. Overall, AEs were reported by a total of 82.6% of subjects in the SCH 697243 group and 71.6% of subjects in the placebo group. Table 32 shows treatment-emergent AE that were reported in > 2% of study subjects. Consistent with other SLIT studies, the category “Gastrointestinal Disorders” (which includes the mouth), and the symptom “Throat Irritation” were increased the treatment group. There were also differences in the rate of respiratory infections between the study drug and placebo groups that are not consistently observed in other studies of this drug and of SLIT in general.

Table 32. Treatment-emergent AE that reported in >2% subjects, Protocol 05038

	SCH 697243 2800 BAU (n=213) Number (%) of Subjects	Placebo (n=225) Number (%) of Subjects	Total (N=438) Number (%) of Subjects
Subjects Reporting Any Adverse Event	155 (72.8)	62 (27.6)	217 (49.5)
Ear and Labyrinth Disorders			
Ear Pruritus	42 (19.7)	3 (1.3)	45 (10.3)
Eye Disorders			
Eye Pruritus	9 (4.2)	7 (3.1)	16 (3.7)
Gastrointestinal Disorders			
Abdominal Discomfort	5 (2.3)	1 (0.4)	6 (1.4)
Dyspepsia	6 (2.8)	0	6 (1.4)
Hypoesthesia Oral	6 (2.8)	3 (1.3)	9 (2.1)
Lip Swelling	10 (4.7)	1 (0.4)	11 (2.5)
Nausea	8 (3.8)	2 (0.9)	10 (2.3)
Edema Mouth	17 (8.0)	1 (0.4)	18 (4.1)
Oral Pruritus	75 (35.2)	7 (3.1)	82 (18.7)
Paresthesia Oral	29 (13.6)	5 (2.2)	34 (7.8)
Stomatitis	16 (7.5)	1 (0.4)	17 (3.9)
Swollen Tongue	10 (4.7)	0	10 (2.3)
Tongue Disorder	8 (3.8)	0	8 (1.8)
General Disorders and Administration Site Conditions			
Chest Discomfort	8 (3.8)	1 (0.4)	9 (2.1)
Nervous System Disorders			
Headache	7 (3.3)	3 (1.3)	10 (2.3)
Paresthesia	9 (4.2)	1 (0.4)	10 (2.3)
Respiratory, Thoracic and Mediastinal Disorders			
Dry Throat	6 (2.8)	1 (0.4)	7 (1.6)
Pharyngeal Erythema	5 (2.3)	1 (0.4)	6 (1.4)
Pharyngeal Edema	14 (6.6)	0	14 (3.2)
Rhinorrhea	6 (2.8)	3 (1.3)	9 (2.1)
Throat Irritation	62 (29.1)	11 (4.9)	73 (16.7)
Skin and subcutaneous Disorders			
Pruritus	10 (4.7)	4 (1.8)	14 (3.2)
Urticaria	1 (0.5)	5 (2.2)	6 (1.4)

6.3.12.3 Deaths Protocol P05238
There was one death, a 28 year-old male subject (Subject 73/013699; SCH 697243 group) who suffered a multiple drug overdose, where toxicology revealed hydrocodone, meprobamate, and carisoprodol; The subject had not taken study medication for approximately 1 month prior to the event. This event was not related to the study drug.

6.3.12.4 Nonfatal Serious Adverse Events Protocol P05238
There were no systemic allergic events, and the only "life-threatening" event was the death due to multiple drug overdose. There were more severe AEs reported in the placebo group (9 subjects) compared with the SCH 697243 group.

The following events, however, were observed only in the study drug group (one subject each): throat irritation, dyspnea, middle ear effusion, diarrhea, and oral pruritus.

Two subjects used auto-injectable epinephrine. The first experienced dysphagia, uvular edema, pharyngeal edema, and flush/macular rash on the chest and back with associated pruritus and chest discomfort within minutes following the first dose of IMP. The subject did not experience wheezing or respiratory distress, and there was no hypotension. The subject was also treated with loratadine and prednisone, and was released within one hour. The investigator listed the event as mild in severity, and the subject was discontinued from the trial.

Reviewer's comment: This is a Grade 2 systemic reaction that may in some circumstances be considered a severe event.

The other use of auto-injectable epinephrine was a subject in the placebo group in the context of an anxiety attack. The subject was discontinued from the trial.

6.3.12.5 Adverse Events of Special Interest (AESI) Protocol P05238
The following events were observed only in the study drug group (one subject each): throat irritation, dyspnea, middle ear effusion, diarrhea, and oral pruritus.

Two subjects used auto-injectable epinephrine. The first experienced dysphagia, uvular edema, pharyngeal edema, and flush/macular rash on the chest and back with associated pruritus and chest discomfort within minutes following the first dose of IMP. The subject did not experience wheezing or respiratory distress, and there was no hypotension. The subject was also treated with loratadine and prednisone, and was released within one hour. The investigator listed the event as mild in severity, and the subject was discontinued from the trial.

Reviewer's comment: This is a Grade 2 systemic reaction that may in some circumstances be considered a severe event.

The other use of auto-injectable epinephrine was a subject in the placebo group in the context of an anxiety attack. The subject was discontinued from the trial.

6.3.12.6 Clinical Test Results Protocol P05238
There were no clinical test results that reflect efficacy or of concern regarding the safety of GRASTEK.

6.3.12.7 Dropouts and/or Discontinuations Protocol P05238
Additional events of interest that precipitated discontinuation from the P05238 were:

- A 29 year old female subject who developed increased asthma symptoms on day 53 of study drug. The symptoms were considered of moderate severity. The subject received treatment with albuterol and discontinued from the study. The subject continued to have increased asthma symptoms following study discontinuation.
- A 26 year old male subject developed gingival swelling immediately following the 11th dose of study drug. The event was assessed as moderate in severity. The subject did not require any treatment for the event. The subject discontinued from the study following this event.
- A 23 year old female subject developed chest discomfort described as sub-sternal pressure following her 5th dose of study drug. No treatment was required for the event. The subject had experienced mild local application site reactions with prior doses. The subject discontinued from the study following the chest discomfort.
- A 35 year old asthmatic subject developed sublingual edema and shortness of breath at home following the 8th dose study drug. She had multiple AEs during the first week of dosing which included local reactions, shortness of breath and chest tightness. She received albuterol on day 3 and 9 of study drug. An unscheduled visit was conducted on day 9 of study medication. The subject had normal PFTs and did not require any further intervention. The subject discontinued from the study on day 9 of IMP. The subject continued to complain of intermittent chest tightness for 1 week following discontinuation from the trial.
- A 40 year old subject developed moderate pharyngeal edema on day 11 of study drug. The edema lasted for a few hours following IMP. No treatment was administered for the reaction. The subject discontinued from the study following the event.
- A 42 year old female subject developed upset stomach on day 4 of study drug. The abdominal discomfort was assessed as moderate in intensity and possibly related to study medication. There was no medication administered to treat the event. Due to the abdominal discomfort, the subject discontinued from the study.

6.3.13 Study Summary and Conclusions Protocol P05238
In Study P05238, GRASTEK was associated with treatment related AE that are predominantly mild or moderate. Most often, these AE did not precipitate withdrawal from the study. There was one systemic reaction (episode of anaphylaxis) in response to the GRASTEK, which occurred after the first dose of therapy; this subject withdrew from the trial.

Study P05238 was well designed to meet its clinical endpoint, an improvement in the TCS in the GRASAX study drug group. The point estimate of that improvement was better than the minimal 15% considered acceptable by CBER. The 95% CI were not criteria for success of this US study, and did not meet CBER's requirements for proof of efficacy.

The results of this study are considered supportive for efficacy and safety of GRAZAX (GRASTEK) for the treatment of adults with ARC.

6.4 Trial #4: Protocol P05239

A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of Sublingual Immunotherapy with SCH 697243 (Phleum Pratense) in Children 5 to <18 Years of Age with a History of Grass Pollen Induced Rhinoconjunctivitis With or Without Asthma

Reviewer's comment: This study was run concurrently with Trial #1, P05238. Except for the study population (children and adolescents vs. adults), the study design was essentially identical, including the planned number subjects (450 recruited, 340 randomized equally between treatment and placebo), and the schedule of study visits.

6.4.1 Objectives (Primary, Secondary, etc) Protocol P05239
See Objectives Trial P05238.

6.4.2 Design Overview Protocol P05239
See design overview for Protocol P05238. Study size and schedule of visits are identical.

6.4.3 Population Protocol P05239
Except for age of subjects, (5-17 years inclusive), the intended population is identical to Protocol P05238.

6.4.4 Study Treatments or Agents Mandated by Protocol P05239
See Section 6.3.4, Protocol P05238.

6.4.5 Directions for Use Protocol P05239
See Section 6.4.5, Protocol P05238.

6.4.6 Sites and Centers Protocol P05239
Protocol P05239 was conducted at 58 centers in the United States and 12 centers in Canada. The distribution of sites is similar to that of P05238.

6.4.7 Surveillance/Monitoring Protocol P05239
See Section 6.3.7, Protocol P05238.

6.4.8 Endpoints and Criteria for Study Success Protocol P05239
Primary and Secondary Efficacy Endpoints:
See Section 6.3.8, P05238

6.4.9 Statistical Considerations & Statistical Analysis Plan Protocol P05239
Identical to Section 6.1.9, Protocol P05238.

6.4.10 Study Population and Disposition Protocol P05239

6.4.10.1 Populations Enrolled/Analyzed Protocol P05239
See Section 6.1.10.1, Protocol P05238.

6.4.10.1.1 Demographics Protocol P05239
Table 33 shows that subjects are distributed similarly among the study drug and placebo groups according to sex, race, age, and asthma status.

Table 33. Demographics of subjects in Protocol P05239.

	SCH 697243 2800 BAU n=175	Placebo n=169	Total N=344
Sex (n,%)			
Female	57 (33)	64 (38)	121 (35)
Male	118 (67)	105 (62)	223 (65)
Race (n,%)			
White	153 (87)	149 (88)	302 (88)
Non-White	22 (13)	20 (12)	42 (12)
Asian	5 (3)	1 (1)	6 (2)
African American	12 (7)	13 (8)	25 (7)
Multiracial	4 (2)	5 (3)	9 (3)
Age (n,%)			
2- <6	0	1 (1)	1 (<1)
6 - <12	73 (42)	60 (36)	133 (39)
12 ≤ 18	102 (58)	108 (64)	210 (61)
Asthma Status (n,%)			
Asthmatics	46 (26)	44 (26)	90 (26)
Non-Asthma ics	129 (74)	125 (74)	254 (74)

From original BLA STN 125473/000; Module 5, CSR p05239, Page 91 of 2350

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population Protocol P08067

As shown above, distribution to the placebo and study drug groups according to asthma status was similar, as was the percent predicted FEV_1 (not shown).

6.4.10.1.3 Subject Disposition Protocol P05239

Table 34. Disposition of subjects in Protocol P05239

Disposition of Subjects	SCH 697243 (2800 BAU)	Placebo Number (%) of Subjects	Total Number (%) of Subjects
Treated	213 (100)	225 (100)	438 (100)
Discontinued Treatment Period	38 (18)	33 (15)	71 (16)
Adverse Event	11 (5)	8 (4)	19 (4)
Lost to follow-up	5 (2)	4 (2)	9 (2)
Subject did not wish to continue for reasons unrelated to assigned study treatment	9 (4)	8 (4)	17 (4)
Noncompliance with protocol	12 (6)	12 (5)	24 (5)
Did not meet protocol eligibility	1 (<1)	1 (<1)	2 (<1)
Completed Treatment Period	175 (82)	192 (85)	367 (84)

Extracted from the original BLA STN 125473/000; Module 5, CSR p05239, Page 85

6.4.11 Efficacy Analyses Protocol P08067

6.4.11.1 Analyses of Primary Endpoint(s) Protocol P08067
The primary efficacy variable to address the treatment effect for this study was the Total Combined Score (TCS) based upon the combined (sum of) rhinoconjunctivitis daily symptom score (DSS) and daily medication score (DMS) averaged over the entire grass pollen season. Table 35 shows that Protocol P05239 met its primary endpoint, with a -26% difference between placebo and treatment groups, and a lower limit of the 95% confidence interval of 10%.

Table 35. Summary and analysis of the TCS during the entire grass pollen season Study P05238

Treatment	Number of Subjects	Total Combined Score (adjusted mean)	Percent change in TCS relative to placebo Point estimate	Percent change in TCS relative to placebo 95% CI
Grastek	149	4.62	-26.1%	-38.2%, -10.1%
Placebo	158	6.25		

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6.4.11.2 Analyses of Secondary Endpoints Protocol P05239
The two key secondary endpoints are the DSS and DMS, which are added together to calculate the TCS. Tables 36 and 37 show that the DSS and RMS of the FAS during the entire GPS. In contrast to the TCS, while the point estimates of these two secondary variables were acceptable evidence of efficacy, the 95% lower CI of 9% and 4% were not. These data affirm the certainty of the DCS as the primary endpoint.

Table 36. Summary and analysis of the DSS during the entire GPS Study P05239

Treatment	Number of Subjects	Total Combined Score (adjusted mean)	Percent change in DSS relative to placebo Point estimate	Percent change in DSS relative to placebo 95% CI
Grastek	149	3.71	-25.0%	-36%, -9%
Placebo	158	4.91		

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Table 37. Summary and analysis of the DMS during the entire GPS P05239

Treatment	Number of Subjects	Total Combined Score (adjusted mean)	Percent change in DMS relative to placebo Point estimate	Percent change in DMS relative to placebo 95% CI
Grastek	149	0.91	-32%	-58%, -4%
Placebo	158	1.33		

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6.4.11.3 Subpopulation Analyses Protocol P08067
There were 15 and 21 asthmatics (~9% and 12.5%, respectively) in the treatment and placebo groups, respectively. All had mild asthma. Use of asthma medications was scored; there was no difference between the two groups.

6.4.11.4 Dropouts and/or Discontinuations Protocol P05239
For consideration of Dropouts or Discontinuations on efficacy data, see P05238 and the Statistician's review of GRASTEK.

6.4.11.5 Exploratory and Post Hoc Analyses Protocol P05239
None reviewed.

6.4.12 Safety Analyses Protocol P05239

6.4.12.1 Methods Protocol P05239
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.

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.

6.4.12.2 Overview of Adverse Events Protocol P05239
A total of 82% of subjects reported an AE during the treatment period, 86.3% of subjects in the SCH 697243 group and 77.5% of subjects in the placebo group. The most commonly reported AEs were oral pruritus and throat irritation (both of which were much more frequent in the treatment group). Also frequently reported but equally distributed among the two groups were nasopharyngitis, upper respiratory tract infection, oropharyngeal pain, headache, and cough. Table 20 shows all treatment emergent AE that were reported in at least 2% of study subjects.

Because of smaller airways in children, reviewers are attentive to safety signals such as the incidence severe shortness of breath. As with the adult treatment emergent AE, neither of these occurred in more than 2% of the study subjects.

Table 38. Treatment-emergent AE reported in > 2% of subjects in pediatric Protocol P05239

	SCH 697243 2800 BAU (n=175) Number (%) of Subjects	Placebo (n=169) Number (%) of Subjects	Total (N=343) Number (%) of Subjects
Subjects Reporting Any Adverse Event	122 (69.7)	43 (25.4)	165 (48.0)
Ear and Labyrinth Disorders			
Ear Pruritus	20 (11.4)	1 (0.6)	21 (6.1)
Eye Disorders			
Eye Pruritus	11 (6.3)	3 (1.8)	14 (4.1)
Gastrointestinal Disorders			
Dysphagia	5 (2.9)	0	5 (1.5)
Lip Swelling	13 (7.4)	0	13 (3.8)
Nausea	4 (2.3)	2 (1.2)	6 (1.7)
Oedema Mouth	18 (10.3)	1 (0.6)	19 (5.5)
Oral Pain	4 (2.3)	0	4 (1.2)
Oral Pruritus	68 (38.9)	6 (3.6)	74 (21.5)
Paraesthesia Oral	7 (4.0)	2 (1.2)	9 (2.6)
Stomatitis	26 (14.9)	2 (1.2)	28 (8.1)
Swollen Tongue	5 (2.9)	0	5 (1.5)
Nervous System Disorders			
Headache	7 (4.0)	4 (2.4)	11 (3.2)
Respiratory, Thoracic and Mediastinal Disorders			
Cough	6 (3.4)	0	6 (1.7)
Dry Throat	7 (4.0)	2 (1.2)	9 (2.6)
Nasal Congestion	7 (4.0)	1 (0.6)	8 (2.3)
Nasal Discomfort	5 (2.9)	0	5 (1.5)
Oropharyngeal Pain	14 (8.0)	4 (2.4)	18 (5.2)
Pharyngeal Erythema	13 (7.4)	3 (1.8)	16 (4.7)
Pharyngeal Edema	7 (4.0)	0	7 (2.0)
Sneezing	6 (3.4)	1 (0.6)	7 (2.0)
Throat Irritation	65 (37.1)	5 (3.0)	70 (20.3)
Skin and Subcutaneous Tissue Disorders			
Pruritus	6 (3.4)	6 (3.6)	12 (3.5)

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Most importantly, there appeared to be no increased safety signal in children 5-11 years of age. Among the 134 (73 treatment, 61 placebo) subjects in this age group, there was one episode of throat tightness (treatment) and three episodes of wheezing (2 in placebo group).

6.4.12.3 Deaths Protocol P05239
There were no deaths in this study.

6.4.12.4 Nonfatal Serious Adverse Events Protocol P05239

Severe AEs were reported by 11 subjects (6 in the placebo group). None were considered life-threatening. Table 39 lists the treatment related severe AE reported in Protocol P05239.

Table 39. Treatment related non-fatal severe AE

	SCH 697243 2800 BAU (n=175)	Placebo (n=169)	Total (N=343)
Subjects Reporting Any Adverse Event	5 (2.9)	6 (3.6)	11 (3.2)
Eye Disorders			
Eye Swelling	1 (0.6)	0	1 (0.3)
Xerophthalmia	0	1 (0.6)	1 (0.3)
Gastrointestinal Disorders			
Vomiting	0	1 (0.6)	1 (0.3)
General Disorders and Administration Site Conditions			
Fatigue	0	1 (0.6)	1 (0.3)
Infections and Infestations			
Gastroenteritis Viral	1 (0.6)	0	1 (0.3)
Upper Respiratory Tract Infection	0	1 (0.6)	1 (0.3)
Viral Infection	1 (0.6)	0	1 (0.3)
Injury, Poisoning and Procedural Complications			
Anesthetic Complication	0	1 (0.6)	1 (0.3)
Ligament Rupture	0	1 (0.6)	1 (0.3)
Nervous System Disorders			
Headache	0	1 (0.6)	1 (0.3)
Migraine	1 (0.6)	0	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders			
Asthma	0	1 (0.6)	1 (0.3)
Nasal Congestion	0	1 (0.6)	1 (0.3)
Oropharyngeal Pain	0	1 (0.6)	1 (0.3)
Skin and Subcutaneous Tissue Disorders			
Pruritus	1 (0.6)	0	1 (0.3)
Pruritus Generalized	1 (0.6)	0	1 (0.3)

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There were five additional serious AE during the study. None of these subjects received the study drug: One subject was a 9 yo male with status asthmaticus who was not randomized to any treatment. The other four subjects were in the placebo group: a 13 yo male with idiopathic thrombocytopenic purpura, a 12 yo female with lymphadenitis, a 16 yo female with pyelonephritis, and a 17 yo male who experienced an anesthetic accident. None of these AE were fatal.

6.4.12.5 Adverse Events of Special Interest (AESI) Protocol P05239
Three subjects (two in the SCH 697243 group) received epinephrine during the trial. Of these, one of the events in the study drug group was related to treatment. The 13 y.o. subject developed lip angioedema, slight dysphagia due to the sensation of a lump in the throat, and intermittent cough within minutes following the first dose of IMP administration. The subject did not experience wheezing, respiratory distress, urticaria, vomiting/diarrhea or hypotension. Epinephrine was administered to the subject and the symptoms resolved within minutes. The investigator graded this event as moderate in severity. The subject fully recovered from the event and was discontinued.

The other subject in the study drug group who was administered epinephrine was because an emergency physician thought that the subject's tonsils may be enlarged because of an allergic reaction. The child had viral pharyngitis. In addition, a 6 year old in the placebo group was treated with epinephrine for wheezing on Day 137 of the study.

There were two events that could possibly be considered a systemic event. The first was an 8-year-old subject who gagged immediately after the first dose of IMP (SCH 697243 group), which was followed by vomiting which resolved within a few minutes. The subject also complained of mild oral pruritus and was noted to have flushed cheeks. The subject did not have urticaria/angioedema, respiratory involvement, or hemodynamic compromise. No treatment was required. On Day 2 of administration, the subject gagged and had mild oral pruritus without any additional symptoms. The parents withdrew consent due to the recurrent gagging. The investigator's assessment was that this child had a particularly strong gag reflex and not a symptom of anaphylaxis.

The second subject was an 11-year-old subject who had shortness of breath, chest discomfort, pruritus of the neck and inside the mouth/ears, "heart racing," and pain in the mouth at home following the eighth dose of IMP (SCH 697243 group). The subject is not considered asthmatic, but may have exercise-induced symptoms. The subject did not require treatment for the reaction and did not notify the site of the event. The symptoms resolved with rest. The subject did not continue with the study following these events.

6.4.12.6 Clinical Test Results Protocol P05239
No clinically relevant changes were observed.

6.4.12.7 Dropouts and/or Discontinuations Protocol P05239
Eighteen subjects withdrew from the study because of AEs, 13 subjects in the study drug group and five in the placebo group. The reasons for withdrawal in the study drug group were chest discomfort, cough, rash, mouth edema, moderate dyspnea with non-cardiac chest pain and palpitations, abdominal discomfort, dysphagia, cough, oral pain vomiting, and pruritus.

Five subjects who withdrew due to these AE: migraine headache, conjunctival, eyelid, and nasal edema, conjunctivitis and asthma, and wheezing.

These AE are consistent with reports of SLIT therapy for environmental allergies, and most importantly, suggest that the safety profile of GRASTEK in children who fit the inclusion criteria of this study is similar to that of otherwise healthy adults with ARC.

6.4.13 Study Summary and Conclusions Protocol P05239

In Study P05239, GRASTEK was associated with treatment related AE that are predominantly mild or moderate, and that did not precipitate withdrawal from the study. There was one systemic reaction (episode of anaphylaxis) in response to the GRASTEK, which occurred after the first dose of therapy; this subject withdrew from the trial.

Study P05239 was well designed to meet its clinical endpoint, an improvement in the TCS in the GRASAX study drug group. The point estimate of that improvement was better than the minimal 15% considered acceptable by CBER. The 95% CI were not criteria for success of this US study, but the 95% CI UL was -10.1%, which meets CBER's requirements for proof of efficacy.

The results of this study are considered pivotal for efficacy and safety of GRAZAX (GRASTEK) for the treatment of children with ARC.

6.5 Trial #5: Protocol P08067

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of Grass (Phleum pratense) Sublingual Tablet (SCH 697243) in Subjects Between 5 and 65 Years of Age, with a History of Grass Pollen-Induced Rhinoconjunctivitis, With or Without Asthma (Protocol No. P08067)

6.5.1 Objectives (Primary, Secondary, etc.) Protocol P08067

See Protocol P05238 for Primary and Key secondary objectives of Protocol P08067.

6.5.2 Design Overview Protocol P08067

Protocol P08067 was designed similarly to P05238 and P05239 with the following key exceptions:

- Treatment with GRASTEK was initiated 12 weeks prior to the anticipated start of GPS (and throughout the 2012 GPS season) rather than 16 weeks.
- There was no "observation year prior to randomization and treatment.

Table 40. Study Schedule of P08067

Visit Number	**1**	**2**	**Telephone Contact[b]**	**Telephone Contact[b]**	**3 (3,3A,3B) c**	**4**	**5**	**6**	**7**	
Visit Description	**Screening**	**Randomization (Start of Treatment With Study Drug)**	**Tel**	**Tel**	**Off GPS**	**Pre GPS**	**On GPS**	**End (End of Treatment With Study Drug)**	**Tel**	**Uns[e]**
Time Point	**Up to 12 Months Prior to 2012 GPS**	**At Least 12 Weeks Prior to 2012 GPS**	**At Home Study Drug Administra - tion**	**At Home Study Drug Administra - tion**	**Midway Between Visit 2 and 4[c]**	**□2 weeks Before Anticipated Start of GPS**	**In Peak GPS[d]**	**□1 Week After End of GPS, No Later Than 31 JUL 2012**	**□7 Days After Visit 6**	
Study Day/Week[a]	**-48 to -0 Weeks**	**Day 1**	**Day 2[b]**	**Day 3[b]**	**Week 5 to 7[c]**	**Week 10 to 14**	**Week 19 to 20**	**Week 26 to 27**	**Week 28**	
Informed Consent/Assent[f]	X									
Inclusion/Exclusion Criteria	X	X								
Demographics	X									
Issue Subject Identification Card	X									
Body Height and Weight	X	X[g]								
Medical History	X	X								
Assess/Record Concomitant Medication	X	X	X[b]	X[b]	X	X	X	X		X
Physical Examination	X							X[h]		X
Vital Signs	X	X			X	X	X	X		X
Electrocardiogram[i]	X									
Pulmonary Function Tests	X	X[j]					X			X
Safety Laboratory Assessments	X	Rev								X[k]
Urine Pregnancy Test (Female Subjects of Childbearing Potential)[l]	X	X			X	X	X	X		X

Visit Number	**1**	**2**	**Telephone Contact[b]**	**Telephone Contact[b]**	**3 (3,3A,3B) c**	**4**	**5**	**6**	**7**	
Visit Description	**Screening**	**Randomization (Start of Treatment With Study Drug)**	**Tel**	**Tel**	**Off GPS**	**Pre GPS**	**On GPS**	**End (End of Treatment With Study Drug)**	**Tel**	**Uns[e]**
Time Point	**Up to 12 Months Prior to 2012 GPS**	**At Least 12 Weeks Prior to 2012 GPS**	**At Home Study Drug Administra - tion**	**At Home Study Drug Administra - tion**	**Midway Between Visit 2 and 4[c]**	**□2 weeks Before Anticipated Start of GPS**	**In Peak GPS[d]**	**□1 Week After End of GPS, No Later Than 31 JUL 2012**	**□7 Days After Visit 6**	
Study Day/Week[a]	**-48 to -0 Weeks**	**Day 1**	**Day 2[b]**	**Day 3[b]**	**Week 5 to 7[c]**	**Week 10 to 14**	**Week 19 to 20**	**Week 26 to 27**	**Week 28**	
Skin Prick Test	X									
IVRS	X	X			X	X	X		X	X
Issue/Instruct in the Use of Electronic Diaries[m]		X								
Issue/Instruct in the Use of Paper Diary Comment Cards		X								
Discuss/Review paper diary cards			X	X	X	X	X	X		
Discuss/Review Electronic Diary Recordings and Compliance			X	X	X	X	X	X		X
Interviewer-Administered Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ)[n]		X				X	X	X		
Discontinue and Collect Electronic Diary and *Paper Diary Comment Cards*								X		X

Visit Number	**1**	**2**	**Telephone Contact[b]**	**Telephone Contact[b]**	**3 (3,3A,3B) c**	**4**	**5**	**6**	**7**	
Visit Description	**Screening**	**Randomization (Start of Treatment With Study Drug)**	**Tel**	**Tel**	**Off GPS**	**Pre GPS**	**On GPS**	**End (End of Treatment With Study Drug)**	**Tel**	**Uns[e]**
Time Point	**Up to 12 Months Prior to 2012 GPS**	**At Least 12 Weeks Prior to 2012 GPS**	**At Home Study Drug Administra - tion**	**At Home Study Drug Administra - tion**	**Midway Between Visit 2 and 4[c]**	**□2 weeks Before Anticipated Start of GPS**	**In Peak GPS[d]**	**□1 Week After End of GPS, No Later Than 31 JUL 2012**	**□7 Days After Visit 6**	
Study Day/Week[a]	**-48 to -0 Weeks**	**Day 1**	**Day 2[b]**	**Day 3[b]**	**Week 5 to 7[c]**	**Week 10 to 14**	**Week 19 to 20**	**Week 26 to 27**	**Week 28**	
Self-Administered Rhinoconjunctivitis Quality of Life Questionnaire With Standardised Activities (RQLQ(S)12+)o		X				X	X	X		
Assess Compliance With RQLQ(S)12+							X	X		
Assessment of AEs		X	X b	X b	X	X	X	X	X	X
Pharmacogenetic Collection by Buccal Swabq		Xq								
Blood Sample for Specific IgE	X									
Examination of Oral Cavity	X	X			X	X	X	X		X
On-Site Dosing of Study Drug		X								
Dispense Study Drugp		X			X	X	X			X
Check/Collect Study Drug					X	X	X	X		X

Visit Number	**1**	**2**	**Telephone Contact[b]**	**Telephone Contact[b]**	**3 (3,3A,3B) c**	**4**	**5**	**6**	**7**	
Visit Description	**Screening**	**Randomization (Start of Treatment With Study Drug)**	**Tel**	**Tel**	**Off GPS**	**Pre GPS**	**On GPS**	**End (End of Treatment With Study Drug)**	**Tel**	**Uns[e]**
Time Point	**Up to 12 Months Prior to 2012 GPS**	**At Least 12 Weeks Prior to 2012 GPS**	**At Home Study Drug Administra - tion**	**At Home Study Drug Administra - tion**	**Midway Between Visit 2 and 4[c]**	**□2 weeks Before Anticipated Start of GPS**	**In Peak GPS[d]**	**□1 Week After End of GPS, No Later Than 31 JUL 2012**	**□7 Days After Visit 6**	
Study Day/Week[a]	**-48 to -0 Weeks**	**Day 1**	**Day 2[b]**	**Day 3[b]**	**Week 5 to 7[c]**	**Week 10 to 14**	**Week 19 to 20**	**Week 26 to 27**	**Week 28**	
Dispense Self Injectable Epinephrine, Instruct on Use, Provide Educational Information and Written Anaphylaxis										
Instruct Subject on proper use of Self Injectable Epinephrine and review Written Anaphylaxis Emergency Action Plan. Re- dispense if needed			X	X	X	X	X	X		X
Education regarding the possible signs and symptoms of systemic allergic reactions		X	X	X	X	X	X			
Dispense Rescue Medication						X	X			X
Check/Collect Rescue Medication							X	X		X
Check/Collect Self Injectable Epinephrine			X	X	X	X	X	X		X

Visit Number	**1**	**2**	**Telephone Contact[b]**	**Telephone Contact[b]**	**3 (3,3A,3B) c**	**4**	**5**	**6**	**7**	
Visit Description	**Screening**	**Randomization (Start of Treatment With Study Drug)**	**Tel**	**Tel**	**Off GPS**	**Pre GPS**	**On GPS**	**End (End of Treatment With Study Drug)**	**Tel**	**Uns[e]**
Time Point	**Up to 12 Months Prior to 2012 GPS**	**At Least 12 Weeks Prior to 2012 GPS**	**At Home Study Drug Administra - tion**	**At Home Study Drug Administra - tion**	**Midway Between Visit 2 and 4[c]**	**2 weeks Before Anticipated Start of GPS**	**In Peak GPS[d]**	**1 Week After End of GPS, No Later Than 31 JUL 2012**	**7 Days After Visit 6**	
Study Day/Week[a]	**-48 to -0 Weeks**	**Day 1**	**Day 2[b]**	**Day 3[b]**	**Week 5 to 7[c]**	**Week 10 to 14**	**Week 19 to 20**	**Week 26 to 27**	**Week 28**	
Compliance and Drug Accountability					X	X	X	X		X

then weekly from Visits 4 to 6.

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6.5.3 Population Protocol P08067
Children, adolescent, and adult (5 to 65 years of age) males and females with a history of grass pollen-induced allergic rhinoconjunctivitis with or without mild asthma were eligible for the study. The inclusion/exclusion criteria are similar to those in North American trials P05238 and P05239. As with those trials, enrollment of asthmatics was limited to those who were not treated with daily inhaled corticosteroids.

6.5.4 Study Treatments or Agents Mandated by Protocol P08067

Table 41. Batch numbers of Study Drug and Placebo Protocol P08067

Drug	MK-7243	Placebo
Strength	2800 BAU	Not Applicable
Batch Numbers	1194744	1194743

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6.5.5 Directions for Use Protocol P08067
One tablet sublingually daily.

6.5.6 Sites and Centers Protocol P08067
There were 173 Sites in this protocol; 145 sites in the US and 28 sites in Canada

6.5.7 Surveillance/Monitoring Protocol P08067
See Protocol P05238 and P05239.

6.5.8 Endpoints and Criteria for Study Success Protocol P08067
The primary efficacy endpoint was the average daily TCS during the entire GPS, calculated for a subject as the sum of daily TCS during GPS divided by the number of days with TCS data available during the GPS. For each site, GPS was defined as the first day of 3 consecutive recorded days with a pollen count of ≥10 grains/m3, to the last day of the last occurrence of 3 consecutive recorded days with a pollen count ≥10 grains/m3, with grass pollen season end date no later than 31 JUL 2012.

6.5.9 Statistical Considerations & Statistical Analysis Plan Protocol P08067
The statistical analysis and considerations for this trial is similar to those for P05238 and P05239. One key difference is that this trial was powered detect a 95% confidence limit upper limit of ≤ -10% in the % difference of TCS.

6.5.10 Study Population and Disposition Protocol P08067

6.5.10.1 Populations Enrolled/Analyzed Protocol P08067
The definitions of the Full Analysis Set, the Per Protocol Set and All Subjects analyzed are identical to Protocols P05238 and P05239.

6.5.10.1.1 Demographics Protocol P08067

Table 42. Demographics of subjects in Protocol 08067

	SCH 697243 2800 BAU n=175	Placebo n=169	Total N=344
Sex (n,%)			
Female	381 (51)	333 (44)	714 (48)
Male	371 (49)	416 (56)	787 (52)
Race (n,%)			
White	613 (82)	641 (86)	1254 (84)
Non-White	138 (18)	108 (14)	246 (16)
Am. Indian/ Alaskan Native	6 (1)	3 (<1)	9 (1)
Asian	36 (5)	28 (4)	64 (4)
Black or African American	74 (10)	61 (8)	135 (9)
Multiracial	19 (3)	16 (2)	35 (2)
Native Hawaiian or Other Pacific Islander	3 (<1)	0	3 (<1)
Missing	1 (<1)	0	1 (<1)
Ethnicity (n,%)			
Hispanic or Latino	50 (7)	40 (5)	90 (6)
Not Hispanic or Latino	702 (93)	709 (95)	1411 (94)
Age (yrs)			
Mean (SD)	32.9 (14.5)	33.5 (14.5)	33.2 (14.5)
Median	34.0	34.0	34.0
Range	5 – 65	5 – 65	5 – 65
Age (n,%)			
5 - <12	58 (8)	51 (7)	109 (7)
12 - <18	86 (11)	88 (12)	174 (12)
18 - <50	515 (68)	491 (66)	1006 (67)
50 - <65	89 (12)	116 (15)	205 (14)
65	4 (1)	3 (<1)	7 (<1)
Asthma Status			
No	570 (75.8)	563 (75.2)	1133 (75.5)
Yes	182(24.2)	186 (24.8)	368 (24.8)

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

6.5.10.1.2 Medical/Behavioral Characterization of the Enrolled Population Protocol P08067

Approximately 25% 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.

6.5.10.1.3 Subject Disposition Protocol P08067

A total of 1501 subjects were randomized at a total of 152 sites (127 sites from US;, 25 sites from Canada) to treatment assignment, and 1498 subjects received at least one dose of study medication: 753 subjects received MK-7243 and 745 received placebo. Of the 1498 subjects randomized and treated, a total of 1255 (84%) subjects overall completed the protocol-specified, double-blind treatment period, while 246 subjects (16%) discontinued investigational treatment early.

The primary reasons for study discontinuation were subject withdrew consent (91 subjects, 6% overall) and adverse events (73 subjects, 5% overall). The proportion of subjects on MK-7243 who discontinued due to an AE was higher than the proportion of subjects in the placebo group. There were no subjects who discontinued from the trial due to treatment failure.

Table 43. Disposition of Subjects, Study P08067

Subject Disposition	MK-7243 n	MK-7243 %	Placebo n	Placebo %	Total n	Total %
Randomized	752	(100)	749	(100)	1501	(100)
Full Analysis Set	744	(99)	744	(99)	1488	(99)
Per Protocol Set	684	(91)	683	(91)	1367	(91)
Discontinued Treatment Phase	149	(20)	97	(13)	246	(16)
Adverse Event	54	(7)	19	(3)	73	(5)
Lost To Follow-Up	16	(2)	16	(2)	32	(2)
Subject Withdrew Consent	52	(7)	39	(5)	91	(6)
Non-Compliance With Protocol	22	(3)	21	(3)	43	(3)
Did Not Meet Protocol Eligibility	3	(<1)	0		3	(<1)
Administrative	2	(<1)	2	(<1)	4	(<1)
Completed Treatment Phase	603	(80)	652	(87)	1255	(84)

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6.5.11 Efficacy Analyses Protocol P08067

6.5.11.1 Analyses of Primary Endpoint(s) Protocol P08067
The primary efficacy variable to address the treatment effect for this study was the Total Combined Score (TCS) based upon the combined (sum of) rhinoconjunctivitis daily symptom score (DSS) and daily medication score (DMS) averaged over the entire grass pollen season. Table 44 shows that Protocol P08067 met its primary endpoint, with a -26% difference between placebo and treatment groups, and a lower limit of the 95% confidence interval of -13%.

Table 44. Summary and analysis of the TCS during the entire grass pollen season Study P08067

Treatment	Number of Subjects	Total Combined Score (adjusted mean)	Percent change in TCS relative to placebo Point estimate	Percent change in TCS relative to placebo 95% CI
Grastek	629	3.24	-23%	-36%, -13%
Placebo	672	4.22		

From original BLA STN 125473/000; Module 5, CSR P08067, Page 84 of 7193

6.5.11.2 Analyses of Secondary Endpoints Protocol P08067
The two key secondary endpoints are the DSS and DMS, which are added together to calculate the TCS. Tables 45 and 46 show that the DSS and RMS of the FAS during the entire GPS.

Table 45. Summary and analysis of the DSS during the entire GPS Study P08067

Treatment	Number of Subjects	Total Combined Score (adjusted mean)	Percent change in DSS relative to placebo Point estimate	Percent change in DSS relative to placebo 95% CI
Grastek	629	2.49	-20%	-32%, -10%
Placebo	672	3.13		

From original BLA STN 125473/000; Module 5, CSR P08067, Page 89 of 7193

Table 46. Summary and analysis of the DMS during the entire GPS P08067

Treatment	Number of Subjects	Total Combined Score (adjusted mean)	Percent change in DMS relative to placebo Point estimate	Percent change in DMS relative to placebo 95% CI
Grastek	629	0.88	-35%	-49%, -21%
Placebo	672	1.36		

From original BLA STN 125473/000; Module 5, CSR P08067, Page 96 of 7193

6.5.11.3 Subpopulation Analyses Protocol P08067
Of subjects with asthma, there was no difference in symptom or medication scores between the GRASTEK and Placebo study groups.

6.5.11.4 Dropouts and/or Discontinuations Protocol P08067
See Study P05238 for handling of Dropouts/Discontinuations.

6.5.11.5 Exploratory and Post Hoc Analyses Protocol P08067
None

6.5.12 Safety Analyses Protocol P08067

6.5.12.1 Methods Protocol P08067
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.

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.

6.5.12.2 Overview of Adverse Events Protocol P08067
A total of 73.5% of subjects reported an AE during the treatment period, 78.8% of subjects in the SCH 697243 group and 68.2% of subjects in the placebo group. The most commonly reported AEs were oral pruritus and throat irritation (both of which were much more frequent in the treatment group). Also frequently reported but equally distributed among the two groups were nasopharyngitis, upper respiratory tract infection, oropharyngeal pain, headache, and cough. Table 47 shows all treatment emergent AE that were reported in at least 2% of study subjects.

Table 47. AE during the treatment period reported by ≥ 2% of Subjects in either GRASTEK or Placebo group.

Adverse Event	MK-7243 (n=753)	MK-7243 (n=753)	Placebo (n=745)	Placebo (n=745)	Total N=1498	Total N=1498
NASOPHARYNGITIS	103	(13.7)	122	(16.4)	225	(15.0)
THROAT IRRITATION	181	(24.0)	29	(3.9)	210	(14.0)
UPPER RESPIRATORY TRACT INFECTION	78	(10.4)	86	(11.5)	164	(10.9)
ORAL PRURITUS	139	(18.5)	21	(2.8)	160	(10.7)
HEADACHE	65	(8.6)	56	(7.5)	121	(8.1)
PARAESTHESIA ORAL	92	(12.2)	24	(3.2)	116	(7.7)
OEDEMA MOUTH	98	(13.0)	9	(1.2)	107	(7.1)
EAR PRURITUS	92	12.2)	12	1.6)	104	(6.9)
COUGH	60	(8.0)	43	(5.8)	103	(6.9)
OROPHARYNGEAL PAIN	46	(6.1)	27	(3.6)	73	(4.9)
RHINORRHOEA	33	(4.4)	37	(5.0)	70	(4.7)
SINUSITIS	35	(4.6)	30	(4.0)	65	(4.3)
NASAL CONGESTION	39	(5.2)	25	(3.4)	64	(4.3)
TONGUE PRURITUS	53	(7.0)	5	(0.7)	58	(3.9)
EYE PRURITUS	25	(3.3)	26	(3.5)	51	(3.4)
LIP SWELLING	46	(6.1)	5	(0.7)	51	(3.4)
SNEEZING	25	(3.3)	24	(3.2)	49	(3.3)
NAUSEA	26	(3.5)	15	(2.0)	41	(2.7)
VIRAL UPPER RESPIRATORY TRACT INFECTION	20	(2.7)	18	(2.4)	38	(2.5)
DYSPEPSIA	33	(4.4)	4	(0.5)	37	(2.5)
HYPOAESTHESIA ORAL	24	(3.2)	10	(1.3)	34	(2.3)
NASAL DISCOMFORT	17	(2.3)	15	(2.0)	32	(2.1)
BRONCHITIS	14	(1.9)	16	(2.1)	30	(2.0)
PRURITUS	17	(2.3)	13	(1.7)	30	(2.0)
VOMITING	16	(2.1)	14	(1.9)	30	(2.0)
DIZZINESS	17	(2.3)	12	(1.6)	29	(1.9)
DYSPNOEA	20	(2.7)	9	(1.2)	29	(1.9)
URTICARIA	17	(2.3)	12	(1.6)	29	(1.9)
CHEST DISCOMFORT	19	(2.5)	9	(1.2)	28	(1.9)
LIP PRURITUS	25	(3.3)	3	(0.4)	28	(1.9)
ORAL MUCOSAL ERYTHEMA	18	(2.4)	9	(1.2)	27	(1.8)
LACRIMATION INCREASED	18	(2.4)	8	(1.1)	26	(1.7)
PHARYNGEAL OEDEMA	25	(3.3)	1	(0.1)	26	(1.7)

Adverse Event	MK-7243 (n=753)	MK-7243 (n=753)	Placebo (n=745)	Placebo (n=745)	Total N=1498	Total N=1498
BACK PAIN	10	(1.3)	15	(2.0)	25	(1.7)
DIARRHOEA	10	(1.3)	15	(2.0)	25	(1.7)
STOMATITIS	20	(2.7)	5	(0.7)	25	(1.7)
SWOLLEN TONGUE	22	(2.9)	0		22	(1.5)
TONGUE OEDEMA	16	(2.1)	6	(0.8)	22	(1.5)
GASTROOESOPHAGEAL REFLUX DISEASE	15	(2.0)	5	(0.7)	20	(1.3)
THROAT TIGHTNESS	17	(2.3)	1	(0.1)	18	(1.2)
DRY THROAT	15	(2.0)	2	(0.3)	17	(1.1)
LIP EDEMA	15	(2.0)	1	(0.1)	16	(1.1)

Extracted from original BLA STN 125473/000; Module 5, CSR P08067, Page 120-121 of 7193

6.5.12.3 Deaths Protocol P08067

One death occurred in a 42 year old male subject who had been in the MK-7243 treatment group. The subject had completed the trial without any AEs reported during the study. The subject had been off study medication for 1 month and all IMP was returned to the site prior to the event. Cause of death was unknown.

6.5.12.4 Nonfatal Serious Adverse Events Protocol P08067

A total of 25 subjects experienced a total of 31 SAE during the trial. Of the 25 subjects, 14 were in the GRASTEK study group and 11 were in the Placebo group. None of the SAE was considered related to treatment.

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

6.5.12.5 Adverse Events of Special Interest (AESI) Protocol P08067

The following three subjects in the GRASTEK study group were treated with epinephrine

- A 36 year old subject tolerated the first dose of study medication with mild local tingling. On day 2 of study medication, the subject experienced mild sublingual swelling following the dose. Twelve hours after study medication, the subject developed a rash, shortness of breath, throat tightness and “heaviness” of the tongue. He administered his epipen and an antihistamine. The next day, he took the 3rd dose without events (no supervision). On Day 4, he dosed study medication under supervision with only mild local tingling. The subject realized that he had been exposed to bed bugs. The PI’s final diagnosis was idiopathic urticaria/bug bites and anxiety. Subject had no further events aside from tolerable local symptoms, however, the subject did not complete the study. He was discontinued on study day 155 due to lost to follow-up.
- An 18 year old male subject developed irritation and swelling in the throat following the 3rd dose of study medication. No difficulty breathing or swallowing was reported. The subject administered the epinephrine pen but did not tell his parent or seek medical attention. The subject’s parent reported on Day 3 phone call that subject wished to discontinue from the trial. Approximately 1 month after the event, the subject presented to the site for early termination visit and reported the event. The event was assessed as severe and possibly related to study medication.

- A 65 year old, female subject had a worsening of oral symptoms over the first weeks of dosing. On Day 14, within 15 minutes of IMP, the subject developed a local reaction. She went to the investigational site. As per PI, lungs were clear and vital signs were normal. Due to the local symptoms and hoarseness, the subject was administered epinephrine and an antihistamine. The event was assessed as a moderate local hypersensitivity reaction probably related to study medication, and the subject discontinued from the trial.

The following two subjects experienced a systemic allergic reaction.

- A 23 year old subject took first 2 weeks of study medication without AEs. Starting on Day 15, subject developed throat tightness lasting ~ 5 minutes. The subject's AEs worsened over the next several weeks, and the subject began experiencing tongue edema. On day 42, the subject developed chest tightness and shortness of breath after taking study medication. The symptoms resolved over 30 minutes. The subject did not require treatment. The event was assessed by the PI as a moderate systemic allergic reaction; the subject discontinued the trial.
- 45 year old female subject tolerated the first dose of study medication with mild local adverse events. Following the second dose of MK-7243, she experienced edema on the lower lips, redness on corners of the mouth and chin, epigastric discomfort and dizziness. Symptoms resolved after 1 hour without treatment. The subject did not seek medical intervention. The event was assessed by the PI as a moderate systemic allergic reaction; the subject discontinued the trial.

6.5.12.6 Clinical Test Results Protocol P08067
No clinically relevant test results were reported.

6.5.12.7 Dropouts and/or Discontinuations Protocol P08067
Fifty-six subjects withdrew from the study because of treatment-related AEs, 46 subjects in the study drug group and 10 in the placebo group. The reasons for withdrawal in the GRASTEK group were predominantly GI and respiratory system disorders, shown in Table 48. Additional reasons for withdrawal include ear pruritus, eye pruritus, chest discomfort/chest pain, urticaria, and "hypersensitivity."

Table 48. Dropouts and Discontinuations due to GI and Respiratory AE

	MK-7243 n=753	MK-7243 n=753	Placebo n=745	Placebo n=745	Total n=1498	Total n=1498
GASTROINTESTINAL DISORDERS	**28**	**(3.7)**	**3**	**(0.4)**	**31**	**(2.1)**
ABDOMINAL PAIN UPPER	1	(0.1)	1	(0.1)	2	(0.1)
DYSPEPSIA	1	(0.1)	0		1	(0.1)
DYSPHAGIA	2	(0.3)	0		2	(0.1)
	MK-7243 n=753	**MK-7243 n=753**	**Placebo n=745**	**Placebo n=745**	**Total n=1498**	**Total n=1498**
ENLARGED UVULA	1	(0.1)	0		1	(0.1)
GASTROOESOPHAGEAL REFLUX DISEASE	1	(0.1)	0		1	(0.1)
LIP PRURITUS	0		1	(0.1)	1	(0.1)
LIP SWELLING	3	(0.4)	0		3	(0.2)
NAUSEA	2	(0.3)	2	(0.3)	4	(0.3)
ODYNOPHAGIA	1	(0.1)	0		1	(0.1)
OEDEMA MOUTH	7	(0.9)	0		7	(0.5)
ORAL DISCOMFORT	3	(0.4)	0		3	(0.2)
ORAL MUCOSAL BLISTERING	2	(0.3)	0		2	(0.1)
ORAL PRURITUS	7	(0.9)	0		7	(0.5)
SALIVARY GLAND ENLARGEMENT	1	(0.1)	0		1	(0.1)
SALIVARY HYPERSECRETION	1	(0.1)	0		1	(0.1)
STOMATITIS	1	(0.1)	0		1	(0.1)
SWOLLEN TONGUE	3	(0.4)	0		3	(0.2)
TONGUE DISORDER	1	(0.1)	1	(0.1)	2	(0.1)
	MK-7243 n=753	**MK-7243 n=753**	**Placebo n=745**	**Placebo n=745**	**Total n=1498**	**Total n=1498**
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**14**	**(1.9)**	**3**	**(0.4)**	**17**	**(1.1)**
COUGH	2	(0.3)	1	(0.1)	3	(0.2)
DRY THROAT	1	(0.1)	0		1	(0.1)
DYSPNOEA	3	(0.4)	1	(0.1)	4	(0.3)
NASAL CONGESTION	0		1	(0.1)	1	(0.1)
NASAL DISCOMFORT	1	(0.1)	0		1	(0.1)
NASAL OEDEMA	0		1	(0.1)	1	(0.1)
PHARYNGEAL OEDEMA	6	(0.8)	0		6	(0.4)
RHINORRHOEA	1	(0.1)	0		1	(0.1)
THROAT IRRITATION	4	(0.5)	1	(0.1)	5	(0.3)
THROAT TIGHTNESS	3	(0.4)	0		3	(0.2)
WHEEZING	0		1	(0.1)	1	(0.1)

6.5.13 Study Summary and Conclusions Protocol P08067

In Study P08067, GRASTEK was associated with treatment related AE that are predominantly mild or moderate, and that did not precipitate withdrawal from the study. There were two systemic reactions (episode of anaphylaxis) in response to the GRASTEK, which occurred after the first dose of therapy; this subject withdrew from the trial.

Study P08067 was well designed to meet its clinical endpoint, an improvement in the TCS in the GRASAX study drug group. The point estimate of that improvement was better than the minimal 15% considered acceptable by CBER. The 95% CI were not criteria for success of this US study, but the 95% CI UL was -13%, which meets CBER's requirements for proof of efficacy.

The results of this study are considered pivotal for efficacy and safety of GRAZAX (GRASTEK) for the treatment of adults with ARC.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1: "GRASTEK is an allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis or conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass and cross-reactive grass pollens. GRASTEK is approved for use in persons 5 through 65 years of age. GRASTEK is not indicated for the immediate relief of allergic symptoms."

7.1.1 Methods of Integration

Data were pooled across four studies (GT-08 [Yr 1], GT-14, P05238, and P08067) for the first year of treatment of adults 18-65 years of age, and across three studies (GT-12, P05239, and P08067) for children 5-17 years of age.

7.1.2 Demographics and Baseline Characteristics

Adapted from original BLA 125473/000; summary of clinical efficacy, Pages 152-156

Efficacy data on adults have been provided from four Phase 3 studies with MK-7243 (GT-08, P05238, GT-14, and P08067 [age 18]). The selection of study populations was based on very similar criteria across studies.

In all of the studies, subjects were required to have a positive SPT to *Phleum pratense*, and in the North American trials, the wheal size requirement was ≥5 mm compared to the ≥3 mm wheal sizes required for the EU studies. A larger wheal size was chosen as an objective measure to select for subjects with a high degree of sensitivity to grass pollen. In North America, the potency of extracts used for skin testing is typically higher than those used in Europe; therefore, a larger wheal size requirement is considered prudent to ensure the appropriately symptomatic subjects. Additionally, in North America, there are potentially many overlapping pollen allergens; so the stringency of the criterion was increased to ensure a more clinically grass-dominant allergic population.

The characteristics (sex, age, and weight) of the recruited subjects were similar across the adult studies. The history, in years, of grass pollen-induced rhinoconjunctivitis was also comparable, as was the prevalence of asthma (~25%).

Differences among the adult studies were:

1. Study P08067 included subjects between 5 and 65 years of age;
2. Study GT-08, subjects were required both to have had rhinoconjunctivitis symptoms and to have used medication to treat their rhinoconjunctivitis symptoms during the two previous GPS.
3. For studies P05238 and P08067, subjects were required both to have a clinical history of significant AR to grass (with or without asthma) diagnosed by a physician and to have received treatment for their disease during the GPS just prior to enrollment.
4. In Study GT-14, subjects had to have a clinical history of grass pollen-induced AR of 2 years or more requiring treatment during the GPS. Additionally in GT-14, subjects had access to only anti-histamines as the rescue medications to use during the GPS; nasal corticosteroids or prednisone were not provided.

Efficacy data for pediatrics have been provided from three Phase 3 studies with MK-7243: Studies GT-12, P05239, and P08067 (age < 18). Subjects were required to have a clinical history of grass pollen-induced rhinoconjunctivitis (with or without asthma) and having received treatment during the previous GPS. A pre-seasonal treatment period of approximately 16 weeks was used in both pediatric studies to ensure sufficient pre-seasonal exposure to GRASTEK.

Differences among the pediatric studies were:

1. Study GT-12 included subjects between 5 and 16 years of age, whereas in Study P05239 the upper age limit was <18 years of age.
2. The minimum FEV1 for each study differed, with subjects with FEV1 <80% being excluded from Study GT-12 and those with FEV1 <70% excluded from Study P05239.
3. Study P08067 included subjects between 5 and 65 years of age and required that subjects have an FEV1 ≥70% of predicted.

7.1.3 Subject Disposition

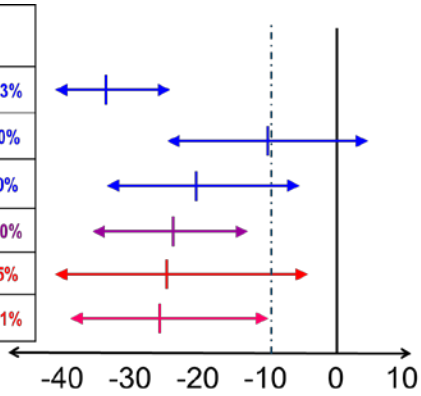
Subject disposition for each study is outlined in Section 6.

7.1.4 Analysis of Primary Endpoint(s)

Figure 4 shows analysis of the primary endpoint, the TCS during the grass pollen season, for each of the clinical studies reviewed for approval of the BLA. The totality of the data indicates that GRASTEK is effective for treatment of AR with or without conjunctivitis.

Figure 4. Median and 95% confidence intervals of the TCS for Year 1 of therapy with GRASKTEK. Adult studies are in blue, pediatric studies are in red: P080657, in violet, included adults and children.

Study	2800 BAU	Placebo	% difference	95% CI
GT-08	282	286	-34.2%	-42.0%, -26.3%
GT-14	139	150	-10.4%	-23.9%, +4.0%
P05238	184	207	-20.5%	-33.0%, -6.0%
P08067	629	672	-23.0%	-36.0%, -13.0%
GT-12	117	121	-24.2%	-41.3%, -4.5%
P05239	149	158	-26.1%	-38.2%, -10.1%



Adapted from presentation to APAC, December 12, 2013.

Data were pooled across four clinical trials of 2605 adults 18-65 years of age. Table 49 shows that the upper bound of the 95% CI for those 18-50 of age is ~ -14.5%. There is no statistically significant effect of adults > 50 years of age.

Table 49. Pooled among adults TCS across four clinical studies.

Parameter	MK-7243 (2800 BAU) (N=1289)	Placebo (N=1316)	Difference (%)	95% CI
Age 18 to <50 n	968	1020		
Raw Mean(SD)	4.93(4.18)	6.31(4.73)		
Adjusted Mean(SE)	5.32(0.14)	6.68(0.15)	-1.36(-20.3%)	(-1.74, -0.97)
Median	4.10	5.64		
Min - Max	(0.00, 32.63)	(0.00, 25.04)		
Age 50 to 65 n	143	168		
Raw Mean(SD)	4.66(4.27)	5.46(4.61)		
Adjusted Mean(SE)	4.82(0.40)	5.68(0.40)	-0.86(-15.1%)	(-1.84, 0.13)
Median	3.73	4.13		
Min - Max	(0.00, 19.62)	(0.00, 19.61)		

SD = Standard Deviation, SE = Standard Error, CI= Confidence Interval;
From BLA 125473/000, Summary of Clinical Efficacy, Page 223

Data were pooled across three clinical trials of 772 children 5-17 years of age. Table XX shows that the upper bound of the 95% CI for those 5-11 years is ~ -10%, and children 12-17 is ~ -2.7%.

Table 50. Pooled data among children ages 5-17 years of age across three clinical studies.

Parameter	MK-7243 (2800 BAU) (N=441)	Placebo (N=431)	Difference (%)	95% CI
Age 5 to <12 N	178	180		
Raw Mean(SD)	4.73(5.19)	6.41(4.93)		
Adjusted Mean(SE)	4.68(0 39)	6.37(0.37)	-1.69(-26.5%)	(-2.74, -0.64)
Median	3.27	5.60		
Min – Max	(0.00, 35.68)	(0.00, 23.95)		
Age 12 to 18 N	211	226		
Raw Mean(SD)	4.63(3 85)	5.53(4.03)		
Adjusted Mean(SE)	4.55(0 27)	5.42(0.27)	-0.88(-16.2%)	(-1.61, -0.15)
Median	3.67	4.77		
Min – Max	(0.00, 17.97)	(0.00, 19.19)		

SD = Standard Deviation, SE = Standard Error, CI= Confidence Interval;
From BLA 125473/000, Summary of Clinical Efficacy, Page 224

7.1.5 Analysis of Secondary Endpoint(s)

The secondary endpoints of the DSS and the RMS are discussed for each study in Section 6. No other secondary endpoints will be discussed in this review.

7.1.6 Other Endpoints

No other endpoints will be discussed in this section.

7.1.7 Subpopulations

Table 50 shows efficacy on subpopulations of adult participants in GT-08, GT-14, P05238, and P08067.

Table 51. Efficacy of subpopulations of adults

Group	N Tx/Placebo	TCS GRASTEK	TCS Placebo	Difference In TCS	Difference (%)	95 % CI TCS
Caucasians	965/1042	5.20	6.21	-1.41	-21.3%	-1.79, -1.04
Non-Caucasians	145/146	6.32	6.88	-0.56	-8.1%	-1.70, +0.58
With Asthma	261/284	4.39	5.77	-1.25	-18.3%	-2.00, -0.49
Without Asthma	850/904	3.87	5.37	-1.31	-20.1%	-1.72, -0.90

Table 51 shows efficacy on subpopulations of pediatric participants in GT-12, P05239, and P08067.

Table 52. Efficacy of subpopulations of children and adolescents

Group	N Tx/Placebo	TCS GRASTEK	TCS Placebo	Difference In TCS	Difference (%)	95 % CI TCS
Caucasians	335/367	4.47	5,85	-1.38	-23.6%	-2.00, -0.76
Non-Caucasians	54/39	6.19	6.49	-0.30	-4.6%	-2.82, +2.23
With Asthma	117/124	4.49	5.16	-0.67	-13.0%	-1.73, +0.39
Without Asthma	272/282	4.66	6.17	-1.51	-24.5%	-2.27, -0.75

Reviewer's note: For adult and pediatric populations, 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.

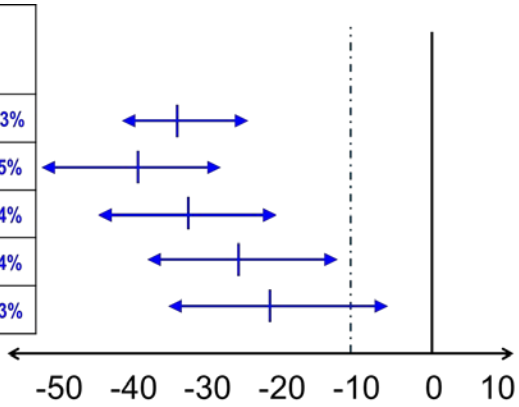
Similarly, the sample sizes for the pediatric subjects with and without asthma are small, and the differences in efficacy appear to reflect differences in placebo TCS rather than the treatment subgroups.

7.1.8 Persistence of Efficacy

Study GT-08, tested for sustained efficacy beyond three years of treatment. As shown in Figure 7, the improvement in the TCS for Year 4 exceeded CBER's criteria of a MCID of -15%, and 95% CI UL of -10%. For Year 5, the 95% CI UL was > -10%.

Figure 5. TCS over treatment Years 1-3 and Observation Years 1-3.

Year	2800 BAU	Placebo	% difference	95% CI
1	282	286	-34.2%	-42.0%, -26.3%
2	172	144	-40.9%	-51.8%, -29.5%
3	160	127	-34.0%	-45.5%, -21.4%
4	142	115	-27.2%	-39.9%, -12.4%
5	137	104	-22.7%	-37.1%, - 6.3%



Adapted from presentation to APAC, December 12, 2013.

7.1.9 Product-Product Interactions

None

7.1.10 Additional Efficacy Issues/Analyses

None

7.1.11 Efficacy Conclusions

GRASTEK is effective for the treatment of AR with or without conjunctivitis in children, adolescents and adults 5-65 years of age. The expected treatment effect is approximately an improvement of 20% of symptoms and medication score.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Across 13 clinical trials (phase 1, 2, and 3) that comprised the pivotal clinical development program for GRASTEK, a total of 4,704 participants were randomized to receive GRASTEK (2,568 participants) or placebo (2,136 participants). Safety analyses presented herein are based on two pooled analyses:

- all adults >18 years of age at entry randomized to receive GRASTEK at a daily dose of 2800 BAU or placebo in phase 2 or 3 studies (includes participants from 6 studies)
- all children and adolescents 5 to 17 years of age at entry randomized to receive GRASTEK at a daily dose of 2800 BAU or placebo in phase 3 studies (includes participants from 3 studies).

These pooled analyses included 2,116 persons randomized to receive GRASTEK at a daily dose of 2800 BAU: 1,669 adults aged 18 through 65 years, 239 adolescents aged 12 through 17 years, and 207 children aged 5 through 11 years . The pooled analyses included 2,080 persons randomized to receive placebo: 1,645 adults aged 18 through 65 years, 245 adolescents aged 12 through 17 years, and 190 children aged 5 through 11 years. Among adult study participants, the mean age was 36.2 years in both the GRASTEK and placebo groups. Among child and adolescent study participants, the mean age was 11.7 years in the GRASTEK group and 11.9 years in the placebo group. Three adult subjects randomized to placebo and 2 pediatric subjects randomized to GRASTEK did not receive treatment.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

In the pooled analyses, the mean duration of exposure to GRASTEK was 175 days (range 1-317 days) for adults and 176.9 days (range 1-258 days) for children and adolescents. The average duration of exposure in the respective placebo recipients was similar to that observed in the GRASTEK recipients.

Persons with a self-reported history of controlled asthma and an FEV1 >70% of predicted value at screening and randomization visits were allowed to enroll in the trials. Persons needing year-round maintenance inhaled corticosteroids or long-acting beta2 agonists treatment were generally excluded. Among the adults included in the pooled analyses, 415 (25%) of those who received GRASTEK and 383 (23%) of those who received placebo had a medical history of asthma at baseline. Among children and adolescents included in the pooled analyses, 140 (31%) of those who received GRASTEK and 136 (31%) of those who received placebo had a medical history of asthma at baseline.

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 first2-4 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

8.4.1 Deaths

There were no deaths.

8.4.2 Nonfatal Serious Adverse Events

In the pooled analysis, at least one serious adverse event was reported in 25 (1.5%) of GRASTEK recipients and 22 (1.3%) of placebo recipients. None of the serious adverse events in GRASTEK recipients included in the pooled analysis were considered treatment-related.

One subject who received GRASTEK 933 BAU (not included in the pooled analysis of 2800 BAU) experienced a serious adverse event considered by the investigator to be probably related to GRASTEK. The subject experienced itching of the tongue with localized edema of the uvula 20 minutes after taking the first GRASTEK tablet. The subject was observed in the clinic for 2 hours and then released to home. No treatment was given and the subject completed the study according to the protocol.

Death was reported in 2 GRASTEK recipients. One death due to multiple drug overdose occurred 35 days after the last dose of GRASTEK. One death due to arteriosclerotic cardiovascular disease with combined drug toxicity occurred 32 days after the last dose of GRASTEK.

8.4.3 Study Dropouts/Discontinuations

In the adult pooled analysis, 4.9% (81/1669) of GRASTEK recipients and 0.9% (15/1,645) of placebo recipients discontinued study participation due to a treatment-related adverse event. The most commonly reported treatment-related adverse events that led to study discontinuation in GRASTEK recipients were oral pruritus (12 study participants), mouth edema (7 study participants), and swollen tongue (6 study participants). Treatment-related adverse events that led to study discontinuation in 2 to 5 GRASTEK recipients were eye pruritus, dyspepsia, dysphagia, lip swelling, nausea, oral mucosal blistering, salivary gland enlargement, stomatitis, chest discomfort, chest pain, hypersensitivity, headache, asthma, cough, dysphonia, dyspnea, pharyngeal erythema, pharyngeal edema, throat irritation, throat tightness, angioedema, pruritus, swelling face, and urticaria.

8.4.4 Common Adverse Events

Treatment-related adverse events were reported at a higher frequency following GRASTEK than placebo. Onset of treatment-related adverse events typically occurred within the first 1-2 weeks of treatment, with the highest percentage of subjects having onset on Day 1. The most commonly reported treatment-related adverse events were oral pruritus (26.7% GRASTEK; 3.5% placebo), throat irritation (22.6% GRASTEK; 2.8% placebo), ear pruritus (12.5% GRASTEK; 1.1% placebo), and mouth edema (11.1% GRASTEK; 0.8% placebo). Other treatment-related adverse events reported in >2.5% of GRASTEK recipients and at a higher frequency than placebo recipients included eye pruritus, lip swelling, oral paresthesia, swollen tongue, tongue pruritus, and pharyngeal edema.

In an analysis of treatment-related adverse events that occurred at an incidence of 2% or greater, a severe event was reported in 49 (2.9%) GRASTEK recipients. Of these 49 participants, 15 participants had severe treatment-related oral swellings, with mouth edema (n=7) and pharyngeal edema (n=5) affecting most of the participants. Severe swollen tongue was reported in 2 participants and severe throat tightness was reported in 1 participant. Such events typically occurred within the first several weeks of treatment. In this analysis, the latest onset of severe oral swelling (swollen tongue) was day 74. In these 15 participants, none of the severe oral swellings resulted in airway compromise. One event (swollen tongue) was treated with epinephrine.

8.4.5 Clinical Test Results

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

8.4.6 Systemic Adverse Events

For an analysis of systemic allergic reactions, the applicant 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.

Based on review of the identified events, guided by FAAN criteria and excluding participants with local symptoms only, the applicant determined that 6 adult participants who received GRASTEK experienced a convincing treatment-related systemic allergic reaction. All events (7 events total) were assessed as non-serious and none were considered severe in intensity. Four events had onset on the first day of GRASTEK treatment. One event had onset on Day 2 in a participant who also had a reported systemic allergic reaction on Day 1. One event had onset on Day 2 in a participant who tolerated the first dose of GRASTEK with mild local adverse events. One reaction (chest tightness and shortness of breath) had onset on Day 42. Epinephrine was administered for two of the seven reactions.

8.4.7 Local Reactogenicity

Local reactions are discussed under Section 8.4.4, "Common Adverse Events."

8.4.8 Adverse Events of Special Interest

The sponsor submitted to the BLA file on April 7, 2014 (Amendment 30) a post-marketing safety report of a 23 year-old who 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.*

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 median onset of most local events was within the first week. For these events: ear pruritus, oral pruritus, palatal edema, oral paresthesia, and throat irritation; the median day of onset was Day 1. Overall, 66.6% of subjects reported Treatment related AE throughout the study. Of these, 88.7% of these AE were reported by Day 7, and 98.2% of these AE (65.4% of the total) were reported by Day 90.

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, GRASTEK 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 or post-marketing studies.

GRASTEK 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. Postmarketing data suggest that life-threatening local and allergic reactions may occur beyond Day 1, particularly in subjects who will be part of the patient population, but were excluded from the clinical studies. These subjects include those with moderate or severe asthma who are on daily inhaled corticosteroids, and subjects with underlying cardiac or other pulmonary disease.

Therefore, the clinical reviewer recommends that patients who are prescribed GRASTEK 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

Three clinical studies addressed safety and efficacy in children 5-17 years of age. Efficacy and safety data from these studies were similar to the efficacy data acquired in adult subjects.

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.

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.
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

GRASTEK is an allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis or conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass and cross-reactive grass pollens. GRASTEK is approved for use in persons 5 through 65 years of age. GRASTEK is not indicated for the immediate relief of allergic symptoms.. Subjects who are allergic to other grass pollens that do not cross-react with Timothy grass pollen, or subjects who are allergic to other pollens in the environment during grass pollen season may not experience the level of treatment effect experienced by the study subjects.

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 children and adults is 2800 BAU 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 53. Risk/Benefit analysis of GRASTEK

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 grass 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 • GRASTEK may increase the use of immunotherapy in grass pollen allergic US patients, and significantly impact on overall quality of life in this population
Clinical Benefit	• The totality of data suggests that GRASTEK improves grass-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 GRASTEK, at least one individual study failed to demonstrate improvement. • It is uncertain whether the treatment effect of GRASTEK is maintained beyond one or multiple courses of treatment. The single long-term study performed in the EU suggested that benefit of GRASTEK is maintained for a fourth year beyond three years of therapy, but not for a fifth year.	• The totality evidence for clinical benefit of GRASTEK suggests 20-25% improvement in symptoms, medication use, or both. • Treatment effects of GRASTEK taken for three consecutive years (with breaks in therapy of about 3-4 months after the end of grass pollen season) may be sustained for one additional year.
Risk	• The most substantial risks of GRASTEK 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 reac ions, 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 GRASTEK. In particular, this includes patients with moderate to severe asthma, and those with underlying cardiac and non-asthmatic pulmonary disease. • GRASTEK has not been studied in adults > 65 years of age	• Overall, the benefit of GRASTEK 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. • Pa ients 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 GRASTEK. • If GRASTEK is approved, it will be indicated for patients 5-65 years of age.
Risk Management	• GRASTEK may result in severe or serious laryngopharyngeal reactions or systemic allergic reactions. Most often, these will occur on Day 1 of herapy.	• If GRASTEK is approved for patients 5-65 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 5-65 years of age with GRASTEK 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 GRASTEK 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 GRASTEK.

11.3 Discussion of Regulatory Options

The clinical reviewer recommends that the GRASTEK 2800 BAU be approved for the treatment of ARC with or without mild asthma.

11.4 Recommendations on Regulatory Actions

1. I recommend approval of GRASTEK for children and adults 5 through 65 years of age for treatment of ARC with or without mild asthma.
2. The first dose of GRASTEK 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 GRASTEK®. The Product Proper Name is Timothy Pollen Allergen Extract Tablet for Sublingual Use.
2. GRASTEK is an allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis or conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass and cross-reactive grass pollens. GRASTEK is approved for use in persons 5 through 65 years of age. GRASTEK is not indicated for the immediate relief of allergic symptoms.
3. The dose of the sublingual tablets is 2800 BAU per day for children and 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 GRASTEK should also be prescribed auto-injectable epinephrine.

11.6 Recommendations on Postmarketing Actions

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 postmarketing study will enroll all new users of GRASTEK based on dispensing claims for three years. This study will also capture exposures to other immunotherapies (e.g. beta-agonist or steroid inhalers). The primary outcome for this study will be local and systemic allergic reactions resulting in hospitalization, emergency department care, or ambulatory visits that are associated with epinephrine injections, as well as all episodes of eosinophilic esophagitis. These data will be ascertained through diagnosis codes for anaphylaxis, anaphylactic reaction, anaphylactic shock, eosinophilic esophagitis, systemic allergic reaction, or upper airway obstruction. Outcomes will also be identified through codes for procedures to treat these conditions, such as emergency endotracheal intubation or surgical airway. Each outcome identified through automated data will be adjudicated by a panel of clinicians who are experts in the field using medical chart review. Because this study is based on dispensing claims, it may not capture events within the first seven days of GRASTEK therapy.

To capture events within the first seven days of GRASTEK therapy, the sponsor proposes to conduct a second postmarketing study that uses an integrated healthcare system with access to electronic medical record (EMR) data. The integrated healthcare system will pick up the events that are associated with the early exposures based on use of the starter-packs as well as events that might occur during longer term therapy exposure, including serious allergic reactions and eosinophilic esophagitis.

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 GRASTEK