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<b>Reviewer Name(s)</b>	Tammy J. Massie, PhD
<b>Review Completion Date / Stamped Date</b>	
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<b>Applicant</b>	Merck, Inc.
<b>Established Name (Proposed) Trade Name</b>	Grastek®
<b>Pharmacologic Class</b>	Allergenic Extract (Timothy Grass)
<b>Formulation(s), including Adjuvants, etc</b>	Tablet
<b>Dosage Form(s) and Route(s) of Administration</b>	Sub-lingual (placed under tongue until dissolved)
<b>Dosing Regimen</b>	2,800 Bioequivalent Allergy Unit (BAU) of the drug substance (per tablet), once per day.
<b>Proposed Indication(s) and Intended Population(s)</b>	Grastek ® (MK-7243) is indicated for 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.

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## GLOSSARY

2M	Patients received active treatment starting 2 months prior to the pollen season
4M	Patients received active treatment starting 4 months prior to the pollen season
AASS	Average Adjusted Symptom Score
ASS	Adjusted Symptom Score
ACS	Average Combined Score
ANCOVA	Analysis of Covariance
ARIA GA2LEN	Allergic Rhinitis and its Impact on Asthma Global Allergy and Asthma European Network
ARMS	Average Rescue Medication Score
ARTSS	Average Rhinoconjunctivitis Total Symptom Score
AUC	Area Under the Curve
BMI	Body Mass Index
CA	Complementary Analysis
CI (or % CI)	Confidence Interval (or % Confidence Interval)
CID	Clinically Important Difference
CMH	Cochran-Mantel-Haenszel
CS	Combined Score
CSR	Clinical Study Report
DRM	Data Review Meeting
DSMB	Data and Safety Monitoring Board
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GES	Global Evaluation Score
GLM	Generalized Linear Model
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IR	Index of Reactivity
ITT	Intention-To-Treat
LS	Least Squares
LOCF	Last Observation Carried Forward
MCID	Minimal Clinically Important Difference
MIVQUE0	Minimum Variance Quadratic Unbiased Estimation
ML	Maximum Likelihood
ND	Not Determined
NS	Not Significant
PP	Per Protocol
PPS	Per Protocol Set
PRO	Patient-Reported Outcome
RC	Rhinoconjunctivitis

REML	Restricted Maximum Likelihood
RMS	Rescue Medication Score
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RRTSS	Retrospective Rhinoconjunctivitis Total Symptom Score
RTSS	Rhinoconjunctivitis Total Symptom Score
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SEM	Standard Error of the Mean
SLIT	Sublingual Immunotherapy
SIT	Specific Immunotherapy
TEAE	Treatment Emergent Adverse Event
VO	Voie Orale (i.e., oral route in French)
WAO	World Allergy Organization

## 1. EXECUTIVE SUMMARY

Merck conducted a multinational clinical development program for MK-7243/Grastek® Timothy grass pollen extract sublingual tablet for the treatment of allergic rhinoconjunctivitis in patients with clinical symptoms due to Timothy grass pollen allergy.

MK-7243/GRASTEK contains allergen extracts of the following grass pollen: Timothy (*Phleum pratense* L.). As per the applicant, this product, MK-7243/Grastek®, is indicated for: *“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.”*

Overall, approximately ~2000 subjects 18 to 65 years of age and nearly 500 children 5-18 years of age participated in the clinical development program of MK-7243/Grastek®, which consisted of a total of fourteen clinical trials in the MK-7243/Grastek® Clinical Development program. The effectiveness and safety of MK-7243/Grastek® was evaluated in the following clinical trials from Phase I to Phase III:

- 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); and
- Six Phase 3 efficacy and safety trials (GT-08 in adults in Europe, GT-14 in adults in the US, P05238 in adults in North America, GT-12 and P05239 in children in Germany and North America, respectively, and P08067 in adults/children in North America).

The majority of these studies were performed over one allergy season. However, a single long-term extension over several allergy seasons within the Phase 3 adult GT-08 trial was performed over up to 5 years and was completed in 2009; data from the 3 treatment years and the 2 follow-up years are provided in the applicant provided application.

A summary of the thirteen efficacy studies, including the purpose of the study and the number of patients exposed to various doses of the Merck MK-7243/Grastek® product, is provided in the table below

NOTE: in the following tables acronyms were utilized including: AIT = allergy immunotherapy tablet; Approx = approximately; BAU = Bioequivalent Allergen Unit; DB = double-blind; MC = multicenter; MD = multiple dose; OL = open label; PC = placebo-controlled; PG = parallel-group; QD = once daily; R = randomized; SD = single dose; SQ-T = standardized quality tablet; SQ-U = standardized quality unit; PD= pharmacodynamic; GPS = grass pollen season; IgE = immunoglobulin E.

### **Table 1:** Summary of Clinical Studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	<a href="#">P05238</a>	Efficacy and Safety	MC, R, DB, PG, PC; Phase 3	Grastek 2,800 BAU QD Placebo Sublingual tablet	438 (213 active; 225 placebo)	Clinical history of significant grass pollen-induced allergic rhinoconjunctivitis; Ages 18 to 65 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i>	Approx 16 weeks prior to and then during the entire 2009 GPS (total of approx 24 weeks)	Completed Full
Efficacy and Safety	<a href="#">P05239</a>	Efficacy and Safety	MC, R, DB, PC, PG; Phase 3	Grastek 2,800 BAU QD Placebo Sublingual tablet	344 (175 active; 169 placebo)	Clinical history of significant grass pollen-induced allergic rhinoconjunctivitis; Ages 5 to <18 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i>	Approx 16 weeks prior to and then during the entire 2009 GPS (total of approx 24 weeks)	Completed Full
Safety	<a href="#">GT-01</a>	Safety	Period 1: R, DB, PC, SD stepwise, dose escalation  Periods 2 and 3: R, DB, PC, MD, PG  Period 4: follow-up visit Phase 1	Grastek 93 BAU <sup>a</sup> (2,500 SQ-U) QD Grastek 933 BAU (25,000 SQ-U) QD Grastek 2,800 BAU (75,000 SQ-U) QD Grastek 4,699 BAU (125,000 SQ-U) QD Grastek 14,097 BAU (375,000 SQ-U) QD Placebo Sublingual tablet	Period 1: 47 (39 active; 8 placebo)  Period 2, 3, and 4: 48 (36 active, 12 placebo)	Clinical history of grass pollen-induced seasonal moderate- to-severe allergic rhinoconjunctivitis; Ages 18 to 65 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i>	Period 1: single dose (outside GPS)  Period 2: 8 weeks (outside GPS)  Period 3: 15 weeks (approx 4 weeks prior to the GPS and during the 2002 GPS)  Period 4: follow-up visit; planned to take place 3 months after the last visit of Period 3	Completed Full

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and safety	GT-02	Efficacy and Safety	MC, R, DB, dose ranging, PG, PC; Phase 2/3	Grastek 93 BAU (2,500 SQ-U) <sup>a</sup> QD Grastek 933 BAU (25,000 SQ-U) QD Grastek 2,800 BAU (75,000 SQ-U) QD Placebo Sublingual tablet	855 (569 active; 286 placebo)	Clinical history of significant grass pollen-induced allergic rhinoconjunctivitis ( $\geq 2$ years); Ages 18 to 65 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i> ; Adequate level of symptomatology in the previous pollen season (observational year 2002)	Approx 8 weeks prior to and during the 2003 GPS (maximum duration of treatment was 24 weeks)	Completed Full
Safety	GT-03	Safety	R, DB, PC, MD, dose-escalation; Phase 1	Grastek 933 BAU (25,000 SQ-U) QD Grastek 2,800 BAU (75,000 SQ-U) QD Grastek 5,600 BAU (150,000 SQ-U) QD Grastek 11,200 BAU (300,000 SQ-U) QD Grastek 18,666 BAU (500,000 SQ-U) QD Grastek 28,194 BAU (750,000 SQ-U) QD Grastek 37,592 BAU (1,000,000 SQ-U) QD Placebo Sublingual tablet	84 (63 active; 21 placebo)	Clinical history of significant grass pollen-induced seasonal allergic rhinoconjunctivitis ( $\geq 2$ years); Ages 18 to 65 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i>	28 days (outside the GPS)	Completed Full



Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	GT-04	Safety	R, DB, PC, MD, dose-escalation; Phase 1	Grastek 2,800 BAU (75,000 SQ-T) QD Grastek 5,600 BAU (150,000 SQ-T) QD Grastek 11,200 BAU (300,000 SQ-T) QD Grastek 18,666 BAU (500,000 SQ-T) QD Placebo Sublingual tablet	43 (32 active; 11 placebo)	Clinical history of significant grass pollen-induced allergic rhinoconjunctivitis ( $\geq 2$ years) and mild- to-moderate asthma (last 2 years, symptoms in GPS); Ages 18 to 65 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i>	28 days (outside the GPS)	Completed Full
Efficacy and Safety	GT-07	Efficacy and Safety	MC, R, DB, PG, PC; Phase 2	Grastek 2,800 BAU (75,000 SQ-T) QD Placebo Sublingual tablet	114 (74 active; 40 placebo)	Clinical history of significant grass pollen-induced allergic rhinoconjunctivitis ( $\geq 2$ years) and grass pollen-induced mild- to-moderate asthma (last 2 years, symptoms in GPS); Ages 18 to 65 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i>	12 $\pm$ 2 weeks prior to and during the 2004 GPS; (maximum duration of treatment was 24 weeks)	Completed Full

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	GT-08	Efficacy and safety	MC, R, DB, PG, PC; Phase 3	Years 1 to 3 <sup>b</sup> : Grastek 2,800 BAU (75,000 SQ-T) QD Placebo  Years 4 and 5: No treatment Sublingual tablet	Year 1: 634 (316 active; 318 placebo)  Year 2: 351 (189 active; 162 placebo)  Year 3: 308 (170 active; 138 placebo)  Year 4: 283 (157 active; 126 placebo) <sup>c</sup>  Year 5: 258 (145 active; 113 placebo) <sup>c</sup>	Clinical history of grass pollen-induced allergic rhinoconjunctivitis (≥2 years); Ages 18 to 65 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i>	Year 1: 4 to 6 months prior to the GPS and during the 2005 GPS  Year 2 and 3: Extensions of GT-08 to the end of the 2006 and 2007 GPS, respectively  Year 4 and 5: No treatment follow-up extensions of GT-08 to the end of the 2008 and 2009 GPS, respectively	Completed Full
Safety	GT-09	Safety	MC, R, DB, PC, PG; Phase 1	Grastek 2,800 BAU (75,000 SQ-T) QD Placebo Sublingual tablet	30 (23 active; 7 placebo)	Clinical history of grass pollen-induced allergic rhinoconjunctivitis; Ages 5 to 12 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i>	28 days (outside the GPS)	Completed Full

<b>Type of Study</b>	<b>Study Identifier</b>	<b>Objective(s) of the Study</b>	<b>Study Design and Type of Control</b>	<b>Test Product(s); Dosage Regimen; Route of Administration</b>	<b>Number of Subjects</b>	<b>Healthy Subjects or Diagnosis of Patients</b>	<b>Duration of Treatment</b>	<b>Study Status; Type of Report</b>
Compliance and Safety	GT-10	Compliance and Safety	MC, R, PG, OL; Phase 3	Grastek 2,800 BAU (75,000 SQ-T) QD Sublingual tablet	460 (460 active)	Clinical history of grass pollen-induced allergic rhinoconjunctivitis; Ages 18 to 65 years; Positive skin prick test to <i>Phleum pratense</i>	Approx 6 to 12 weeks prior to and during the 2006 GPS	Completed Full
Safety	GT-11	Safety	MC, R, DB, PC, PG; Phase 1	Grastek 2,800 BAU (75,000 SQ-T) QD Placebo Sublingual tablet	30 (22 active; 8 placebo)	Clinical history of grass pollen-induced allergic rhinoconjunctivitis; Ages 5 to 12 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i>	28 days (outside the GPS)	Completed Full
Efficacy and Safety	GT-12	Efficacy and Safety	MC, R, DB, PC, PG; Phase 3	Grastek 2,800 BAU (75,000 SQ-T) QD Placebo Sublingual tablet	253 (126 active; 127 placebo)	Clinical history of grass pollen-induced allergic rhinoconjunctivitis; Ages 5 to 16 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i>	At least 16 weeks prior to and then during the entire 2007 GPS	Completed Full
Efficacy and Safety	GT-14	Efficacy and Safety	MC, R, DB, PG, PC; Phase 3	Grastek 2,800 BAU (75,000 SQ-T) QD Placebo Sublingual tablet	329 (163 active; 166 placebo)	Clinical history of grass pollen-induced allergic rhinoconjunctivitis ( $\geq 2$ years); Ages 18 to 65 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i>	At least 8 to 16 weeks prior to and during the 2007 GPS	Completed Full

<b>Type of Study</b>	<b>Study Identifier</b>	<b>Objective(s) of the Study</b>	<b>Study Design and Type of Control</b>	<b>Test Product(s); Dosage Regimen; Route of Administration</b>	<b>Number of Subjects</b>	<b>Healthy Subjects or Diagnosis of Patients</b>	<b>Duration of Treatment</b>	<b>Study Status; Type of Report</b>
Safety and tolerance	GT-15	Observational safety and tolerance	MC, R, OL; Phase 4	Grastek 2,800 BAU (75,000 SQ-T) QD Sublingual tablet	628 (628 active) <sup>d</sup>	Presenting with grass pollen-induced allergic rhinitis; Ages >18 years; Previous positive skin prick test and/or specific IgE to <i>Phleum pratense</i>	At least 4 months prior to and during the 2008 GPS (maximum 10 months)	Completed Full
Immunology	GT-16	Investigate changes in immunological parameters and cutaneous reactivity	MC, R, DB, PC, PG; Phase 3b	Grastek 2,800 BAU (75,000 SQ-T) QD Placebo Sublingual tablet	78 (52 active; 26 placebo)	Clinical history of grass pollen-induced allergic rhinitis (≥ 1 year); Ages 18 to 65 years; <sup>e</sup> Positive skin prick test and specific IgE to <i>Phleum pratense</i>	Approx 2 to 4 months prior to and during the 2007 GPS	Completed Full
Compliance	GT-17	Compliance	MC, R, PG, OL Phase 4	Grastek 2,800 BAU (75,000 SQ-T) QD Sublingual tablet	261 (261 active)	Clinical history of grass pollen-induced allergic rhinoconjunctivitis (≥ 2 years); Ages >18 to <65 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i>	Approx 48 weeks of treatment	Completed Full
Immunology	GT-18	Investigate PD effect and tolerability of Grastek	MC, R, DB, PC, PG; Phase 3	Grastek 2,800 BAU (75,000 SQ-T) QD Placebo Sublingual tablet	276 (219 active; 57 placebo)	Clinical history of moderate-to-severe persistent grass pollen-induced allergic rhinoconjunctivitis (≥ 2 years); Ages 18 to 65 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i>	At least 8 weeks of treatment initiated during the GPS	Completed Full

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	GT-19	Safety (local allergic reactions) of Grastek in combination with desloratadine	R, DB, Crossover; Phase 3	Grastek 2,800 BAU (75,000 SQ-T; sublingual tablet) SD + desloratadine 2.5 mg or placebo (melting tablet) SD	46 (all subjects received single doses of each treatment)	Clinical history of moderate-to-severe persistent grass pollen-induced allergic rhinoconjunctivitis ( $\geq 2$ years); Ages 18 to 65 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i> ; Treatment-related local application site reaction in mouth	Single doses	Completed Full
Efficacy and Safety	P08067	Efficacy and Safety	MC, R, DB, PG, PC; Phase 3	MK-7243 2,800 BAU QD Placebo Sublingual tablet	1501 (752 active; 749 placebo)	Clinical history of significant allergic rhinoconjunctivitis to grass (with or without asthma); Ages 5 to 65 years; Positive skin prick test and specific IgE to <i>Phleum pratense</i>	Approx 12 weeks prior to and then during the entire 2012 GPS (total of approx 24 weeks)	Completed Full

Table summarizes data provided within applicant provided datasets:

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

The studies provided in this submission appear to support the applicant's conjecture that the Grastek® 2800 BAU product is safe and effective in the treatment of allergic rhinoconjunctivitis, using CBER's pre-specified criterion for efficacy based on the Combined Symptom Score that incorporates both rescue medication and symptom scores. Furthermore, similar positive trends are observed for the individual endpoints of Total Symptom Scores as well as the Total Rescue Medication Scores.

Based on the data submitted and reviewed, Grastek® 2800 BAU per dose, appears to be effective for immunotherapy treatment of allergic rhinoconjunctivitis due to sensitivity to the Timothy grass pollen included in the product for both youths 5-18 years of age as well as adults 18-65 years of age. Furthermore, the product appears to be safe for youths 5-18 years of age as well as adults 18-65 years of age, based on the statistical analyses examined and performed by the reviewing statistician.

## 2. CLINICAL AND REGULATORY BACKGROUND

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

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

An alternative to SCIT is sublingual immunotherapy (SLIT) in which treatment is administered orally rather than by injection. Two items to note with SLIT treatment presented in the literature include 1) 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 by the patient, and 2) safe use of SCIT requires administration in a clinic that is capable of responding to systemic allergic reactions.

In Europe, Merck markets one solution for SLIT as a "named patient product," and the sublingual immunotherapy tablet, Grazax®/Grastek®, that is the subject of this BLA. Grazax®/Grastek® is a tablet comprised of extracts from one single grass pollen Timothy (*Phleum pratense* L.). This grass belongs to the taxonomic (botanical) family *Poaceae* (formerly known as Gramineae) and subfamily *Pooideae* and is among the standardized grasses approved by CBER for the skin-test diagnosis and SCIT.

Grastek® is currently marketed throughout the European Union (under the trade name Grazax®), and has successfully completed Phase 3 testing in the U.S. The applicant proposes the following indication:

*“GRASTEK® is indicated for 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.”*

As in Europe, the dosage of the tablets to be used in the U.S. is 2800 BAU (Bioequivalent Allergy Units) -- an in-house potency measurement, which is discussed further in the clinical review of this product.

Adults will initiate therapy at 2800 BAUs per day (one tablet, sublingually administered per day). The first dose of Grastek® should only be administered in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. After receiving the first dose, the patient should be kept under observation for 30 minutes to monitor for signs or symptoms of a severe systemic or severe local allergic reaction. If the first dose is adequately tolerated, subsequent doses may be taken at home. Grastek® should only be administered to children under adult supervision. Finally, treatment with Grastek® can be initiated at any time during the year. For symptom improvement during the first grass pollen season, treatment with Grastek® should be initiated at least 8 to 12 weeks prior to the season.

## **2.1 Disease or Health-Related Condition(s) Studied**

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

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

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

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

There are no allergenic products for grasses licensed or approved for administration in adults or children via SLIT in the U.S. However, several European countries have approved SLIT products for grasses as well as other extracts including Merck's Grazax® (the European equivalent to Grastek®/MK-7243).

A total of 13 clinical trials comprise the Grastek® Clinical Program conducted to evaluate the efficacy and safety of Grastek®. This included 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); and six Phase 3 efficacy and safety trials (GT-08 in adults in Europe, GT-14 in adults in the US, P05238 in adults in North America, GT-12 and P05239 in children in Germany and North America, respectively, and P08067 in adults/children in North America).

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

**Table 2.4.1.** Number of Subjects Included in the 13 Studies Comprising the MK-7243 Clinical Development Program by Study and Age Range

<b>Clinical Studies in Adult Subjects</b>	<b>Phase</b>	<b>Study Location</b>	<b>Number of Subjects</b>	<b>Number of Subjects</b>	<b>Number of Subjects</b>	<b>Age Range (Years)</b>
<b>Study Number</b>			<b>Total</b>	<b>Active</b>	<b>Placebo</b>	
GT-01	1	EU	47	39	8	20 to 57
GT-03	1	EU	84	63	21	20 to 61
GT-04	1	EU	43	32	11	18 to 42
GT-02	2/3 Dose finding	EU	855	569	286	18 to 66
GT-07	2	EU	114	74	40	18 to 64
GT-08						
Year 1	3	EU	634	316	318	18 to 65
Year 2	3	EU	351	189	162	18 to 63
Year 3	3	EU	308	170	138	18 to 63
Year 4	3	EU	283	157	126	18 to 63
Year 5	3	EU	258	145	113	18 to 63
GT-14	3	US	329	163	166	18 to 65
P05238	3	North America	438	213	225	18 to 63
P08067	3	Norm America	1218	608	610	18 to ≥65
<b>Total Number of Adult Subjects Enrolled</b>			<b>3762</b>	<b>2077</b>	<b>1685</b>	<b>18 to 66</b>
<b>Clinical Studies in Pediatric Subjects</b>	<b>Phase</b>	<b>Study Location</b>	<b>Number of Subjects</b>	<b>Number of Subjects</b>	<b>Number of Subjects</b>	<b>Age Range (Years)</b>
<b>Study Number</b>			<b>Total</b>	<b>Active</b>	<b>Placebo</b>	
GT-09	1	EU	30	23	7	5 to 12
GT-11	1	EU	30	22	8	5 to 12



GT-12	3	Germany	253	126	127	5 to 16
P05239	3	North	344	175	169	5 to 18b
P08067	3	North	283	144	139	5 to <18
<b>Total Number of Pediatric Subjects Enrolled</b>			<b>940</b>	<b>490</b>	<b>450</b>	<b>5 to 18</b>

Source: Table created by reviewing statistician utilizing data provided in:  
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Additional experience can be found in the medical officer’s review.

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

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

### 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

This submission includes the summary of thirteen (13) pre-marketing studies of which nine (9) studies included efficacy endpoints, and all thirteen (13) pre-marketing studies gathered safety data. These studies included approximately 2,500 subjects exposed to the Grastek® product, with study product administered prior to allergy season then efficacy data collected up to a year post dose. One study, GT-08, an adult phase 3 study performed in Europe, was completed in 2009 and included 5 years of safety and efficacy data collected. Two large Phase III studies were performed under US-IND, while the majority of the remaining studies were not performed under US-IND; however, these studies had similar endpoints and time frames.

#### 3.1 Submission Quality and Completeness

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

#### 3.2 Compliance with Good Clinical Practices and Data Integrity

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

### 4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

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

## 5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

The BLA submission provided by Merck can be found in the following location:

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This file path includes the clinical overview, summary of safety, summary of efficacy, as well as datasets for the 9 efficacy studies and 13 safety studies that were examined and analyzed by the reviewing statistician in the evaluation of this product.

The datasets were SAS datasets. A comprehensive “define” document was provided by the applicant and included descriptions of the various datasets as well as variables within each dataset. In addition to the raw data collected from the Case Report Forms (CRFs) and Patient Reported Outcomes (PROs), the applicant also provided derived datasets. These datasets were confirmed by the reviewing statistician, utilizing a variety of methods, including comparisons of PROC FREQ results.

### 5.1 Review Strategy

The applicant provided a summary and detailed results as well as the datasets of 9 efficacy studies and 13 safety studies. The primary studies of interest include the Phase III study under US IND. The data and the detailed and comprehensive write up of the studies are found within Module 2 and Module 4 of the original submission of this BLA, 125473 amendment 0, submitted to CBER on January 18, 2013.

This BLA includes the following 13 clinical trials that comprise the clinical program which were conducted to evaluate the efficacy and safety of MK-7243:

- Five Phase I trials
  - Adults
    - GT-01 Europe
    - GT-03 Europe
    - GT-04 Europe
  - Children
    - GT-09 Europe
    - GT-11 Europe
- One Phase II safety and efficacy trial in
  - Adults with Allergic Rhinitis (AR) and asthma
    - GT-07 Europe
- One dose-finding Phase II/III efficacy and safety trial in
  - Adults
    - GT-02 Europe
- Six Phase III efficacy and safety trials:

- Adults:
  - GT-08 Europe
  - GT-14 US
  - P05238 North America (US & Canada)
- Children:
  - GT-12 Germany
  - P05239 North America (US & Canada)
- Adults and Children
  - P08067 North America (US & Canada).

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

The Phase III studies that are of most interest were the studies performed under US-IND. These include: P05238 (Adults), P05239 (Children), P08067 (Adults and Children), and GT-14 (adults).

Although GT-14 was a 12-month study conducted in the US including adults 18-65 years of age in 2006, it failed to demonstrate efficacy, and thus is not comprehensively reviewed in this document. Additionally, Study P05238 was a 12-month study conducted in the US and Canada, including adults 18-65 years of age conducted in 2009. While the point estimate of the difference between treatment and placebo groups suggested that the product was effective, the 95% Confidence Interval did not meet the pre-specified criterion for efficacy. The study is considered supportive, but did not meet its primary endpoint and thus is not comprehensively reviewed in this document.

Study P05239 was a 12-month study of children 5-17 years old and demonstrated efficacy based on pre-specified criteria related to total combined symptom score. Additionally, Study 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 collected and analyzed from Study P08067 demonstrated efficacy among all subjects and in the subsets of children 5-17 years of age, and adults 18-65 years of age.

The applicant also submitted, under the heading “Other Study Reports,” brief summaries and data from six additional studies that the applicant does not consider as pertinent to the claimed indication; however, they do provide additional insight into the Grastek® product. While safety data from these studies will be included in the overall safety evaluation, the individual studies will not be discussed in detail in this review. These studies are:

- GT-10, P05440, an open-label Phase 3 trial to assess treatment compliance with Grastek® (in adults with grass-induced ARC)
- GT-15, P07022; Observational national clinical trial of safety and tolerance in patients suffering from an allergic grass pollen rhinitis and treated by GRAZAX® in real life settings



### **5.3 Table of Studies/Clinical Trials**

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

**Table 5.3.a.** Summary of Efficacy Studies Performed to Examine the Effect of Merck Grastek®: 2800 BAU dose

Study #	Location	Years/ Age Range	Study Type	Treatment Dose	Number of Subjects
GT-08	EU	2004-2009 18-65 year	Safety/Efficacy Field	2800 BAU Placebo	316 318
P08067	US, Canada	2012 5-56 year	Safety/Efficacy Field	2,800 BAU Placebo	752 749
GT-14	US	2006-2007 18-65year	Safety/Efficacy Field	2,800 BAU Placebo	166 163
P05238	US, Canada	2008-2009 18-65year	Safety/Efficacy Field	2,800 BAU Placebo	166 163
GT-12	Germany	2006–2007 5-16 year	Safety/Efficacy Field	2,800 BAU Placebo	126 127
P05239	US, Canada	2008–2009 5-18 year	Safety/Efficacy Field	2,800 BAU Placebo	175 169

Table summarizes data provided within applicant provided datasets:

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All studies examined within this submission were single-season field studies that examined subjects' responses for only one allergy season.

These utilized studies collected safety data; however, there were several additional studies explicitly designed to provide insight into safety/tolerability of this product. A summary of the safety studies can be examined in the following table:

**Table 5.3.b. Grastek® Sublingual Tablet Clinical Studies and Design Features**

Study #	Location	Age Range	Study Type	Treatment Dose	Number of Subjects	
					Period 1	Period 2/3/4
GT-01	EU	18-65 years old	Phase 1 Safety/Tolerability	2800 BAU Placebo	39 8	36 12
GT-03	EU	18-65 years old	Phase 1 Dose Escalation Safety/Tolerability	933 BAU 2800 BAU 5600 BAU 11,200 BAU 18,666 BAU 28,194 BAU 37,592 BAU Placebo		9 9 9 9 9 9 9 21
GT-04	EU	18-65 years old	Phase 1 Dose Escalation Safety/Tolerability	2800 BAU 5600 BAU 11,200 BAU 18,666 BAU Placebo		8 8 8 8 11
GT-02	EU	18-65 years old	Phase 2 Dose Finding Safety/Tolerability	93 BAU 933 BAU 28,000 BAU Placebo		189 189 190 286
GT-07	EU	18-65 years old	Phase 2 Efficacy Safety/Tolerability	28,000 BAU Placebo		74 40
GT-08	EU	18-65 years old	Phase 3 Safety/Efficacy Field	2800 BAU Placebo		316 318
P08067	US, Canada	5-56 years old	Phase 3 Safety/Efficacy Field	2,800 BAU Placebo		752 749
GT-14	US	18-65year	Phase3 Safety/Efficacy Field	2,800 BAU Placebo		166 163
P05238	US, Canada	18-65year	Phase 3 Safety/Efficacy Field	2,800 BAU Placebo		166 163
GT-12	Germany	5-16 year	Phase 3 Safety/Efficacy Field	2,800 BAU Placebo		126 127
P05239	US, Canada	5-18 year	Phase 3 Safety/Efficacy Field	2,800 BAU Placebo		175 169

Table summarizes data provided within applicant provided datasets:

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A summary of the analyses based on the Combined Score for the first year of all efficacy studies is provided in Table 5.3.c, below.

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

Study #	Location	Age Range	Treatment Dose	Number of Subjects	Met US-FDA Criteria for Efficacy*	% Difference TCS <sup>(*)</sup> Pt Est (95% CI)
GT-08	EU	18-65yr	2800 BAU Placebo	316 318	Yes	<b>-34%</b> <b>(-42, -26%)</b>
P08067	US, Canada	5-56yr	2,800 BAU Placebo	752 749	Yes	<b>-23%</b> <b>(-36%, -13%)</b>
GT-14	US	18-65yr	2,800 BAU Placebo	166 163	No	-10% (-24%, 4%)
P05238	US, Canada	18-65yr	2,800 BAU Placebo	166 163	No	-21% (-33%, -6%)
GT-12	Germany	5-16yr	2,800 BAU Placebo	126 127	No	-24% (-41%, -4%)
P05239	US, Canada	5-18yr	2,800 BAU Placebo	175 169	Yes	<b>-26%</b> <b>(-45, -14%)</b>

Source: Table summarizes data provided within applicant provided datasets:

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\* Based on the Upper Limit of the 95% CI of the % difference between placebo and treatment being less than -10%



**Table 5.3.d** Grastek® Summary of Primary Efficacy Results Based on Combined Medication and Symptom Score, Daily Symptom Score, and Daily Medication Score

Study	TCS	DSS	DMS
[Difference (95% CI)]			
[% Reduction Relative to Placebo (p-Value)]			
Pivotal Trials			
GT-08 Yr 1	-2.32 (-2.98, -1.67) 34% (p<0.001)	-1.29 (-1.68, -0.90) 31% (p<0.0001)	-1.03 (-1.44, -0.63) 38% (p<0.0001)
GT-14	-0.78 (-1.83, 0.26) 10% (p=0.142)	-0.37 (-1.16, 0.41) 6% (p=0.3475)	-0.40 (-0.85, 0.05) 27% (p=0.0827)
P05238	-1.31 (-2.22, -0.40) 20% (p=0.005)	-0.86 (-1.46, -0.26) 18% (p=0.015) <sup>a</sup>	-0.45 (-0.96, 0.06) 26% (p=0.084)
P08067 <sup>c</sup>	-0.98 (-1.2, -0.4) 23% (p <0.001)	-0.64 (-0.7, -0.2) 20% (p=0.001)	-0.48 (-0.73,-0.22) 35% (p=0.0003)
Supportive Trials			
GT-02 <sup>b</sup>	-1.04 (-1.93, -0.16) 21% (p=0.021)	-0.46 (-0.96, 0.04) 16% (p=0.071)	-0.58 (-1.16, -0.01) 28% (p=0.047)
GT-07	-2.01 (-4.08,0.07) 29% (p=0.058)	-0.78 (-1.56, 0.001) 25% (p=0.0503)	-1.21 (-2.81, 0.39 ) 32% (p=0.1355)

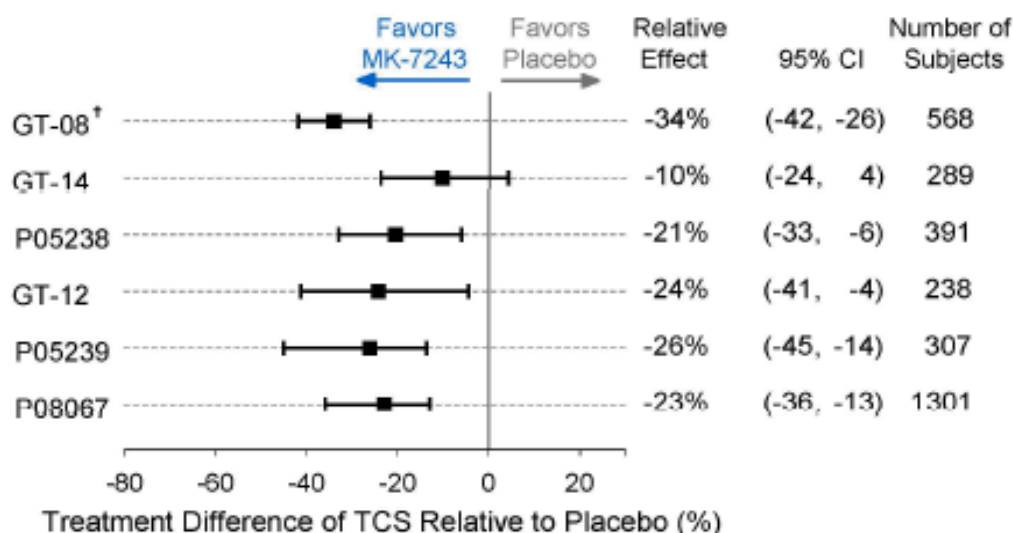
Yr = Year; TCS = Total combined score (DSS + DMS); DSS = Rhinoconjunctivitis Daily Symptom Score; DMS = Rhinoconjunctivitis Daily Medication Score; CI = Confidence Interval.

Note: All studies compared MK-7243 (2800 BAU) with placebo; all scores presented are for the entire GPS; percent reduction: (placebo- MK-7243)/placebo X 100%.

Source: sBLA 125473/000; Summary of Clinical Efficacy, Page 154

Source: sBLA 125473/000; Summary of Clinical Efficacy, Page 154

**Figure 5.3.e.** Grastek® Summary of Primary Efficacy Results Based on Combined Medication and Symptom Score



Source: sBLA 125473/000; Summary of Clinical Efficacy, Page 164

## 5.4 Consultations

### 5.4.1 Advisory Committee Meeting

An Advisory Committee meeting was held on December 12, 2013 to discuss Merck’s Grastek® product. The Advisory Committee voting results suggested that the data for this product support the contention of adequate safety and efficacy in individuals 18-65 years of age.

## 5.5 Literature Reviewed

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

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

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

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

- GT-07 (Phase II/III: European safety/tolerability and efficacy in Adults)
- GT-02 (Phase II/III: European safety/tolerability and Dose finding study in Adults)

- GT-08 (Phase III: European safety/tolerability and efficacy study in Adults)
- GT-14 (Phase III: US safety/tolerability and efficacy study in Adults)
- P05238 (Phase III: North American safety/tolerability and efficacy study in Adults)
- P05238 (Phase III: North American safety/tolerability and efficacy study in Adults)
- P05239 (Phase III: North American and German safety/tolerability and efficacy study in Children)
- P08067 (Phase III: North American safety/tolerability and efficacy study in Adults and Children)

Additionally, the applicant examined the safety/tolerability of this product in five additional studies that included either Adults or Children.

- GT-01 (Phase I: European safety study in Adults)
- GT-03 (Phase I: European safety study in Adults)
- GT-04 (Phase I: European safety study in Adults)
- GT-09 (Phase I: European safety study in Children)
- GT-11 (Phase I: European safety study in Children)

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

- P05238 (Phase III: North American safety/tolerability and efficacy study in Adults)
- P05239 (Phase III: North American and German safety/tolerability and efficacy study in Children)
- P08067 (Phase III: North American safety/tolerability and efficacy study in Adults and Children)

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

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

### **Randomization**

In all studies, patients who fulfilled all the inclusion criteria and none of the exclusion criteria were randomized to active therapy or placebo, with a treatment assignment ratio (or allocation ratio) typically leading to groups of equal size (ratio 1:1, 1:1:1, 1:1:1:1 for studies with placebo and one, two, or three dosage levels of active treatment, respectively). Once the final dosage of 2,800 BAU was selected as the optimal dose, all

future studies randomized patients in a 1:1 ratio. A computer-generated randomization list was prepared for each study. All multicenter studies were stratified by study center by allocating complete blocks to each center.

### **Control treatment**

The efficacy studies were placebo-controlled.

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

### **Blinding**

All studies addressed in this document were double-blind.

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

### **Treatment Schedules**

The various study treatment schedules were not consistent between all studies; thus, separate discussions of individual studies will be provided when examining specific studies. However, in general there was a baseline time period in which subjects' allergic symptoms were collected. Subsequent administration of product occurred 16 to 12 weeks prior to the anticipated pollen season, and during the pollen season, subjects noted their allergic symptoms within daily diary cards. Additionally, during and after the treatment dosing time frame, adverse events were collected within diary cards or during clinic visits.

### **Patient population**

The patients enrolled in the clinical development program included both adults and/or children, depending on the study and were consistent with the population consulting allergy practices for treatment of grass pollen-related allergic rhinoconjunctivitis.

### **Choice and description of study endpoints**

The clinical development program of Grastek® sublingual tablet began by Merck (originally ALK Abello) in 2001.

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

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

Throughout the program, the applicant designed the studies in line with appropriate health authority guidelines, including the US-FDA with respect to the single study performed under US-IND. The field exposure studies provided in this submission had similar endpoints and time frames for administration and data collection, while the safety studies had similar endpoints with safety data collected over time spans consisting of 28 days from initial exposure to Oralair® through up to 3 years post-exposure to the product.

**Symptom Score**

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

**Table 6.a.** Daily Symptom Score

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

Table summarizes the definition of symptom scores based on definitions provided within summary of clinical efficacy:

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**Daily Medication Score**

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

would escalate the use of rescue medication as the symptoms developed and became more severe.

**Table 6.b.** Daily Rescue Medication Score

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

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

### Total Combined Symptom and Medication Score

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

$$TCS = DSS + DMS.$$

### General Statistical approach

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

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

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

The normality assumption of the ANOVA model was examined for the key efficacy endpoints. When the normality assumption was severely violated, analysis based on appropriate parametric methods (e.g., square root and log transformation of the data, and a zero-inflated log-normal model) or nonparametric analysis (e.g., Wilcoxon rank sums test and Hodges-Lehmann analysis of median differences) was adopted as the primary efficacy analysis. In addition, when ANOVA remained as the primary analysis approach, sensitivity analyses using such transformed data or non-parametric methods were utilized to corroborate the results for the primary ANOVA analysis approach. Further, the interaction of treatment with other model covariates was examined via subgroup analyses by each level of the covariates.

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

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

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

### **Analysis sets**

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

## 6.1 Trial #1: P05238-US and Canadian Adult Phase III Field Study

Merck's trial P05238 was submitted to CBER under US-IND to be "a multi-center, double-blind, randomized, placebo controlled, parallel-group study evaluating the efficacy and safety of grass (Phleum Pratense) sublingual tablet (SCH 697243) in adult subjects with a history of grass pollen induced rhinoconjunctivitis with or without asthma."

### 6.1.1 Objectives (Primary, Secondary, etc)

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

#### **Primary Objective:**

To evaluate the efficacy of grass sublingual tablet (Grastek®) versus placebo in the treatment of grass pollen-induced rhinoconjunctivitis based on the combined sum (CS) of rhinoconjunctivitis daily symptom scores (DSS) and rhinoconjunctivitis daily medication scores (DMS) averaged over the entire grass pollen season (GPS).

#### **Key Secondary Objectives:**

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

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

### 6.1.2 Design Overview

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study in subjects 18 to 65 years of age, of either sex and of any race, with a history of grass pollen-induced rhinoconjunctivitis with or without asthma.

There was an observational grass pollen season period in year 2008 where no investigational medicinal product (IMP) was administered. Open-label rescue medications for the rhinoconjunctivitis and asthma symptoms were provided during this year.

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

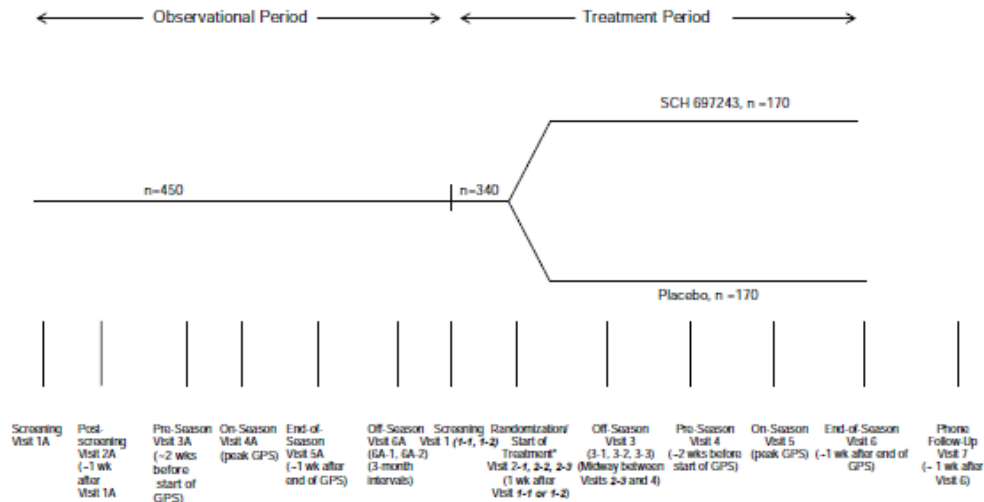


In the treatment period, the subjects were treated once daily with either Grastek® (Timothy grass allergy immunotherapy tablet [grass AIT]) or placebo for approximately 16 weeks prior to the GPS and during the GPS.

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

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

**Figure 6.1.2.a. Study Design Diagram**



Source: Original BLA 125473/000 Clinical Study Report P05238 page 35

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

**Reviewer Comment:** *The study as proposed and implemented was acceptable to the statistical reviewer. Initially, CBER had suggested a different and more stringent threshold for the upper bound of the 95% confidence interval; however, based upon feedback from many applicants and discussions held during the May 2011 APAC, it was*

*determined that a -10% margin for the upper bound of the 95% CI was sufficient. This revised upper bound threshold was agreeable to CBER, and it was utilized as the standard criterion for efficacy for all field studies for seasonal allergies caused by grass pollens.*

### 6.1.3 Population

The treatment population consisted of male or female patients aged 18 to 65 years (inclusive) in the United States and Canada with documented grass pollen-related allergic rhinoconjunctivitis, based on a clinical history of significant allergic rhinoconjunctivitis to grass (with or without asthma) diagnosed by a physician and who had received treatment for their disease for the previous grass pollen season, had a positive SPT to Timothy grass (wheal diameter  $\geq 5$  mm, greater than the negative control), and were positive for specific IgE against *Phleum pratense* ( $\geq$  IgE Class 2;  $\geq 0.7$  kAU/L) at the screening visit.

### 6.1.4 Study Treatments or Agents Mandated by the Protocol

In this study, two treatments were to be examined and compared: 2800 BAU Grastek® tablets and Placebo tablets that matched the 2800 BAU Grastek® tablets. Both the active treatment and placebo were to be administered sublingually (under the tongue) every day at the same time during the approximate 4 to 6-month treatment period, depending on the location of the treatment site.

### 6.1.6 Sites and Centers

This study was to include 59 centers in various locations within the United States and 10 centers within Canada with expected exposure to grass pollen.

### 6.1.7 Surveillance/Monitoring

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

### 6.1.8 Endpoints and Criteria for Study Success

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

#### Primary efficacy variable:

The daily combined symptom score (CS) is a daily patient-specific score taking into account the patient's daily rhinoconjunctivitis symptom scores (DSS) and daily rescue

medication scores (DMS), assuming equivalent importance of symptoms and medication scores.

The TCS score is calculated as:  $TCS = DSS + DMS$ .

The DSS is described in Section 6, including tables that specifically provide the scoring mechanisms and methods.

Secondary efficacy variables:

- Daily Symptom Scores (DSS): The DSS is the sum of the six (non-missing) rhinoconjunctivitis symptom scores as evaluated by the patient using a score from 0 to 3.
- Daily Rescue Medication Score (DMS): The DMS was assigned daily to the different medications used as rescue medication.
- Rhinoconjunctivitis symptoms (RSS): The severity of each of the six individual rhinoconjunctivitis symptoms was scored daily.

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

- The proportion of patients who used rescue medication during the pollen period and worst pollen period while on treatment.
- The proportion of days rescue medication was used during the pollen period and worst pollen period while on treatment.
- Proportion of Symptom-Controlled Days (PSCD) as defined by a DSS score of "0."
- Overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score.
- Global assessment and evaluation of the efficacy of the treatment by the patient.
- Asthma status and severity.
- Immunological markers (IgE and IgG4 specific for Timothy grass pollen allergen) and Skin Prick Test (SPT) results.

Safety variables:

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

### 6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis sets:

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

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

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

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

**Secondary Efficacy Endpoints:** The secondary endpoints were evaluated using a linear model with asthma status, treatment, and study site effects in the model. For the following key secondary endpoints, the type 1 error rate was controlled using the Hochberg procedure:

- SCH 697243 vs placebo on the average rhinoconjunctivitis DSS for the entire GPS
- SCH 697243 vs placebo on the average rhinoconjunctivitis DMS for the entire GPS
- SCH 697243 vs placebo on the average weekly rhinoconjunctivitis quality of life total score for the entire GPS.

The secondary endpoints were adjusted for multiplicity using the Benjamini and Hochberg method to control the overall alpha level of 0.05 among the secondary efficacy tests of interest. The key secondary analyses were to be performed only if the primary analysis was statistically significant at two-sided  $\alpha = 0.05$ .

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

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

**Determination of sample size:** In the observational period, up to 450 subjects were to be enrolled. Assuming 25% dropout from the observational period, approximately 340 subjects were to be enrolled in the treatment period the following year. New subjects were also to be enrolled after the start of the Year 1 (2008) observational period GPS if additional subjects were needed to meet the targeted sample size. In the treatment period, the subjects were to be randomized in a 1:1 ratio to either Grastek® 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). This sample size was based on an estimated placebo effect of the combined score (CS) of 7.07, an estimated pooled standard deviation of 4.77, and a difference of effect from placebo to treatment of 1.62 (or 23%), all of which were estimated based on prior Phase I/II studies of Grastek®.

**Reviewer Comment:** *The applicant initially proposed utilizing a point estimate in which an improvement of greater than 20% based on the combined score of the Grastek® treated individuals over the placebo comparator was to be considered the primary endpoint. This was agreeable to CBER; however, it was suggested that the study also meet a clinically meaningful margin of -10% for the upper bound of the 95% CI. This study was created in 2007 and started in 2008, well before the feedback provided and issues discussed during the May 2011 APAC meeting in which this advice for standards for field studies was presented in a public format.*

#### 6.1.10 Study Population and Disposition

The study population and baseline demographics of the enrolled patients are similar for both treatment groups. In this study, 439 patients were randomized to treatment.

##### 6.1.10.1 Populations Enrolled/Analyzed

The following table illustrates the population distribution in study P05238.

**Table 6.1.10.1.1.** Summary of Patient Population

	<b>Grastek 2800 BAU N (%)</b>	<b>Placebo N (%)</b>	<b>Total N (%)</b>
Patients Randomized	213 (100%)	225 (100%)	438 (100%)
Patients in Safety Set	213 (100%)	225 (100%)	438 (100%)
Patients in Full Analysis Set	213 (100%)	225 (100%)	438 (100%)
Protocol Evaluable Data Set	164 (77%)	188 (84%)	352 (80%)

Source: Table created by reviewing statistician utilizing data provided in:

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##### 6.1.10.1.1 Demographics

The demographics of the individuals included in this study can be seen in the following table. Within the table the number of individuals and percent of individuals is noted for each treatment group, based on the demographic variables of gender, age, and race. This table illustrates that the baseline characteristics were similar for both treatment groups.

**Table 6.1.10.1.1** Baseline Demographics of the Patient Population

Baseline Demographic	2800 BAU N=213	Placebo N=225	Total N=438
<b>Gender [n (%)]</b>			
Female	109 (51)	112 (50)	221 (50)
Male	104 (49)	113 (50)	217 (50)
<b>Age (years)</b>			
Range	18 – 63	18 – 61	18 – 63
<b>Race [n (%)]</b>			
White/Caucasian	182 (85)	187 (83)	369 (84)
Black or African American	21 (10)	21 (9)	42 (10)
Asian	4 (2)	9 (4)	13 (3)
American Indian/Alaska Native/Pacific Islander	0 (0)	3 (1)	3 (1)
Other	6 (3)	5 (2)	11 (3)

Source: Table created by reviewing statistician utilizing data provided in:  
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#### 6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

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

**Table 6.1.10.1.2** Baseline Medical/Behavioral Characteristics of the Patient Population

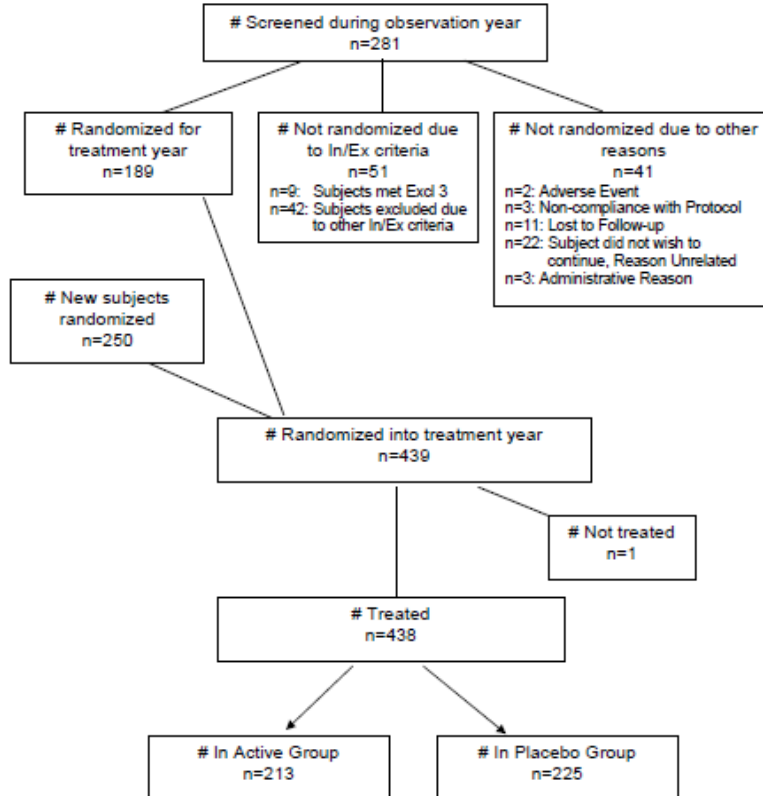
Baseline Demographic	2800 BAU N=213	Placebo N=225	Total N=438
<b>BMI (kg/m<sup>2</sup>)</b>			
Mean (SD)	27.5 (5.7)	27.9 (6.0)	27.8 (5.9)
Range	17-47.8	11.6-48.4	11.6-48.4
<b>Asthma Status [n (%)]</b>			
Asthmatic	45 (21%)	56 (26%)	104 (24%)
Non-Asthmatic	168 (79%)	166 (74%)	334 (76%)
<b>Sensitization [n (%)]</b>			
Grass	213 (100%)	225 (100%)	438 (100%)
Other Allergens	181 (85%)	191 (85%)	372 (85%)

Source: Table created by reviewing statistician utilizing data provided in:  
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#### 6.1.10.1.3 Subject Disposition

The following figure illustrates the randomization, allocation, and withdrawal of patients for this study. This graphic notes which treatment arm subjects were randomized to and subsequently lists the reason for dropout, including the number of subjects and percentage of subjects that withdrew prior to study completion. It is of interest to note the adverse event rate is slightly higher in the active treatment group; however, other reasons for dropout were fairly similar between the placebo and treatment groups.

**Table 6.1.10.1.3.1. Patient Disposition through Randomization**



Source: Original BLA 125473/000 Clinical Study Report P05238 page 82

The disposition of subjects can be further examined in the following table that illustrates which randomized subjects were followed throughout the entire study period. Considering the tabulation of subjects that discontinued or were lost to follow-up within the study, it appears that the placebo and treated group had similar dropout patterns.

**Table 6.1.10.1.3.2. Patient Disposition after Randomization**

Disposition of Subjects	Number (%) of Subjects		
	SCH 697243 (2800 BAU)	Placebo	Total
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)

Source: Original BLA 125473/000 Clinical Study Report P05238 page 83

### 6.1.11 Efficacy Analyses

The applicant proposed and implemented the following efficacy analysis within this study.

#### Primary Efficacy Analysis

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

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 the treatment groups, with appropriate adjustments made. For the primary endpoint, subjects with at least one post-baseline diary record with DSS and DMS within the defined pollen season were to be included. The combined average score was to be based on all available data during the GPS for each subject.

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

#### Secondary Efficacy Analysis

The secondary efficacy variable to address the treatment effect for this study was the DSS and DMS.

The DSS is composed of six rhinoconjunctivitis symptoms recorded daily, including runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes; the symptoms were measured on a scale of 0 (no symptoms) to 3 (severe symptoms), and a higher score indicated a higher level of symptoms. The DMS is



composed of a sum of the scores associated with rescue medication use per day, where a lower medication score indicated less use of rescue medication. The DSS and DMS data were collected during the GPS in which the duration of the GPS was defined as the total number of days for which a subject had data during the GPS.

#### Safety Analysis

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

##### 6.1.11.1 Analyses of Primary Endpoint(s)

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

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

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

The linear model results for the primary efficacy analysis of the TCS during the pollen period for the FAS are summarized below. The point estimate is the LS Means difference between 2800 BAU and placebo, and the relative LS Means difference is equal to (LS Mean difference/LS Mean for the Placebo group) x 100.

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

The mixed model is a combination of fixed and random effects parameters and is written as follows:

$$y = X\beta + Z\gamma + \epsilon$$

where  $y$  denotes the vector of observed  $y_{ij}$ 's,  $X$  is the known matrix of  $x_{ij}$ 's,  $\beta$  is the unknown fixed effects parameter vector.  $Z$  is the known design matrix of  $z_{ij}$ 's,  $\gamma$  is the

vector of unknown random effects parameters, and  $\epsilon$  is the unobserved vector of independent and identically distributed Gaussian random errors.

The results in the third and fourth columns of Table 6.1.11.1.a. below are the estimates from the mixed model, including the linear estimate for the contrast vector (L) and the approximate standard error for the LS Mean (computed as the square root of  $L(X'V^{-1}X)^{-1}L'$ , where V is the variance/covariance structure).

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

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

**Table 6.1.11.1.a.** Primary Efficacy Analysis: ANCOVA of the TCS during the Pollen Period – FAS

Treatment	n	LS Mean	LS Mean difference vs Placebo	LS Mean difference vs Placebo	Relative LS Mean difference (%)	Relative LS Mean difference (%)	Relative LS Mean difference (%)
			Point Est	95% CI	Point Est	95% CI	95% CI (using the delta method)
Grastek®	184	5.08	-1.31	[-2.22, -0.40]	-20%	[-33%, -6%]	[-34%, -5%]
Placebo	207	6.39					

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

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

The difference in LS means of the daily TCS during the entire grass pollen period between the 3400 BAU group and the Placebo group was statistically significant. The treatment effect was estimated as the difference in LS means of -1.31, corresponding to a relative LS Mean difference of -20% from placebo. The 95% CI expressed as percentages was [-33%, -6%]. Furthermore, utilizing the delta method, the 95% CI expressed as percentages was [-34%, -5%], which does not satisfy CBER’s suggested criterion of meeting a 10% threshold for reduction of combined symptom scores, nor does it meet the applicant’s pre-specified treatment difference of 23%. However, both the point estimate and the upper confidence bound of the 95% CI do suggest a positive trend for reducing treatment symptoms and rescue medication when comparing Grastek® to placebo.

### 6.1.11.2 Analyses of Secondary Endpoints

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

Table 6.1.11.2.a. illustrates the difference between the placebo and treatment groups for the entire grass pollen season. Within this table the DDS, and DMS sample size in each treatment arm, point estimate of the LS Mean per treatment arm as well as LS Mean difference, 95% CI of the LS Mean and relative LS Mean Difference are presented.

**Table 6.1.11.2.a** Secondary Efficacy Analysis: ANCOVA of the DDS and DMS during the Grass Pollen Season (GPS) – FAS

Treatment	n	LS Mean	LS Mean difference vs Placebo  Point Est (95% CI)	Relative LS Mean difference vs Placebo (%)  Pt Est	Relative LS Mean difference vs Placebo (%)  95% CI
<b>DDS</b>					
Grastek®	184	3.8	-0.9	18%	(-29%, -6%)
Placebo	207	4.7	(-1.5, -0.3)		
<b>DMS</b>					
Grastek®	184	1.3	-0.5	-25%	(-49, -5%)
Placebo	207	1.7	(-1.0, -0.1)		

Source: Table created by reviewing statistician utilizing data provided in:

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

Table 6.1.11.2.b. illustrates the difference between the placebo and treatment groups for the peak grass pollen season. Within this table the TCS, DDS, and DMS sample size in each treatment arm, point estimate of the LS Mean per treatment arm as well as LS Mean difference, 95% CI of the LS Mean and relative LS Mean Difference are presented. This is a secondary analysis in which the study was not powered to detect differences between treatment groups nor were alpha adjustments made for these hypothesis tests; however, the trends observed within the table suggest that the treatment reduces the symptoms, use of rescue medication, or the combination of both when compared to individuals randomized to the placebo treated group.

**Table 6.1.11.2.b.** Secondary Efficacy Analysis: ANCOVA of the TCS, DDS and DMS during the Peak Grass Pollen Season – FAS

Treatment	n	LS Mean	LS Mean difference vs Placebo  Point Est (95% CI)	Relative LS Mean difference vs Placebo (%)  Pt Est	Relative LS Mean difference vs Placebo (%)  95% CI
<b>TCS</b>					
Grastek®	184	5.8	-1.6	-21%	(-36%, -4%)
Placebo	207	7.3	(-2.8, -0.4)		
<b>DDS</b>					
Grastek®	184	4.2	-1.1	-21%	(-32%, -7%)
Placebo	207	5.2	(-1.8, -0.4)		
<b>DMS</b>					
Grastek®	184	1.6	-0.5	-22%	(-50%, 16%)
Placebo	207	2.1	(-1.2, 0.3)		

Source: Table created by reviewing statistician utilizing data provided in:

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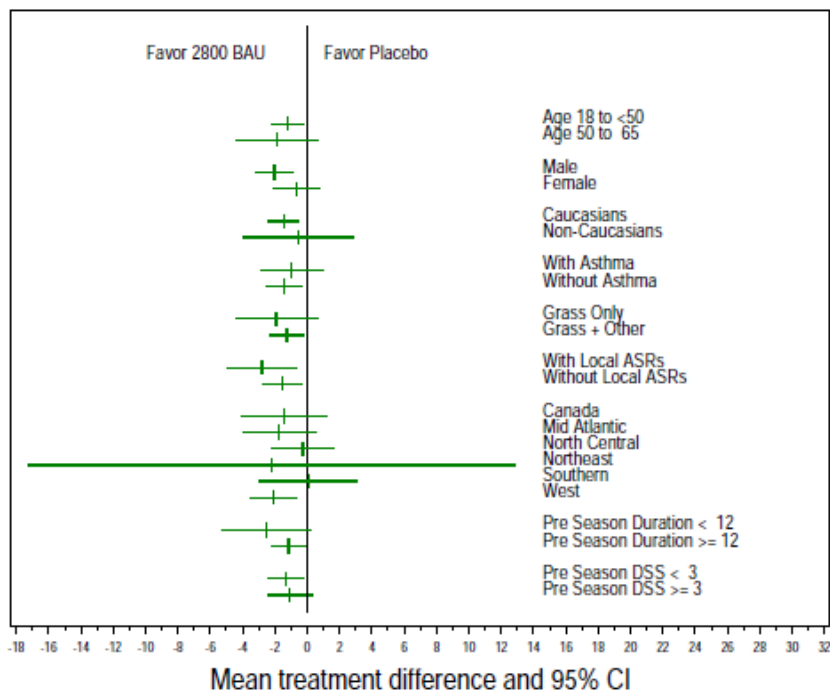
Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, asthma status using SAS Proc MIXED procedure.

### 6.1.11.3 Subpopulation Analyses

Several subpopulations were of interest to the review team: grass pollen sensitivity, geographic location, and asthma status. Additionally, based on current regulations, there should be analyses based on gender, age, and race. In this study, nearly 85% of the enrolled subjects were Caucasian/white; thus, subgroup analysis of the primary endpoint based on specific races is not expected to be informative. However, comparisons of the treatment response when considering male vs female outcomes as well as those from 18-50 years of age (at study enrollment) versus those 50 to 65 years of age were performed by the reviewing statistician. These results provide consistent positive trends that demonstrate Grastek® reduces total combined symptom and rescue medication scores when compared to placebo.

From Figure 6.1.11.3.1 below, it can be seen that there is an observable positive treatment effect for both male and female subjects, but the effect appears to be slightly greater among males. Other comparisons of groups, including sensitivity to grasses, asthma status, and geographic location are presented and illustrate positive trends in the effect of the Grastek® treatment in reducing symptoms.

**Figure 6.1.11.3.1.** Subpopulation Analysis for Age, Gender, Race, Grass Sensitivity, and Region when examining the TCS during GPS including mean and 95% Confidence Interval



Source: Original BLA 125473/000 Clinical Study Report P05238 page 136 results confirmed by reviewing statistician

#### 6.1.11.4 Dropouts and/or Discontinuations

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

For each of the primary and key secondary endpoints of TCS, DSS, and DMS, 11% (24/208) of subjects in the Grastek® group and 8% (18/225) of subjects in the placebo group had no data during GPS. The dropouts in each of the treatment arms were within the expected dropout/missing values suggested within the IND phase of the study (10%).

Consistent with the primary analysis methodology, the primary endpoint and two of three key secondary endpoints meet the criterion for declaring significant difference between the active group and placebo group using the non-parametric methods.

#### Sensitivity Analysis based on Missing Values

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

1. LOCF (Last Observation Carried Forward) method – Impute any missing daily values of TCS by the last observed non-missing daily value of TCS carried forward until next non-missing daily TCS value is found.
2. Worst Case Scenario – Impute missing values of TCS on a given day by the opposite treatment group’s mean value for TCS in GPS. Thus, a subject in the active group with a missing value in TCS on a given day will have that missing value replaced by the mean TCS value for the placebo group and vice versa.
3. Alternative definition of the pollen season – Instead of using the method described in the protocol to define the pollen season (i.e., first day of 3 consecutive days of pollen counts  $\geq 10$  grains/m<sup>3</sup> through last day of the last of 3 consecutive days with pollen count  $\geq 10$  grains/m<sup>3</sup>), an alternative approach was explored. This method selected the four weeks, where each week started on Monday and ended on Sunday, with the highest pollen counts in the pollen season.

Analyses of the primary efficacy data utilizing the various imputation methodologies demonstrate consistent positive results with respect to the point estimate, as well as the 95% CI of the relative difference between the active group and placebo group. In the following table, it can be seen that the point estimates for the % relative difference based on the different imputation mechanisms are: -19%, -12%, and -20%. The “worst case scenario” sensitivity analysis does not meet the -10% upper bound for the 95% CI of the relative difference; however, the other imputation methods would have met CBER’s criterion for success.

**Figure 6.1.11.4.1.** Sensitivity Analysis of Primary Variables during GPS

Table 4 Sensitivity Analysis of Primary Variable during GPS

TCS Analysis	2800 BAU (N=208)	Placebo (N=225)	Difference (%)	P-value	95% CI
LOCF					
Adjusted Mean (SE)	5.08 (0.41)	6.31 (0.38)	-1.23 (-19%)	0.008	(-2.13, -0.33)
Worst Case					
Adjusted Mean (SE)	5.36 (0.35)	6.10 (0.33)	-0.74 (-12%)	0.046	(-1.47, -0.01)
Alternative Pollen Season					
Adjusted Mean (SE)	5.64 (0.46)	7.05 (0.43)	-1.40 (-20%)	0.007	(-2.42, -0.38)

Source: Original BLA 125473/000 Clinical Study Report P05238 page 2497 results of LOCF and Worst case confirmed by reviewing statistician.

**Reviewer comment:** *The proposed treatment of exclusions and missing values is acceptable. In addition, comparisons of missing value rates were made and were deemed comparable for both treatment groups for primary endpoints as well as key secondary endpoints.*

6.1.11.5 Exploratory and Post Hoc Analyses

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

6.1.12 Safety Analyses

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

**Table 6.1.12.a.** Summary of Adverse Events Observed in the Treated and Placebo Groups during the Entire Study Period

Adverse Event Category	Number (%) of Subjects		
	SCH 697243 2800 BAU (n=213)	Placebo (n=225)	Total (N=438)
Any Adverse Event	176 (82.6)	161 (71.6)	337 (76.9)
Related Adverse Events <sup>a</sup>	155 (72.8)	62 (27.6)	217 (49.5)
Severe/Life-threatening Adverse Events	7 (3.3)	9 (4.0)	16 (3.6)
Serious Adverse Events <sup>b</sup>	2 (0.9)	5 (2.2)	7 (1.3)

Source: Original BLA 125473/000 Clinical Study Report P05238 page 145 (confirmed by reviewing statistician).

A summary of the types of serious adverse events observed during the study can be seen in the following table that was confirmed by the reviewing statistician via JMP. Within Table 6.1.12.b shows that 9 patients had SAEs in the Placebo group and 7 patients had SAEs within the Grastek® group. Additionally, other less serious adverse events are included within the table, showing similar trends in adverse events occurring in both the active treated and placebo treatment groups.



Table 6.1.12.b. Summary of Serious Adverse Events

	Number (%) of Subjects		
	SCH 697243 2800 BAU (n=213)	Placebo (n=225)	Total (N=438)
<b>Subjects Reporting Any Adverse Event</b>	176 (82.6)	161 (71.6)	337 (76.9)
<b>Ear and Labyrinth Disorders</b>			
Ear Pruritus	42 (19.7)	3 (1.3)	45 (10.3)
<b>Eye Disorders</b>			
Eye Pruritus	11 (5.2)	8 (3.6)	19 (4.3)
<b>Gastrointestinal Disorders</b>			
Abdominal Discomfort	5 (2.3)	1 (0.4)	6 (1.4)
Dry Mouth	0	7 (3.1)	7 (1.6)
Dyspepsia	11 (5.2)	3 (1.3)	14 (3.2)
Hypoaesthesia Oral	6 (2.8)	3 (1.3)	9 (2.1)
Lip Swelling	10 (4.7)	1 (0.4)	11 (2.5)
Nausea	10 (4.7)	7 (3.1)	17 (3.9)
Oedema Mouth	17 (8.0)	1 (0.4)	18 (4.1)
Oral Pruritus	75 (35.2)	7 (3.1)	82 (18.7)
Paraesthesia Oral	29 (13.6)	5 (2.2)	34 (7.8)
Stomatitis	16 (7.5)	1 (0.4)	17 (3.9)
Swollen Tongue	11 (5.2)	0	11 (2.5)
Tongue Disorder	8 (3.8)	0	8 (1.8)
<b>General Disorders and Administration Site Conditions</b>			
Chest Discomfort	8 (3.8)	3 (1.3)	11 (2.5)
<b>Infections and Infestations</b>			
Bronchitis	7 (3.3)	3 (1.3)	10 (2.3)
Influenza	3 (1.4)	8 (3.6)	11 (2.5)
Nasopharyngitis	17 (8.0)	29 (12.9)	46 (10.5)
Sinusitis	8 (3.8)	11 (4.9)	19 (4.3)
Upper Respiratory Tract Infection	38 (17.8)	25 (11.1)	63 (14.4)
Viral Upper Respiratory Tract Infection	5 (2.3)	8 (3.6)	13 (3.0)
<b>Musculoskeletal and Connective Tissue Disorders</b>			
Arthralgia	2 (0.9)	6 (2.7)	8 (1.8)
Neck Pain	5 (2.3)	3 (1.3)	8 (1.8)
<b>Nervous System Disorders</b>			
Headache	15 (7.0)	16 (7.1)	31 (7.1)
Paraesthesia	10 (4.7)	1 (0.4)	11 (2.5)
<b>Psychiatric Disorders</b>			
Insomnia	3 (1.4)	6 (2.7)	9 (2.1)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>			
Cough	7 (3.3)	8 (3.6)	15 (3.4)
Dry Throat	6 (2.8)	2 (0.9)	8 (1.8)
Nasal Congestion	3 (1.4)	9 (4.0)	12 (2.7)
Nasal Discomfort	4 (1.9)	5 (2.2)	9 (2.1)
Oropharyngeal Pain	10 (4.7)	12 (5.3)	22 (5.0)
Pharyngeal Erythema	5 (2.3)	1 (0.4)	6 (1.4)
Pharyngeal Oedema	14 (6.6)	0	14 (3.2)
Rhinorrhoea	10 (4.7)	4 (1.8)	14 (3.2)
Sneezing	7 (3.3)	5 (2.2)	12 (2.7)
Throat Irritation	63 (29.6)	11 (4.9)	74 (16.9)
<b>Skin and Subcutaneous Tissue Disorders</b>			
Pruritus	11 (5.2)	6 (2.7)	17 (3.9)
Rash	0	5 (2.2)	5 (1.1)
Urticaria	1 (0.5)	6 (2.7)	7 (1.6)

Source: Original BLA 125473/000 Clinical Study Report P05238 Section 12.2.1.1 Table 36 Page 146, results confirmed by reviewing statistician.

Additional details related to safety events can be seen in the medical officer's and epidemiologist's reviews.

**Reviewer's comment:** *Overall, the treatment group had slightly more adverse events than the placebo; however, as an active treatment designed to elicit a response via the*

*product instead of the pollens during the pollen season, this finding is not surprising. Additional and more detailed comments can be found in the medical officer's and epidemiologist's reviews.*

#### 6.1.12.1 Methods

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

#### 6.1.12.3 Deaths

One death was observed in this study but was considered by the applicant as well as the medical officer to be unrelated to study drug, as the subject suffered a multiple drug overdose of non-study drugs several months after the study drug was discontinued. Further details and discussion can be found in the medical officer's review.

#### 6.1.12.4 Nonfatal Serious Adverse Events

No important findings were noted in the 16 observed non-fatal serious adverse events. The number of SAE's were fairly balanced between the two treatment groups: 9 placebo and 7 active treatment, representing less than 5% of study subjects. Furthermore, all serious adverse events were self-limiting and were resolved upon discontinuation of study treatment. For further details and additional discussion, please refer to the medical officer's review.

#### 6.1.12.5 Adverse Events of Special Interest (AESI)

The statistician defers to the medical officer.

#### 6.1.12.6 Clinical Test Results

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

#### 6.1.12.7 Dropouts and/or Discontinuations

A total of 43 subjects prematurely withdrew from the study: 17 (7.1%) from the placebo group and 11 (11.2%) from the study drug group. Two of the dropouts in the placebo group and 15 subjects in the study drug group withdrew because of AEs.

**Summary and conclusion:** Although Study P05238 *did not meet its objectives with respect to the primary efficacy endpoint, this study provided supportive evidence that this product reduces the TCS, DDS, and DMS scores when comparing Grastek® treated individuals to those treated with placebo. The safety profile of Grastek® in this study appears to be acceptable, with only 16 documented serious adverse events that were all self-limiting, resolved, and had comparable rates when considering the placebo versus Grastek® treated subjects. One death occurred due to ingestion of multiple drugs including hydrocodone, meprobamate, and carisoprodol; the subject had not taken study medication for approximately 1 month prior to the event. Furthermore, the adverse events observed during the study treatment period were similar to other similar allergenic products or those experiencing symptoms related to exposure to the grass allergens.*

## **6.2 Trial #2: P05239-US and Canadian Pediatric Phase III Field Study**

Merck’s trial P05239 was submitted to CBER under US-IND to be “a multi-center, double-blind, randomized, placebo controlled, parallel-group study evaluating the efficacy and safety of grass (Phleum Pratense) sublingual tablet (SCH 697243) in children 5 to <18 years of age with a history of grass pollen induced rhinoconjunctivitis with or without asthma.”

### **6.2.1 Objectives (Primary, Secondary, etc.)**

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

#### **Primary Objective:**

To evaluate the efficacy of grass sublingual tablet (Grastek®) versus placebo in the treatment of grass pollen-induced rhinoconjunctivitis based on the combined sum (CS) of rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS) averaged over the entire grass pollen season (GPS).

#### **Key Secondary Objectives:**

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

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

### 6.2.2 Design Overview

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study in subjects 5 to <18 years of age, of either sex and of any race with a history of grass pollen-induced rhinoconjunctivitis with or without asthma.

There was an observational grass pollen season period in year 2008 where no investigational medicinal product (IMP) was administered and a second year in 2009 in which the experimental treatment was administered. Open-label rescue medications for the rhinoconjunctivitis and asthma symptoms were provided during this first year.

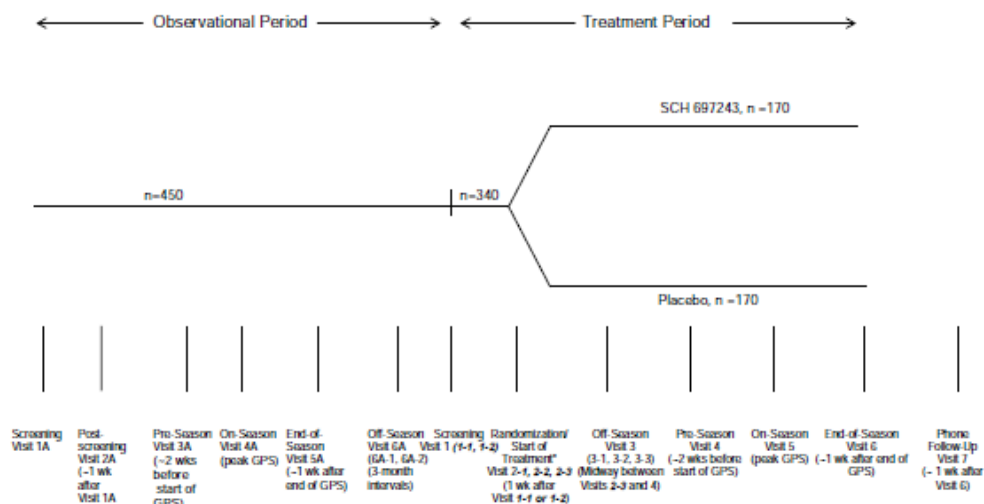
Eligible subjects were to visit the study site for at least 6 visits: Screening, Post-screening, Pre-season, On-season, End-of-season, and Off-season Visits, and at Unscheduled Visits as appropriate. Additional Off-season Visits were scheduled depending on the timing of the Randomization Visit in relation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

In the treatment period, the subjects were treated once daily with either Grastek® (Timothy grass allergy immunotherapy tablet [grass AIT]) or placebo for approximately 16 weeks prior to the GPS and during the GPS.

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

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

Figure 6.2.2.a. Study Design Diagram



Source: Original BLA 125473/000 Clinical Study Report P05239 page 35

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

### 6.2.3 Population

The treatment population consisted of male and female patients aged 5 to <18 years in the United States and Canada with documented grass pollen-related allergic rhinoconjunctivitis, based on a clinical history of significant allergenic rhinoconjunctivitis to grass (with or without asthma) diagnosed by a physician and who had received treatment for their disease for the previous grass pollen season, had a positive SPT to Timothy grass (wheal diameter  $\geq 5$  mm, greater than the negative control), and were positive for specific IgE against Phleum pratense ( $\geq$  IgE Class 2;  $\geq 0.7$  kAU/L) at the screening visit.

### 6.2.4 Study Treatments or Agents Mandated by the Protocol

In this study, two treatments were to be examined and compared: 2800 BAU Grastek® tablets and Placebo tablets that matched the 2800 BAU Grastek® tablets. Both the active treatment and placebo were to be administered sublingually (under the tongue) every day at the same time during the approximate 4 to 6-month treatment period, depending on the location of the treatment site.

### 6.2.6 Sites and Centers

This study was to include 52 centers in various locations within the United States and 10 centers within Canada with expected exposure to grass pollen.

### 6.2.7 Surveillance/Monitoring

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

### 6.2.8 Endpoints and Criteria for Study Success

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

A comprehensive summary of the endpoints and criteria for study success can be seen in Section 6.1.8., an adult study that was nearly identical to this pediatric study.

### 6.2.9 Statistical Considerations & Statistical Analysis Plan

#### Analysis sets:

For the purpose of this study, three analysis sets were defined, namely, the Safety Set, the Full Analysis Set (FAS), and the Per Protocol Analysis Set (PPS).

A comprehensive summary of the analysis for this study can be seen in Section 6.1.9., an adult study that was nearly identical to this pediatric study.

### 6.2.10 Study Population and Disposition

The study population and baseline demographics of the enrolled patients are similar for both treatment groups. In this study, 344 patients were randomized to treatment.

#### 6.2.10.1 Populations Enrolled/Analyzed

The following table displays the population distribution in study P05239.

**Table 6.2.10.1.1. Summary of Patient Population**

	Grastek® 2800 BAU N (%)	Placebo N (%)	Total N (%)
Patients Randomized	175 (100%)	169 (100%)	344 (100%)
Patients in Safety Set	175 (100%)	169 (100%)	344 (100%)
Patients in Full Analysis Set	175 (100%)	169 (100%)	344 (100%)
Protocol Evaluable Data Set	135 (77%)	124 (73%)	259 (75%)

Source: Table created by reviewing statistician utilizing data provided in:

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### 6.2.10.1.1 Demographics

The demographics of the individuals included in this study can be seen in the following table. The number and percentage of individuals are noted for each treatment group based on the demographic variables of gender, age, and race. This table shows that the baseline characteristics were similar for both treatment groups.

**Table 6.2.10.1.1 Baseline Demographics of the Patient Population**

Baseline Demographic	Grastek® N=175	Placebo N=169	Total N=344
<b>Gender [n (%)]</b>			
Female	57 (33%)	64 (38%)	121 (35%)
Male	118 (67%)	105 (62%)	223 (65%)
<b>Age (years)</b>			
Mean (SD)	12.1 (3.0)	12.6 (3.0)	12.3 (3.0)
Range	6-17	5-18	5-18
<b>Race [n (%)]</b>			
White/Caucasian	153 (87%)	149 (88%)	302 (88%)
Black or African American	12 (7%)	13 (8%)	25 (7%)
Asian	5 (3%)	1 (1%)	6 (2%)
American Indian/Alaska Native/Pacific Islander	1 (1%)	1 (1%)	2 (1%)
Other	4 (2%)	5 (3%)	9 (3%)

Source: Table created by reviewing statistician utilizing data provided in:

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### 6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

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

**Table 6.2.10.1.2** Baseline Medical/Behavioral Characteristics of the Patient Population

<b>Baseline Demographic</b>	<b>Grastek® N=175</b>	<b>Placebo N=169</b>	<b>Total N=344</b>
<b>BMI (kg/m<sup>2</sup>)</b>			
Mean (SD)	20.3 (5.0)	20.7 (4.2)	20.5 (4.6)
Range	13.5-48.8	13.8-37.1	13.5-48.8
<b>Asthma Status [n (%)]</b>			
Asthmatic	46 (26%)	44 (26%)	90 (26%)
Non-Asthmatic	129 (74%)	125 (74%)	254 (74%)
<b>Sensitization [n (%)]</b>			
Grass	174 (99%)	168 (99%)	342 (99%)
Other Allergens	152 (87%)	154 (91%)	306 (89%)

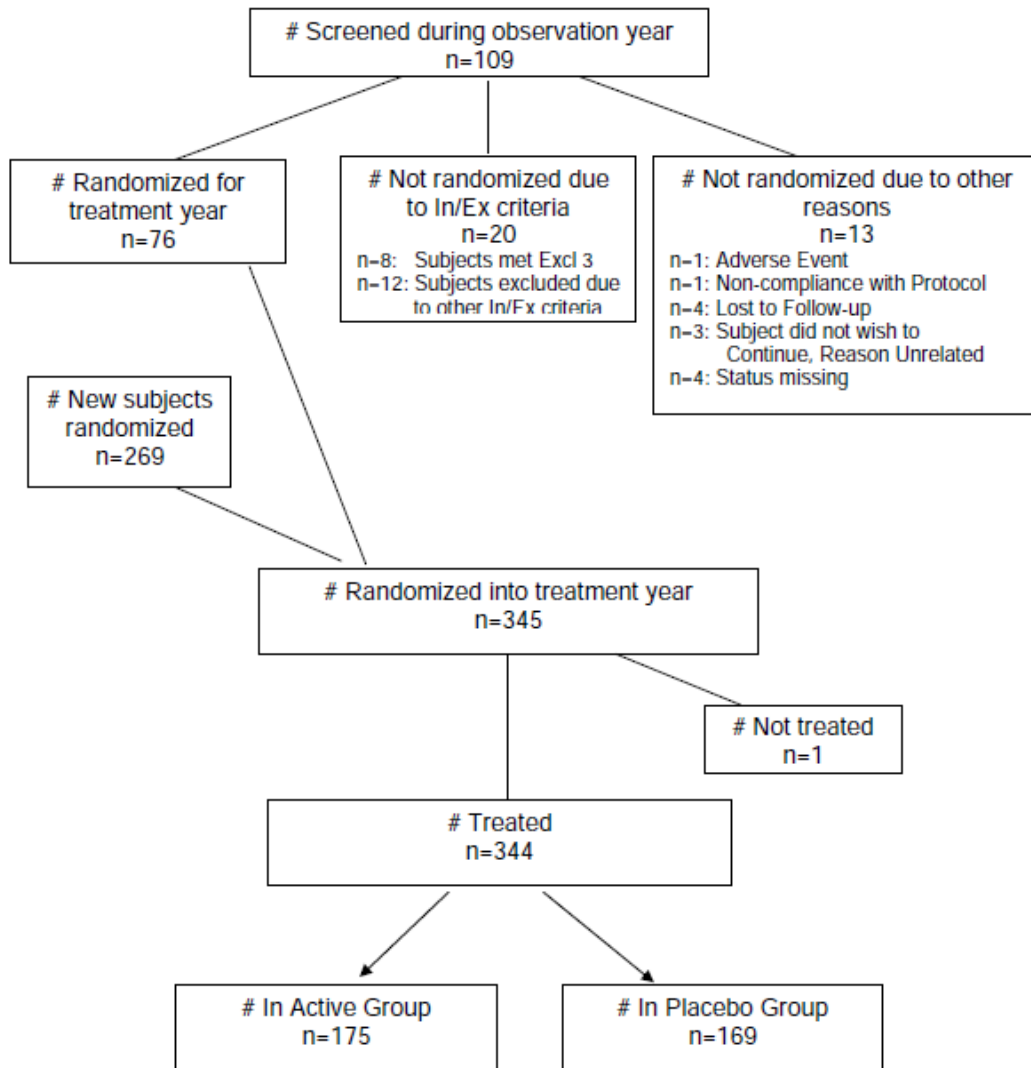
Source: Table created by reviewing statistician utilizing data provided in:  
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### 6.2.10.1.3 Subject Disposition

The following figure illustrates the randomization, allocation, and withdrawal of patients for this study. This graphic notes which treatment arm subjects were randomized to and subsequently lists the reason for dropout, including the number of subjects and percentage of subjects that withdrew prior to study completion. It is of interest to note the adverse event rate is slightly higher in the active treatment group; however, other reasons for dropout were fairly similar between the placebo and treatment groups.



**Table 6.2.10.1.3.1. Patient Disposition through Randomization**



Source: Original BLA 125473/000 Clinical Study Report P05239 page 85

The disposition of subjects can be further examined in the following table that shows which randomized subjects were followed throughout the entire study period. Considering the tabulation of subjects that discontinued or were lost to follow-up within the study, it appears that the placebo and treated group had similar dropout patterns.

**Table 6.2.10.1.3.2. Patient Disposition after Randomization**

	Number (%) of Subjects	
	SCH 697243 (2800 BAU)	Placebo
Treated	175 (100)	169 (100)
Subjects Excluded from the Efficacy-Evaluable Data Set	40 (23)	45 (27)
Reasons for Exclusion from the Efficacy-Evaluable Data Set <sup>a</sup>		
Did not meet entrance criteria <sup>b</sup>	2 (1)	2 (1)
Insufficient efficacy data	26 (15)	11 (7)
Unacceptable concomitant medications <sup>c</sup>	5 (3)	10 (6)
Insufficient washout (concomitant medications)	1 (1)	4 (2)
Noncompliance with study treatment	18 (10)	28 (17)
Protocol Evaluable Data Set	135 (77)	124 (73)

Source: Original BLA 125473/000 Clinical Study Report P05239 page 88

### 6.2.11 Efficacy Analyses

The applicant proposed and implemented the following efficacy analyses within this study.

#### Primary Efficacy Analysis

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

A more detailed and comprehensive summary of the analysis and criteria for study success for the primary efficacy, secondary efficacy, and safety analysis can be seen in Section 6.1.11, the adult study that was nearly identical to this pediatric study.

#### 6.2.11.1 Analyses of Primary Endpoint(s)

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

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

A comprehensive and detailed summary of the endpoints and analyses as well as the criteria for study success can be seen in Section 6.1.11.1., an adult study that was nearly identical to this pediatric study.

These results of statistical analysis of the primary endpoint comparing the TCS scores of the Grastek® treated group versus the placebo group can be seen in the below table.

These results confirmed the applicant’s results and provided an additional analysis supporting the applicant’s conjecture that the Grastek® product reduces the total combined symptom and rescue medication score when compared to placebo.

**Table 6.2.11.1.a.** Primary Efficacy Analysis: ANCOVA of the TCS during the Grass Pollen Season – FAS

Treatment	n	LS Mean	LS Mean difference vs Placebo  Point Est	LS Mean difference vs Placebo  95% CI	Relative LS Mean difference (%)  Point Est	Relative LS Mean difference (%)  95% CI	Relative LS Mean difference (%)  95% CI (using the delta method)
Grastek®	149	4.62	-1.63	[-2.60, -0.66]	-26%	[-38%, -10%]	[-37.%, -11%]
Placebo	158	6.25					

Source: Table created by reviewing statistician utilizing data provided in:  
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Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, asthma status. SAS: PROC MIXED with repeated effect based on Subject and Compound Symmetry as Variance/Covariance structure. As an additional analysis method, the delta method was used to calculate the confidence intervals.

The difference in LS means of the daily TCS during the entire grass pollen period between the Grastek® group and the Placebo group was statistically significant. The treatment effect was estimated as the difference in LS means of -1.63, corresponding to a relative LS Mean difference of -26% from placebo. The 95% CI expressed as percentages was [-38%, -10%]. Furthermore, utilizing the delta method, the 95% CI expressed as percentages was [-37%, -11%], which satisfies CBER’s suggested criterion of meeting a 10% threshold for reduction of combined symptom scores, and it also meets the applicant’s pre-specified treatment difference of 20%. The positive effect of the treatment in reduction of TCS scores compared to placebo were obtained with other variance/covariance structures, including AR(1), as well as other methods for estimation including Fieller’s method, when considering data analyzed from this pediatric study, P05239.

#### 6.2.11.2 Analyses of Secondary Endpoints

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

**Table 6.2.11.2.a** Secondary Efficacy Analysis: ANCOVA of the DDS and DMS during the Grass Pollen Season (GPS) – FAS

Treatment	n	LS Mean	LS Mean difference vs Placebo  Point Est (95% CI)	Relative LS Mean difference vs Placebo (%)  Pt Est	Relative LS Mean difference vs Placebo (%)  95% CI
<b>DDS</b>					
Grastek®	149	3.7	-1.2	-25%	(-36%, -9%)
Placebo	158	4.9	(-1.95, -0.5)		
<b>DMS</b>					
Grastek®	149	0.9	-0.4	-32%	(-58, -4%)
Placebo	158	1.3	(-0.9, 0.0*)		

Source: Table created by reviewing statistician utilizing data provided in:

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Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, asthma status. SAS: PROC MIXED with repeated effect based on Subject and Compound Symmetry as Variance/Covariance structure.

(\*): the computed value is 0.03, not 0,

Table 6.2.11.2.c illustrates the difference between the placebo and treatment groups for the peak grass pollen season. Within this table the TCS, DDS, and DMS, sample size in each treatment arm, point estimate of the LS Mean per treatment arm, as well as LS Mean difference, Relative LS Mean Difference, and 95% CI for the Relative LS Mean Difference are presented. This is a secondary analysis in which the study was not powered to detect differences between treatment groups, nor were alpha adjustments made for these hypothesis tests; however, the trends observed within the table indicate that the treatment reduces the symptoms, use of rescue medication or the combination of both when compared to individuals randomized to the placebo treated group.

**Table 6.2.11.2.c** Secondary Efficacy Analysis: ANCOVA of the TCS, DDS and DMS during the Peak Grass Pollen Season – FAS

Treatment	n	LS Mean	LS Mean difference vs Placebo  Point Est (95% CI)	Relative LS Mean difference vs Placebo (%)  Pt Est	Relative LS Mean difference vs Placebo (%)  95% CI
<b>TCS</b>					
Grastek®	147	4.7	-2.1	-31%	(-48%, -14%)
Placebo	153	6.9	(-3.3, -0.9)		
<b>DDS</b>					
Grastek®	147	3.8	-1.5	-28%	(-43%, -13%)
Placebo	153	5.3	(-2.3, -0.7)		
<b>DMS</b>					
Grastek®	147	0.9	-0.5	-41%	(-81%, 0%)
Placebo	153	1.6	(-1.3, 0.0)		

Source: Table created by reviewing statistician utilizing data provided in:

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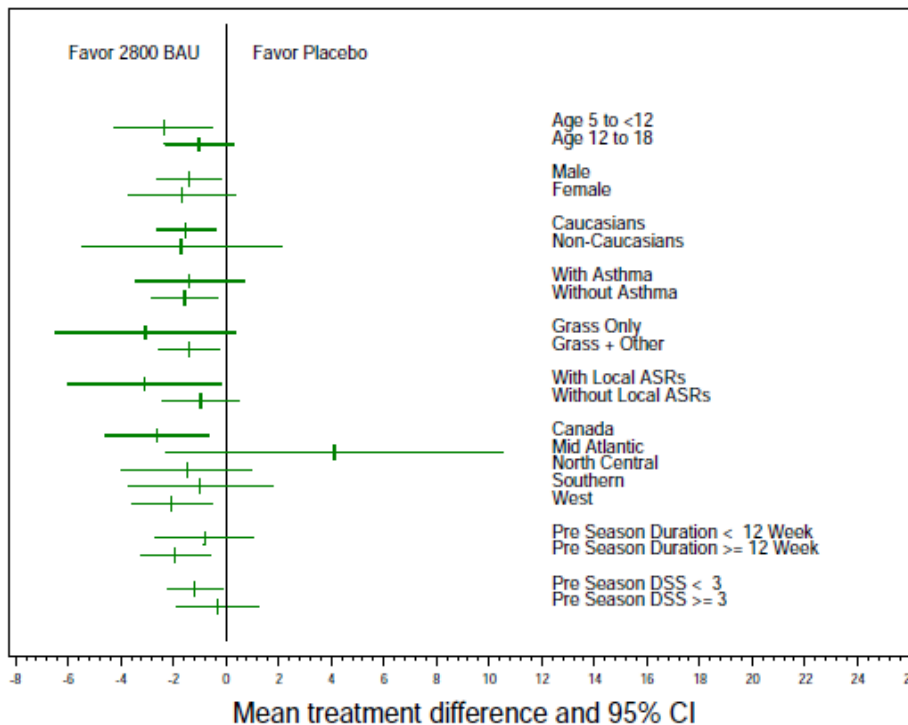
Model utilized: ANCOVA with patient/subject ID, pooled (geographically) center, asthma status. SAS: PROC MIXED with repeated effect based on Subject and Compound Symmetry as Variance/Covariance structure.

### 6.2.11.3 Subpopulation Analyses

Several subpopulations were of interest to the review team: grass pollen sensitivity, geographic location, and asthma status. Additionally, based on current regulations, there should be subgroup analyses based on gender, age, and race. In this study, nearly 90% of the enrolled subjects were Caucasian/white; thus, subgroup analysis of the primary endpoint based on specific races is not necessarily informative. However, comparisons of the treatment response when considering male vs female outcomes, as well as those from 5 to <12 years of age (at study enrollment) versus those 12 to 18 years of age were performed by the reviewing statistician, confirming the results presented by the applicant. These results provide consistent positive trends that demonstrate Grastek® reduces total combined symptom and rescue medication scores when compared to placebo.

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

**Figure 6.2.11.3.1.** Subpopulation Analysis for Age, Gender, Race, Grass Sensitivity, and Region when examining the TCS during GPS, including mean and 95% Confidence Interval



Source: Original BLA 125473/000 Clinical Study Report P05239 page 141 results confirmed by reviewing statistician

#### 6.2.11.4 Dropouts and/or Discontinuations

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

For each of the primary and key secondary endpoints of TCS, DSS, and DMS, 14% (24/173) of subjects in the Grastek® group and 9% (9/167) of subjects in the placebo group had no data recorded during the Grass Pollen Season (GPS). The dropouts in each of the treatment arms were within the expected dropout/missing values anticipated during the IND phase of the study (15%). Although there is a slight imbalance in the missing values in treatment arms, sensitivity analyses were performed to determine if the missing values may have influenced the results and conclusions (see below).

The primary endpoint and two of three key secondary endpoints met the criterion for declaring that there was a statistically significant and clinically meaningful difference between the active group and placebo group.

##### Sensitivity Analyses based on Missing Values

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

1. LOCF (Last Observation Carried Forward) method – Impute any missing daily value of TCS by the last observed non-missing daily value of TCS carried forward until next non-missing daily TCS value is found.
2. Worst Case Scenario – Impute missing values of TCS on a given day by the opposite treatment group’s mean value for TCS in GPS. Thus, a subject in the active group with a missing value in TCS on a given day will have that missing value replaced by the mean TCS value for the placebo group and vice versa.
3. Alternative definition of the pollen season – Instead of using the method described in the protocol to define the pollen season (i.e., first day of 3 consecutive days of pollen counts  $\geq 10$  grains/m<sup>3</sup> through last day of the last of 3 consecutive days with pollen count  $\geq 10$  grains/m<sup>3</sup>), an alternative approach was explored. This method selected the four weeks, where each week starts on Monday and ends on Sunday, with the highest pollen counts in the pollen season.

Analyses of the primary efficacy data utilizing the various imputation methodologies demonstrate consistent positive results with respect to the point estimate, as well as the 95% CI of the relative difference between the active group and placebo group. In the following table, it can be seen that the point estimate for each of the imputation mechanisms described above are: -26%, -14%, and -32%. The “worst case scenario” sensitivity analysis does not meet the -10% upper bound for the 95% CI of the relative difference; however, the other imputation methods would have met CBER’s criterion for success.

**Figure 6.2.11.4.1. Sensitivity Analysis of Primary Variables during GPS**

Endpoint	2800 BAU (N=173)	Placebo (N=167)	Difference(%)	P-value	95% CI
TCS_LOCF					
Adjusted Mean (SE)	4.61 (0.53)	6.25 (0.52)	-1.64 (-26%)	0.001	(-2.61, -0.67)
TCS_WC					
Adjusted Mean (SE)	5.21 (0.43)	6.12 (0.42)	-0.91 (-15%)	0.019	(-1.67, -0.15)
TCS_ATL					
Adjusted Mean (SE)	4.45 (0.60)	6.52 (0.61)	-2.08 (-32%)	<0.001	(-3.19, -0.96)

Source: Original BLA 125473/000 Clinical Study Report P05239 page 2238 results of LOCF and Worst case confirmed by reviewing statistician.

**Reviewer comment:** *The proposed treatment of exclusions and missing values was deemed acceptable to the reviewing statistician. Comparisons of missing value rates were made and revealed slight differences between the treatment groups. However, sensitivity analyses demonstrated similar trends and conclusions for the primary endpoint and key secondary endpoints, supporting the contention that the Grastek® product improves the TCS scores when compared to placebo treated individuals.*

#### 6.2.11.5 Exploratory and Post Hoc Analyses

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

#### 6.2.12 Safety Analyses

Safety data were collected for the entire study period. Subjects were able to note safety events on the daily diary cards, and also received periodic follow-up from study personnel. Overall, there were slightly more adverse events in the treatment group compared to the placebo group; however, there were no serious adverse events noted in

either the treatment or placebo group. A summary of the adverse events can be seen in the applicant's following table, which includes the number (and percentage) of subjects experiencing adverse events, stratified by the treatment group (confirmed via JMP tabulations by the reviewing statistician).

**Table 6.2.12.a.** Summary of Adverse Events Observed in the Treated and Placebo Groups during the Entire Study Period

Adverse Event Category	Number (%) of Subjects		
	SCH 697243 2800 BAU (n=175)	Placebo (n=169)	Total (N=344)
Any Adverse Event	151 (86.3)	131 (77.5)	282 (82.0)
Related Adverse Events <sup>a</sup>	122 (69.7)	43 (25.4)	165 (48.0)
Severe/Life-threatening Adverse Events	5 (2.9)	6 (3.6)	11 (3.2)
Serious Adverse Events <sup>b</sup>	0	4 (2.4)	5 (1.2) <sup>c</sup>

Source: Original BLA 125473/000 Clinical Study Report P05239 page 149 (confirmed by reviewing statistician).

A summary of the types of serious adverse events observed during the study can be seen in the following table that was confirmed by the reviewing statistician via JMP. Within this table it can be seen that 10 patients had SAEs in the Placebo group and 5 patients had SAEs within the Grastek® group; one patient who was not randomized to treatment had an SAE. Additionally, other less serious adverse events are included within the applicant's below table and reveal similar trends in adverse events occurring in both the active and placebo treatment groups.



Table 6.2.12.b. Summary of Serious Adverse Events

	Number (%) of Subjects		
	SCH 697243 2800 BAU (n=175)	Placebo (n=169)	Total (N=344)
<b>Subjects Reporting Any Adverse Event</b>	151 (86.3)	131 (77.5)	282 (82.0)
<b>Blood and Lymphatic System Disorders</b>			
Lymphadenopathy	0	4 (2.4)	4 (1.2)
<b>Ear and Labyrinth Disorders</b>			
Ear Pain	4 (2.3)	2 (1.2)	6 (1.7)
Ear Pruritus	21 (12.0)	1 (0.6)	22 (6.4)
<b>Eye Disorders</b>			
Eye Pruritus	15 (8.6)	4 (2.4)	19 (5.5)
<b>Gastrointestinal Disorders</b>			
Abdominal Discomfort	2 (1.1)	5 (3.0)	7 (2.0)
Abdominal Pain Upper	5 (2.9)	8 (4.7)	13 (3.8)
Dysphagia	6 (3.4)	0	6 (1.7)
Lip Swelling	13 (7.4)	0	13 (3.8)
Nausea	8 (4.6)	3 (1.8)	11 (3.2)
Oedema Mouth	19 (10.9)	1 (0.6)	20 (5.8)
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)	1 (0.6)	6 (1.7)
Vomiting	6 (3.4)	6 (3.6)	12 (3.5)
<b>General Disorders and Administration Site Conditions</b>			
Chest Discomfort	5 (2.9)	2 (1.2)	7 (2.0)
Chest Pain	4 (2.3)	0	4 (1.2)
Pyrexia	9 (5.1)	12 (7.1)	21 (6.1)
<b>Infections and Infestations</b>			
Gastroenteritis	5 (2.9)	1 (0.6)	6 (1.7)
Gastroenteritis Viral	6 (3.4)	4 (2.4)	10 (2.9)
Influenza	6 (3.4)	9 (5.3)	15 (4.4)
Nasopharyngitis	26 (14.9)	32 (18.9)	58 (16.9)
Pharyngitis Streptococcal	5 (2.9)	6 (3.6)	11 (3.2)
Sinusitis	5 (2.9)	9 (5.3)	14 (4.1)
Upper Respiratory Tract Infection	21 (12.0)	22 (13.0)	43 (12.5)
Viral Infection	4 (2.3)	2 (1.2)	6 (1.7)
Viral Upper Respiratory Tract Infection	11 (6.3)	12 (7.1)	23 (6.7)
<b>Injury, Poisoning and Procedural Complications</b>			
Procedural Pain	3 (1.7)	6 (3.6)	9 (2.6)
<b>Musculoskeletal and Connective Tissue Disorders</b>			
Arthralgia	0	6 (3.6)	6 (1.7)
Pain in Extremity	4 (2.3)	3 (1.8)	7 (2.0)
<b>Nervous System Disorders</b>			
Dizziness	2 (1.1)	4 (2.4)	6 (1.7)
Headache	19 (10.9)	20 (11.8)	39 (11.3)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>			
Cough	16 (9.1)	19 (11.2)	35 (10.2)
Dry Throat	7 (4.0)	2 (1.2)	9 (2.6)
Dyspnoea	5 (2.9)	1 (0.6)	6 (1.7)
Epistaxis	5 (2.9)	7 (4.1)	12 (3.5)
Nasal Congestion	11 (6.3)	8 (4.7)	19 (5.5)
Nasal Discomfort	5 (2.9)	0	5 (1.5)
Oropharyngeal Pain	23 (13.1)	19 (11.2)	42 (12.2)
Pharyngeal Erythema	13 (7.4)	3 (1.8)	16 (4.7)
Pharyngeal Oedema	7 (4.0)	0	7 (2.0)
Rhinorrhoea	5 (2.9)	4 (2.4)	9 (2.6)
Sneezing	9 (5.1)	2 (1.2)	11 (3.2)
Throat Irritation	65 (37.1)	5 (3.0)	70 (20.3)
Throat Tightness	4 (2.3)	0	4 (1.2)
<b>Skin and Subcutaneous Tissue Disorders</b>			
Pruritus	8 (4.6)	7 (4.1)	15 (4.4)
Rash	4 (2.3)	3 (1.8)	7 (2.0)
Urticaria	7 (4.0)	6 (3.6)	13 (3.8)

Source: Original BLA 125473/000 Clinical Study Report P05239 Page 150, results confirmed by reviewing statistician.

Additional details related to safety events can be seen in the medical officer's and epidemiologist's reviews.

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

#### 6.2.12.1 Methods

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

#### 6.2.12.3 Deaths

No deaths were observed in this study.

#### 6.2.12.4 Nonfatal Serious Adverse Events

No important findings were noted in the 16 observed non-fatal serious adverse events. The number of SAE's were fairly balanced between the two treatment groups: 9 placebo and 7 active treatment, representing less than 5% of study subjects. Furthermore, all serious adverse events were self-limiting and were resolved upon discontinuation of study treatment. For further details and additional discussion, please refer to the medical officer's review.

#### 6.2.12.5 Adverse Events of Special Interest (AESI)

The statistician defers to the medical officer.

#### 6.2.12.6 Clinical Test Results

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

#### 6.2.12.7 Dropouts and/or Discontinuations

A total of 19 subjects (4.7%) discontinued from the treatment period due to AEs; a slightly higher number of subjects in the Grastek® group (13 subjects [7.4%]) than in the placebo group (5 subjects [3%]) discontinued from the trial due to an AE. In addition, one subject not randomized to any treatment also discontinued from the study due to an adverse event.

**Summary and conclusion:** *Study P05239 met its objectives with respect to the primary efficacy endpoint based on an acceptable point estimate of a 26% reduction in combined symptom and rescue medication scores (TCS). The study also met CBER's criterion for efficacy based on a clinically meaningful difference defined as an upper bound of the 95% CI of at least -10% (observed to be -14% in this study). Additionally, this study provided supportive evidence that this product does reduce the TCS, DDS, and DMS scores when comparing Grastek® treated individuals to those treated with placebo. The safety profile of Grastek® in this study appears to be acceptable, with only 16 total documented serious adverse events (including one patient that had not received any treatment) that were all self-limiting, resolved, and had comparable rates between the placebo and Grastek® treated subjects. No deaths occurred in this study. Furthermore, the adverse events observed during the study treatment period were consistent with those elicited by other similar allergenic products or symptoms related to exposure to the grass allergens.*

## 7. INTEGRATED OVERVIEW OF EFFICACY

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

### 7.1 Indication #1

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

*MK-7243 is indicated for 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.*

#### 7.1.1 Methods of Integration

Overall, approximately 2000 subjects 18 to 65 years of age and nearly 500 children 5-18 years of age participated in the clinical development program of MK-7243, which consisted of fourteen clinical trials. The effectiveness and safety of MK-7243 was evaluated in the following clinical trials from Phase I to Phase III:

- 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); and
- Six Phase 3 efficacy and safety trials (GT-08 in adults in Europe, GT-14 in adults in the US, P05238 in adults in North America, GT-12 and P05239 in children in Germany and North America, respectively, and P08067 in adults/children in North America).

The majority of these studies were performed over one allergy season. However, a single long-term extension over several allergy seasons within the Phase 3 adult GT-08 trial was conducted over up to 5 years and was completed in 2009; data from the 3 treatment years and the 2 follow-up years are included in the applicant provided submission.

A summary of the thirteen efficacy studies, including the purpose of the study and number of patients exposed to various doses of the Merck Grastek® product, is provided in the table below.

**Table 7.1.1.a.** Efficacy Studies provided within the BLA for Merck’s Grastek®

Adults	Dose (QD)	Randomized (n)	Approximate Treatment Duration
GT-02 Dose-finding trial	Placebo Placebo+Loratadine 93 BAU +Loratadine 933 BAU+Loratadine 2800 BAU +Loratadine 2800 BAU + Placebo	150 136 136 139 141 153	24 weeks (approximately 8 weeks prior to and during the 2003 GPS)
GT-07 Safety and efficacy in mild-moderate asthma	2800 BAU Placebo	74 40	24 weeks (approximately 10 to 14 weeks prior to and during the 2004 GPS)
GT-08 5-year efficacy and safety <sup>a</sup>	2800 BAU Placebo (Years 1-3) <sup>b</sup> and no treatment (Years 4 and 5)	316 318	<u>Year 1:</u> 4 to 6 months prior to the GPS and during the 2005 GPS. <u>Year 2:</u> Extension of GT-08 to the end of the 2006 GPS. <u>Year 3:</u> Extension of GT-08 to the end of the 2007 GPS.
GT-14 Efficacy and safety	2800 BAU Placebo	163 166	24 weeks (approximately 8 to 16 weeks prior to and during the 2007 GPS)
P05238 Efficacy and safety	2800 BAU Placebo	213 225	24 weeks (approximately 16 weeks prior to and during the 2009 GPS)
Children	Dose (QD)	Randomized (n)	Treatment Duration
GT-12 Efficacy and Safety	2800 BAU Placebo	126 127	24 weeks (approximately 16 weeks prior to and during the 2007 GPS)
P05239 Efficacy and Safety	2800 BAU Placebo	175 169	24 weeks (approximately 16 weeks prior to and during the 2009 GPS)
Adults and Children	Dose (QD)	Randomized (n)	Treatment Duration
P08067 Efficacy and safety	2800 BAU Placebo	752 749	24 weeks (approximately 12 weeks prior to and during the 2012 GPS)

Source: Original BLA 125473/000 Clinical Overview page 20-21

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

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

Integration of results was to incorporate both the primary endpoints as well as secondary endpoints of the various studies in order to utilize and compare the TCS as the primary

efficacy endpoint. Furthermore, the clinically meaningful difference was to be set utilizing the US standard, based on the May 2011 Advisory Committee agreed upon standard of -10% as the clinically meaningful upper bound for the % difference between treatment and placebo responses in the TCS endpoint.

The following table provides a summary of endpoints based on protocols submitted by the applicant and consists of all studies considered within the integrated study of efficacy. This table includes a listing of primary and key secondary endpoints, the study, as well as the type of analysis performed.

**Table 7.1.1.b.** Summary of Endpoints based on Protocols submitted by Merck and considered for the Integrated Study of Efficacy for Grastek®

Endpoint	Adults Phase 3 Trials	Adults Phase 3 Trials	Adults Phase 3 Trials	Adults Phase 2 Trials	Adults Phase 2 Trials	Pediatrics Phase 3 Trials	Pediatrics Phase 3 Trials	Adult & Pediatrics Phase 3 Trial
	GT-08	P05238	GT-14	GT-02	GT-07	GT-12	P05239	P08067
TCS entire GPS	S	P	S			S	P	P
TCS peak GPS		S	S			S		KS
DSS entire GPS	P	KS	P	P	S	P	KS	KS
DSS peak GPS	S	S	S	KS		KS	S	S
DMS entire GPS	P	KS	KS	P	S	P	KS	KS
DMS peak GPS	S	S	S	KS		KS	S	S
RQLQ entire GPS	S	KS	KS				KS	KS
RQLQ peak GPS*								

**Notes:** DSS=daily symptom score; DMS=daily medication score; GPS=grass pollen season; P=primary; KS=key secondary; S=secondary; RQLQ= Rhinoconjunctivitis Quality of Life Questionnaire; TCS=total combined score  
\*for subjects ≥12 years of age

Source: Statistical Summary based on SAPs provided in BLA 125473/000

In all studies, the primary efficacy endpoint (i.e., the symptom score or symptom/rescue medication score) was analyzed using a linear model, specifically an ANCOVA with treatment as main effect, pooled study center/geographic location as stratification factor for the multicenter studies, and several covariates (including: baseline symptom, baseline rescue medication scores, asthma status, and potentially other covariates depending on study) which could potentially impact the clinical score.

### 7.1.2 Demographics and Baseline Characteristics

Across studies, no notable differences in demographic characteristics were observed between the active and placebo treatment groups. The racial profile of subjects was predominantly white/Caucasian (85-90%) in all studies performed by the applicant. In various studies, the distribution of gender did slightly differ, as can be seen in the below table (in which males tended to be more predominant, with 52% to 62% of participants and females varied from 38% to 48% of participants); however, between the randomized treatment groups, no imbalances were noted. Specific details related to demographic and baseline characteristics can be seen in the following table, which examines the number and percentage of individuals in the Full Analysis set stratified by treatment group, age, gender, race/ethnicity, BMI, asthma status, sensitivity to grass pollens, and baseline retrospective symptom scores.

**Table 7.1.2.a. Summary of Demographic and Baseline Characteristics**

POOLED PROTOCOL NOS. PULSIS, U1-U2, U1-U1, U1-U3 (1ST YEAR), U1-14, and PUSUO/

	MK-7243 93 BAU n=136 <sup>a</sup>	MK-7243 933 BAU n=139 <sup>a</sup>	MK-7243 2800 BAU n=1669	All Active n=1944	Placebo n=1645	Total n=3589
<b>Sex (n,%)</b>						
Female	52 ( 38 )	47 ( 34 )	801 (48)	900 (46)	735 (45)	1635 (46)
Male	84 ( 62 )	92 ( 66 )	867 (52)	1043 (54)	911 (55)	1954 (54)
<b>Race (n,%)</b>						
White	131 ( 96 )	130 ( 94 )	1464 (88)	1725 (89)	1450 (88)	3175 (88)
Non-White	5 ( 4 )	9 ( 6 )	203 (12)	217 (11)	196 (12)	413 (12)
American Indian or Alaskan Native	0	0	5 (<1)	5 (<1)	3 (<1)	8 (<1)
Asian	3 ( 2 )	3 ( 2 )	56 (3)	81 (3)	40 (2)	101 (3)
Black or African American	1 ( 1 )	2 ( 1 )	109 (7)	112 (6)	116 (7)	228 (6)
Multiracial	1 ( 1 )	0	21 (10)	22 (1)	22 (1)	44 (1)
Native Hawaiian or Other Pacific Islander	0	0	2 (<1)	2 (<1)	4 (<1)	6 (<1)
Other	0	4 ( 3 )	11 (1)	15 (1)	11 (1)	26 (1)
Missing	0	0	1 (<1)	1 (<1)	0	1 (<1)
<b>Ethnicity (n, %)</b>						
Hispanic or Latino	0	0	40 (2)	40 (2)	30 (2)	70 (2)
Not Hispanic or Latino	0	0	508 (34)	508 (29)	580 (35)	1148 (32)
Missing	136 (100)	139 (100)	1080 (64)	1335 (69)	1036 (63)	2371 (66)
<b>Age (yrs)</b>						
Mean (SD)	33.8 ( 9.3)	33.6 ( 9.8)	36.2 (10.9)	35.8 (10.8)	36.2 (10.8)	36.0 (10.8)
Median	33.0	32.0	36.0	35.0	36.0	35.0
Range	18 - 81	19 - 58	18-85	18-85	18-85	18-85
<b>Age (n, %)</b>						
18 - <50	127 ( 93 )	128 ( 92 )	1467 (88)	1722 (89)	1434 (87)	3156 (88)
50 - <65	9 ( 7 )	11 ( 8 )	195 (12)	215 (11)	208 (13)	423 (12)
65 or Older	0	0	6 (<1)	6 (<1)	4 (<1)	10 (<1)
<b>Weight (kg)</b>						
Mean (SD)	73.56 (12.20)	74.85 (13.91)	79.08 (18.35)	78.39 (17.78)	80.78 (19.16)	79.49 (18.46)
Median	74.10	75.00	77.10	76.60	78.47	77.11
Range	45.0 - 109.0	45.4 - 119.3	42.2-189.0	42.2-189.0	39.0-174.6	39.0-189.0
Missing	0	0	0	0	4	4
<b>Height (cm)</b>						
Mean (SD)	174.09 (9.48)	174.69 (9.66)	172.08 (9.90)	172.40 (9.88)	172.67 (9.97)	172.53 (9.92)
Median	175.00	174.00	172.00	172.70	173.00	172.70
Range	147.0 - 197.0	154.0 - 200.0	147.3-203.2	147.0-203.2	146.0-210.0	146.0-210.0
Missing	0	0	0	0	2	2
<b>BMI</b>						
Mean (SD)	24.18 ( 2.90)	24.43 ( 3.56)	26.57 (5.66)	26.25 (5.44)	26.95 (5.75)	26.57 (5.59)
Median	24.45	24.10	25.40	25.10	25.80	25.40
Range	16.7 - 31.6	18.2 - 35.2	14.0-67.7	14.0-55.5	11.6-55.5	11.6-67.7
Missing	0	0	0	0	4	4
<b>Asthma Status (n,%)</b>						
Asthmatics	12 ( 9 )	11 ( 8 )	415 (25)	438 ( 23 )	383 ( 23 )	821 (23)
Non-Asthmatics	124 ( 91 )	128 ( 92 )	1253 (75)	1505 ( 77 )	1263 ( 77 )	2768 ( 77 )
<b>Sensitization to Grass* Allergens (n,%)</b>						
No	0	0	0	0	1(<1)	1(<1)
Yes	136 ( 100 )	139 ( 100 )	1668 (100)	1943 (100)	1645 (100)	3588 (100)
<b>Sensitization to Other* Allergens (n,%)</b>						
No	28 ( 21 )	36 ( 26 )	332 ( 20 )	396 ( 20 )	321 ( 20 )	717 ( 20 )
Yes	108 ( 79 )	103 ( 74 )	1336 ( 80 )	1547 ( 80 )	1325 ( 80 )	2872 ( 80 )
<b>Timothy Grass Specific IgE (kU/L)</b>						
Mean (SD)	26.96 (29.03)	24.53 (28.28)	23.09 (27.57)	23.48 (27.74)	21.41 (26.30)	22.53 (27.10)
Median	15.15	12.20	11.80	12.10	10.10	11.07
Range	0.8 - 100.0	0.8 - 100.0	0.7 - 101.0	0.7 - 101.0	0.6 - 101.0	0.6 - 101.0
Missing	0	0	79	79	70	149

Source: Original BLA 125473/000 Clinical Overview page 68-71

### 7.1.3 Analysis of Primary Endpoint(s)

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

The primary efficacy endpoint (dependent variable), TCS score, was analyzed using a linear model, specifically an ANCOVA with treatment as main effect, pooled study center as stratification factor for the multicenter studies, and several covariates (including: baseline symptom/rescue medication scores, asthma status, and other covariates depending on the study) which could potentially impact the clinical score. It is important to note that each study utilized its own statistical model that was pre-specified in the protocol rather than a common model for all the studies. The table below summarizes the difference in LS Means (and 95% CI) of the treated group versus placebo as well as the relative LS Mean difference (and 95% CI) utilizing the TCS endpoint for all of the field studies that collected efficacy data provided in this submission. The results demonstrate that the treatment (particularly the dosage proposed of 2800 BAU Grastek®) reduces the TCS score when compared to placebo, based on both the point estimate of the difference as well as the 95% CI considering the LS Mean values.

Across the trials a consistent trend in favor of Grastek® was observed, with some variation in overall magnitude of effect as expected in seasonal allergic rhinitis trials. One trial did not achieve statistical significance over placebo (GT-14 Trial), although the numerical trends in the results favored treatment with Grastek®. As a consequence of this study which did not meet the pre-specified success criterion, Merck conducted three additional trials (P05238, P05239, and P08067) in North America. The last trial was powered based on the upper 95% confidence limit of the relative difference in scores between placebo and Grastek® groups being no less than -10%, yielding a study of approximately 1500 individuals. Although results of the first two trials were statistically significant, the adult study did not meet CBER's criterion stated in the May 2011 Allergenic Advisory Committee meeting of -10% for the upper bound of the relative % difference between treatment and placebo based on the 95% CI. Although not powered for such, the pediatric trial (P05239) met this clinically meaningful criterion based on the 95% CI. The last trial (P08067), in children and adults, demonstrated that Grastek® improved the TCS more than placebo during the entire grass pollen season (treatment difference relative to placebo -23%, 95% CI: -36% to -13%). Therefore, the results of 3 of 6 confirmatory trials also met the statistical criterion based on the 95% confidence limit, set by CBER's review team: an upper bound of -10%. Specific results for the TCS, DDS, and DMS from the Phase III studies can be seen in the following table.



**Table 7.1.3.a.** Summary of all Phase III studies based on the Analysis for the Grass Pollen Season for the TCS, DSS, and DMS

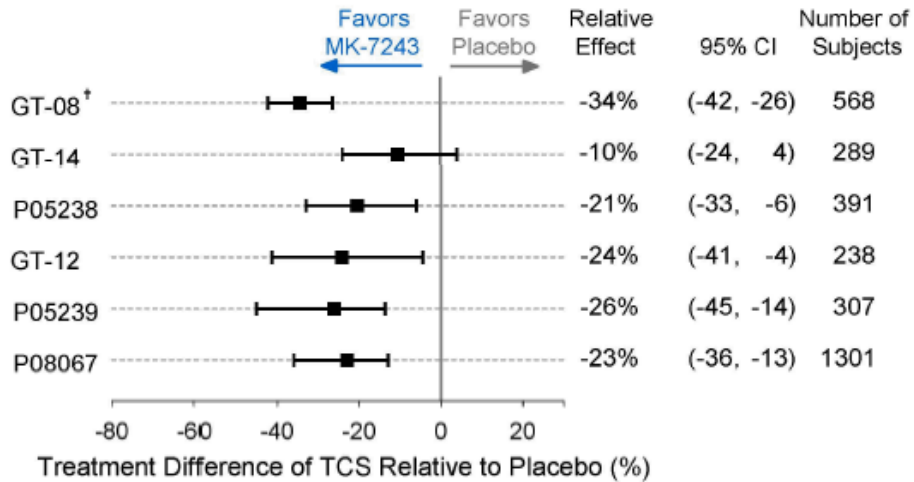
Protocol Nos. [GT-08 \(Year 1\)](#), [GT-14](#), [P05238](#), [GT-12](#), [P05239](#), and [P08067](#)

Study/ Endpoint	MK-7243 Mean (N)	Placebo Mean (N)	Treatment Difference (MK-7243 – Placebo)			Difference Relative to Placebo (%) <sup>†</sup>	
			Estimate	95% CI	p-value	Estimate	95% CI
<b>Study GT-08 Year 1</b>							
TCS	(N=282) 4.46	(N=286) 6.78	-2.32	(-2.98, -1.67)	<0.001	-34.2	(-42.0, -26.3)
DSS	(N=282) 2.85	(N=286) 4.14	-1.29	(-1.68, -0.90)	<0.001	-31.2	(-38.8, -23.4)
DMS	(N=282) 1.65	(N=286) 2.68	-1.03	(-1.44, -0.63)	<0.001	-38.4	(-49.8, -26.5)
<b>Study P05238</b>							
TCS	(N=184) 5.08	(N=207) 6.39	-1.31	(-2.22, -0.40)	0.005	-20.5	(-33.0, -6.0)
DSS	(N=184) 3.83	(N=207) 4.69	-0.86	(-1.46, -0.26)	0.015 <sup>e</sup>	-18.3	(-29.4, -5.7)
DMS	(N=184) 1.25	(N=207) 1.70	-0.45	(-0.96, +0.06)	0.084 <sup>e</sup>	-26.5	(-49.1, 5.4)
<b>Study GT-14</b>							
TCS	(N=139) 6.74	(N=150) 7.53	-0.78	(-1.83, +0.26)	0.142	-10.4	(-23.9, 4.0)
DSS	(N=139) 5.69	(N=150) 6.06	-0.37	(-1.16, +0.41)	0.348	-6.1	(-19.8, 7.1)
DMS	(N=139) 1.07	(N=150) 1.47	-0.40	(-0.85, +0.05)	0.083	-27.2	(-47.3, 6.9)
<b>Study GT-12</b>							
TCS <sup>b</sup>	(N=117) 3.70	(N=121) 4.87	-1.18	(-2.17, -0.19)	0.022	-24.2	(-41.3, -4.5)
DSS <sup>b</sup>	(N=117) 2.18	(N=121) 2.80	-0.62	(-1.15, -0.10)	0.022	-22.1	(-38.7, -4.8)
DMS <sup>c</sup>	(N=117) 0.78	(N=121) 1.19	-0.41	(-0.68, -0.01)	0.016	-34.5	(-60.4, 0.1)
<b>Study P05239</b>							
TCS	(N=149) 4.62	(N=158) 6.25	-1.63	(-2.60, -0.66)	0.001	-26.1	(-38.2, -10.1)
DSS	(N=149) 3.71	(N=158) 4.91	-1.20	(-1.95, -0.45)	0.005 <sup>e</sup>	-24.4	(-36.4, -9.1)
DMS	(N=149) 0.91	(N=158) 1.33	-0.42	(-0.88, +0.03)	0.066 <sup>e</sup>	-31.6	(-57.7, 4.0)
<b>Study P08067</b>							
TCS <sup>c</sup>	(N=629) 3.24	(N=672) 4.22	-0.98	(-1.2, -0.4)	<0.001	-23.0	(-36.0, -13.0)
DSS <sup>c</sup>	(N=629) 2.49	(N=672) 3.13	-0.64	(-0.7, -0.2)	0.001	-20.0	(-32.0, -10.0)
DMS <sup>d</sup>	(N=629) 0.88	(N=672) 1.36	-0.48	(-0.73, -0.22)	0.0003	-35.0	(-49.3, -20.8)

Source: Original BLA 125473/000 Clinical Overview page 34-35 (results confirmed by reviewing statistician)

A corresponding forest plot for the primary endpoint of interest to the Agency, TCS, is provided below.

**Figure 7.1.4.a.** Analysis of the (TCS), the Combined Total Daily Symptom Score and Rescue Medication Score: Summary of Studies based on Phase III studies submitted by Merck-FAS



Source: Original BLA 125473/000 Clinical Overview page 52 (confirmed by reviewing statistician)

The data from each of the field studies can be combined and pooled with similar positive results, illustrating that this product reduces both the symptoms as well as the use of rescue medication.

**Table 7.1.3.b.** Summary of a Pooled Analysis for the Grass Pollen Season for the TCS, DSS, and DMS based on all the Phase III Studies submitted by the applicant

Pooled Analyses Across All 6 Studies							
TCS	(N=1500) 5.19	(N=1594) 6.47	-1.28	(-1.59, -0.97)	<0.001	-19.8	(-24.1, -15.5)
DSS	(N=1500) 3.74	(N=1594) 4.50	-0.75	(-0.96, -0.55)	<0.001	-16.8	(-21.0, -12.5)
DMS	(N=1500) 1.45	(N=1594) 1.97	-0.53	(-0.70, -0.35)	<0.001	-26.7	(-34.4, -18.6)

Source: Original BLA 125473/000 Clinical Overview page 36 (confirmed by reviewing statistician)

From the tabulations and the forest plot, it can be observed that the studies provided within this BLA suggest there is a consistent trend of a reduction of symptoms and use of rescue medication based on the TCS score in the active treatment group compared to the placebo group.

#### 7.1.4 Analysis of Secondary Endpoint(s)

Although the applicant considered a variety of endpoints in the different studies to be secondary endpoints, when given the opportunity for feedback within the IND phase of studies, the review team within CBER consistently proposed Daily Rhinoconjunctivitis

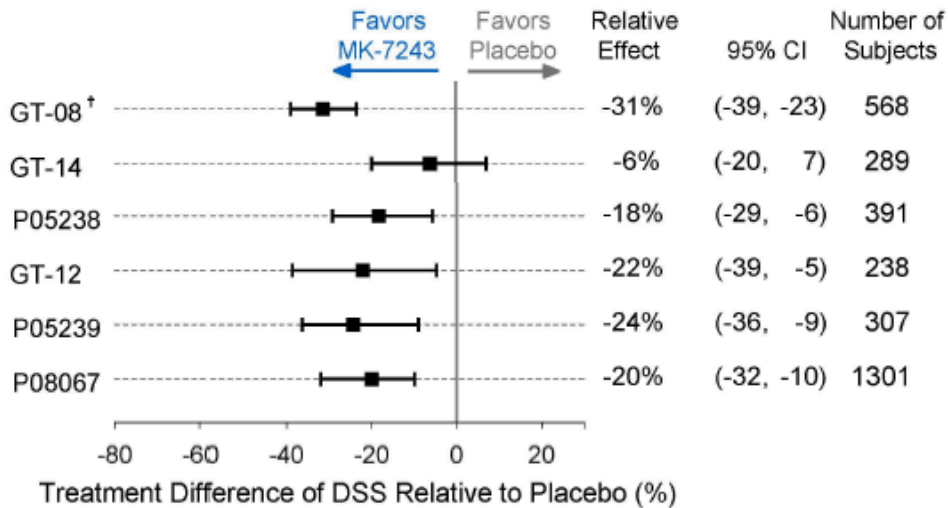
Symptom Scores (DSS) and Daily Rescue Medication Scores (DMS) to be secondary endpoints. Thus, in this integrated summary of efficacy, these results of the DSS and DMS will be presented.

As in the above analysis for the primary TCS endpoint, the members of the review team agree that utilizing the pre-specified ANCOVA model provided within the protocol is considered appropriate for each study and is preferable to using one single post-hoc model for all the studies. However, other models, including covariates such as treatment group, baseline scores, geographic region, and various other fixed and random effects, were examined and yielded similar results and conclusions.

Table 7.1.3.a. summarizes the difference in LS Means (and 95% CI) of the treated group versus placebo as well as the Relative LS Mean difference (and 95% CI) utilizing the DSS endpoints for the field studies. The results demonstrate that the treatment (particularly the dosage proposed of 2800 BAU of the Grastek® product) reduces the DSS score when compared to placebo, based on both the point estimate of the difference as well as the 95% CI considering the LS Mean values.

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

**Figure 7.1.5.a.** Analysis of the Daily Symptom Score (DSS): Summary of Studies based on Phase III studies submitted by Merck-FAS

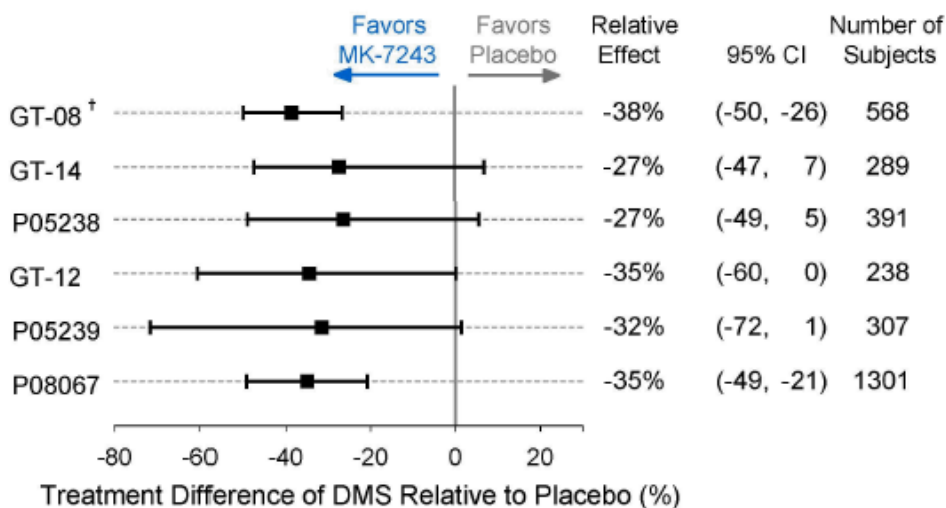


Source: Original BLA 125473/000 Clinical Overview page 53 (confirmed by reviewing FDA statistician)

Comparisons of Rescue Medication Scores based on treatment administered can be seen in Table 7.1.4.a. in the previous section. These results suggest that again there is a reduction in the rescue medication scores in the Grastek® treated individuals compared to the placebo control individuals. The results also demonstrate that the treatment (particularly the dosage proposed of 2800 BAU of Grastek®) reduces the RMS score when compared to placebo, based on both the point estimate of the difference as well as the 95% CI considering the LS Mean values.

A forest plot of these values, provided by the applicant, illustrates the effect of the treatment versus placebo difference for RTSS. This figure provided by the applicant shows both the 95% CI of the Difference in LS Means as well as the relative location with respect to the line denoting “0” or no difference. Also provided are the 95% CIs of the Relative Difference, which can be compared to CBER’s standard for the upper bound of -10%.

**Figure 7.1.5.b.** Forest Plot of the Daily Rescue Medication Score (DMS): Summary of Studies based on Phase III studies submitted by Merck-FAS



Source: Original BLA 125473/000 Clinical Overview page 54 (confirmed by reviewing FDA statistician)

The results and figures included in this section provide evidence that Grastek® reduces the use of daily relief medication (DMS) as well as the daily symptom score (DSS) for the LS Means, utilizing the pre-specified model. This finding is consistent with the results found regarding the primary efficacy endpoint.

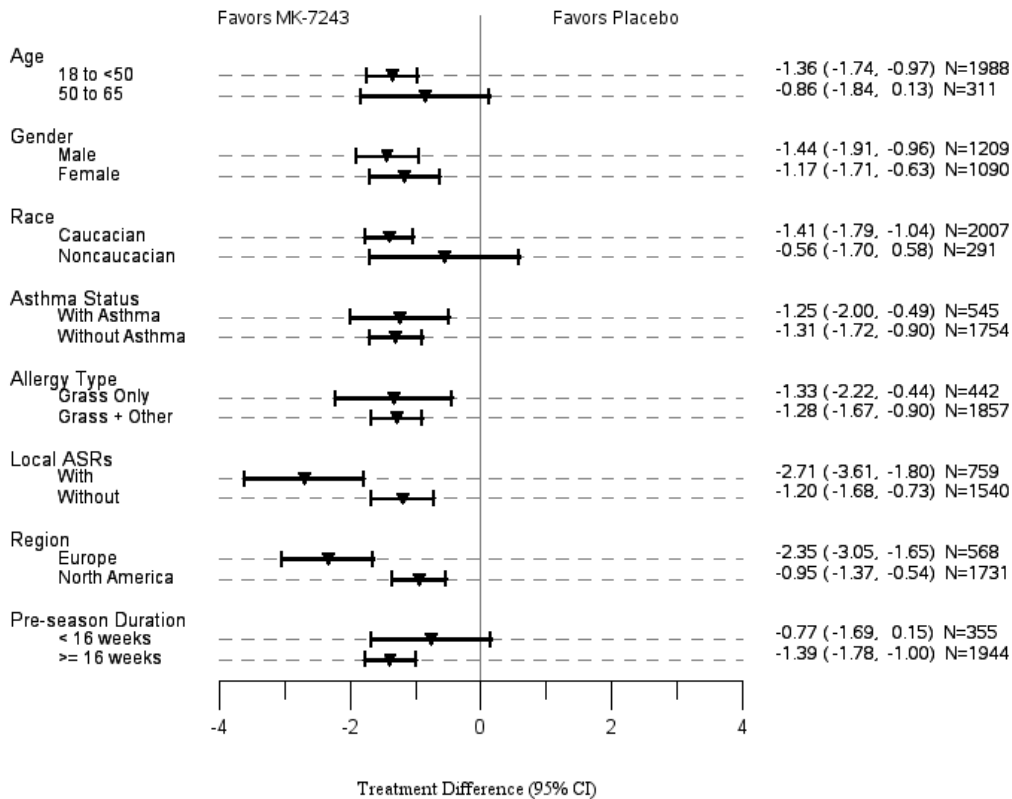
### 7.1.6 Other Endpoints

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

7.1.7 Subpopulations

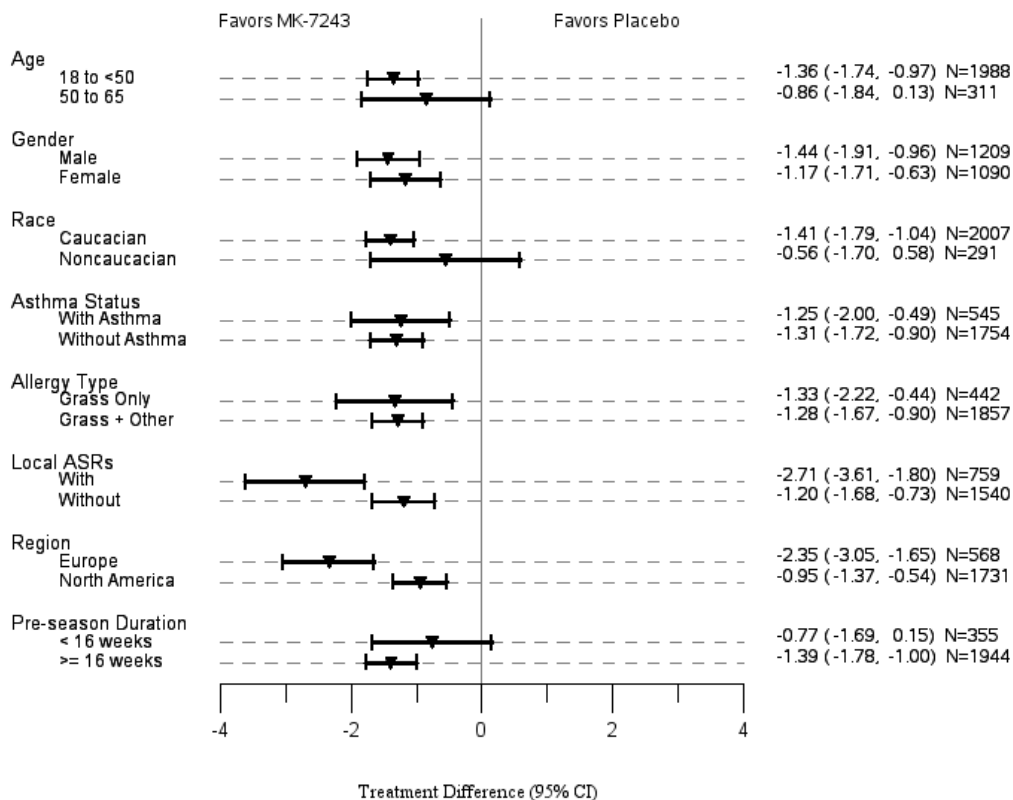
Based on the results provided by the applicant and select analyses performed by the reviewing statistician, there do not appear to be significant differences in efficacy between subjects who were mono-sensitized (defined as sensitive to the group of five-grass pollen allergens), and between Caucasians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

**Figure 7.1.7.a.** Point Estimate and 95% CI for the Difference in the Total Combined Symptom and Rescue Medication Score (TCS) in select subgroups during the Grass Pollen Season-ITT Analysis Population in Adult Studies



Source: Original BLA 125473/000 Summary of Clinical Efficacy page 185

**Table 7.1.7.b.** Point Estimate and 95% CI for the Difference in the Total Combined Symptom and Rescue Medication Score (TCS) in select subgroups during the Grass Pollen Season-ITT Analysis Population in Pediatric Phase III Studies



Source: Original BLA 125473/000 Summary of Clinical Efficacy page 186

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

#### 7.1.10 Additional Efficacy Issues/Analyses

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

#### 7.1.11 Efficacy Conclusions

The overall results of the efficacy data suggest that there is a reduction in symptoms and use of rescue medication when comparing individuals who were randomized and received Grastek® study treatment compared to individuals who received a nearly identical placebo product.

The applicant's proposed indication is:

***“Grastek® (MK-7243) is indicated for 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..”***

Based on the applicant's data and analyses, which were confirmed by the reviewing statistician, this indication appears to be supported. However, it is important to note that no study included patients greater than 65 years of age.

The statistical analyses of the various efficacy studies suggest that the product reduced the use of daily rescue medication (DMS) as well as Daily Symptom Score (DSS), based on LS Means utilizing pre-specified ANCOVA models. Furthermore, since CBER consistently recommended a total combined score (TCS), incorporating both symptoms and rescue medication, regardless of the applicant's primary endpoint, this combined score was considered the primary endpoint for this review. This issue is particularly relevant to the non-US IND studies, which may have been planned and implemented without CBER's input. Since this methodology was consistently recommended and implemented by CBER, type I error should not be affected by the change in endpoint.

An additional challenge that was influenced by the non-US-IND studies is the definition of a clinically meaningful endpoint. Several of these studies were designed simply to meet a simple difference between treatment groups ( $H_0: \mu_T - \mu_P < 0$ ) with a p-value less than 0.05. CBER had a more stringent criterion, requiring the upper bound of the 95% CI of the Relative Difference meeting a clinically meaningful margin of -10%. Many of the non-US studies were not designed or powered for this endpoint. However, it is important to note that several of these studies did meet the US criterion, and other studies demonstrated trends suggesting that the Grastek® treatment group reduces combined scores when compared to the placebo treated group.

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

## 8. INTEGRATED OVERVIEW OF SAFETY

## 8.1 Safety Assessment Methods

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

## 8.2 Safety Database

### 8.2.1 Studies/Clinical Trials Used to Evaluate Safety

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

### 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

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

The following table summarizes the extent of exposure to any treatment (including placebo and dosages of Grastek® not submitted for consideration in this BLA) in all studies provided within this BLA. This table includes the number of patients, mean exposure, and range of exposure for adults as well as children and adolescents.

**Table 8.2.a.** Exposure to Treatment or Placebo of All Subjects Stratified by Age groups

	All	MK-7243	Placebo
All Ages	4465	2389	2076
≥18 yrs	3587	1944	1643
12-17 yrs	481	237	244
5-11 yrs	397	208	189

Source: Original BLA 125473/000 Summary of Clinical Safety page 24

The previous table can be further examined by considering the extent of exposure to treatment. It is important to note that the primary dosage of interest is 2800 BAU of the Grastek® product.



**Table 8.2.b.** Extent of Exposure to Treatment or Placebo for All Subjects  
ADULTS

Duration (day)	MK-7243 2800 BAU n=1669 (%)	Placebo n=1645 (%)
Received any treatment	1669 (100)	1642 (100)
≥ 1 (Day 1 )	1669 (100)	1640 (100)
≥ 7 (Week 1 )	1642 (98)	1628 (99)
≥ 28 (Week 4 )	1579 (95)	1603 (97)
≥ 84 (Week 12)	1505 (90)	1539 (94)
≥ 168 (Week 24)	1022 (61)	1094 (67)
≥ 252 (Week 36)	181 (11)	173 (11)
Unknown	0	2 (<1)
Randomized, not treated	0	3 (<1)

CHILDREN

Duration (day)	MK-7243 2800 BAU n=447 (%)	Placebo n=434 (%)
Received any treatment	445 (100)	434 (100)
≥ 1 (Day 1 )	442 (99)	433 (100)
≥ 7 (Week 1 )	430 (96)	429 (99)
≥ 28 (Week 4 )	415 (93)	425 (98)
≥ 84 (Week 12)	397 (89)	411 (95)
≥ 168 (Week 24)	327 (73)	333 (77)
≥ 252 (Week 36)	6 (1)	8 (2)
Unknown	3 (1)	1 (<1)
Randomized, not treated	2 (<1)	0

Source: Original BLA 125473/000 Summary of Clinical Safety page 26

The following table provides insight into the demographics of individuals in the studies provided within this submission. The table includes the sample size (n) and percentage of individuals for the Safety Analysis set based on age, gender, height, weight, and BMI stratified by treatment group. Overall, the demographics appear to be similar between the treatment groups when pooling all the studies that collected safety data; however, as can be seen in the below table, it is of note that there are slightly more males in these studies than females (52% and 55% for the active and placebo treated groups in the Adult studies and 66 and 64% for the active and placebo treated groups in the Pediatric studies, respectively).

**Table 8.2.c.** Demographic and Baseline Characteristics of Subjects Randomized to Treatment or Placebo for All Subjects in Phase II/III Studies

	Adult		Pediatric	
	MK-7243 2800 BAU n=1668	Placebo n=1646	MK-7243 2800 BAU n=446	Placebo n=435
Male (%)	867 ( 52)	911 ( 55)	295 ( 66)	279 ( 64)
Age Mean (SD)	36.2 (10.9)	36.2 (10.8)	11.7 (3.2)	11.9 (3.3)
Age (n,%)				
<12	-	-	207 ( 46)	190 ( 44)
12 to <18	-	-	239 ( 54)	245 ( 56)
18 to <50	1467 ( 88)	1434 ( 87)	-	-
50 to <65	195 ( 12)	208 ( 13)	-	-
>65	6 (<1)	4 (<1)	-	-
Race (n,%)				
White (%)	1464 ( 88)	1450 ( 88)	384 ( 86)	394 ( 91)
Non-White	203 ( 12)	196 ( 12)	62 ( 14)	41 ( 9)
American Indian or Alaskan Native	5 (<1)	3 (<1)	1 (<1)	1 (<1)
Asian	55 ( 3)	40 ( 2)	13 ( 3)	6 ( 1)
Black or African American	109 ( 7)	116 ( 7)	30 ( 7)	20 ( 5)
Multiracial	21 ( 1)	22 ( 1)	15 ( 3)	11 ( 3)
Native Hawaiian or Other Pacific Islander	2 (<1)	4 (<1)	2 (<1)	1 (<1)
Other	11 ( 1)	11 ( 1)	1 (<1)	2 (<1)
Missing	1 (<1)	0	0	0
Geographic Region(n,%)				
Canada	131 ( 8)	131 ( 8)	11 ( 2)	10 ( 2)
European Union	591 ( 35)	549 ( 33)	126 ( 28)	127 ( 29)
US	946 ( 57)	966 ( 59)	309 ( 69)	298 ( 69)
Asthmatics (%)	415 ( 25)	383 ( 23)	140 ( 31)	136 ( 31)
Duration of Allergic Rhinitis (yrs.)				
Mean (SD)	19.44 (11.87)	19.67 (12.24)	5.47 (3.46)	5.44 (3.81)
Median	18.00	18.00	5.00	5.00
Range	0.0 - 60.0	0.0 - 63.0	0.0 - 17.0	0.0 - 30.0
Missing	159	166	3	1
Pre-Seasonal Duration of Treatment (days)				
Mean (SD)	129.04 (42.07)	130.36 (41.87)	120.10 (24.59)	120.70 (25.91)
Median	129.00	130.00	121.00	123.00
Range	31.0 - 246.0	34.0 - 240.0	30.0 - 190.0	2.0 - 177.0
Missing	66	69	10	8
Timothy Grass IgE				
Mean (SD)	23.09 (27.57)	21.41 (26.30)	37.62 (36.96)	42.33 (36.25)
Median	11.80	10.10	23.70	32.00
Range	0.7 - 101.0	0.6 - 101.0	0.7 - 101.0	0.1 - 101.0
Missing	79	70	3	1
Sensitization to Grass Allergens (n,%)				
No	0	1 (<1)	1 (<1)	1 (<1)
Yes	1668 (100)	1645 (100)	445 (100)	434 (100)
Sensitization to Other Non-Grass Allergens (n,%) <sup>b</sup>				
No	332 ( 20)	321 ( 20)	61 ( 14)	50 ( 11)
Yes	1336 ( 80)	1325 ( 80)	385 ( 86)	385 ( 89)

Source: Original BLA 125473/000 Summary of Clinical Safety page 37

Based on the above table it, appears there is balance between the two treatment groups for the majority of baseline characteristics (gender being the only subgroup trait that may be slightly imbalanced; however, the predominance of males, particularly in the pediatric subjects, is consistent between the treatment and placebo groups).

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

Since these studies were performed in a variety of locations and under different INDs (some non-US INDs), caution should be used when interpreting results. However, considering that the results and trends were consistent regardless of studies, this may be less of a concern than if conclusions depended on the individual study.

## 8.4 Safety Results

A summary of the adverse events can be seen in the table below. Based on the tabulated values, similar trends of adverse events can be seen in both the treatment and placebo treated patients (82% and 68%, respectively, for adults and 82% versus 79% for pediatric subjects). The table below provides a brief description of the adverse event, the count, and % of observed subjects with the Adverse Event, stratified by treatment group. It is important to note that this table combines all treatment doses of the active treatment.

**Table 8.4.1.a** Overview of Adverse Events-Safety Analysis Set-All Doses from All Studies- Adult Subjects

Category	MK-7243 2800 BAU (N=1669) n(%)	Placebo (N=1645) n(%)
At Least One AE	1383( 82.9)	1118( 68.0)
Treatment Related AE	1111( 66.6)	389( 23.6)
Serious AE	20( 1.2)	20( 1.2)
Treatment Related Serious AE	0	1( 0.1)
Discontinued Due to AE <sup>a</sup>	97( 5.8)	41( 2.5)
Discontinued Due to Treatment Related AE <sup>a</sup>	81( 4.9)	15( 0.9)
Discontinued Due to Serious AE <sup>a</sup>	3( 0.2)	6( 0.4)
Discontinued Due to Treatment Related Serious AE <sup>a</sup>	0	0
Death	2( 0.1)	1( 0.1)

<sup>a</sup> Numbers of subject that discontinued due to an Adverse Event are determined from the adverse event data

Source: Original BLA 125473/000 Summary of Clinical Safety page 55

**Table 8.4.1.b** Overview of Adverse Events-Safety Analysis Set-All Doses from All Studies-Pediatric Subjects

Category	MK-7243 2800 BAU (N=447) n(%)	Placebo (N=434) n(%)
At Least One AE	367( 82.1)	343( 79.0)
Treatment Related AE	260( 58.2)	104( 24.0)
Serious AE	3( 0.7)	4( 0.9)
Treatment Related Serious AE	0	0
Discontinued Due to AE <sup>a</sup>	29( 6.5)	8( 1.8)
Discontinued Due to Treatment Related AE <sup>a</sup>	28( 6.3)	3( 0.7)
Discontinued Due to Serious AE <sup>a</sup>	1( 0.2)	0
Discontinued Due to Treatment Related Serious AE <sup>a</sup>	0	0
Death	0	0

<sup>a</sup> Numbers of subject that discontinued due to an Adverse Event are determined from the adverse event data

Source: Original BLA 125473/000 Summary of Clinical Safety page 56

Considering treatment emergent adverse events listed in the table above, the treated group had a greater likelihood of TEAEs with 66% versus 23% (Adults) and 58% versus 24% (Pediatric subjects), when comparing the treatment group to the placebo treated individuals.

The types of adverse events observed during this study can be seen in the following tables, which include events common (>3% of subjects experiencing the adverse event) in Adult and Pediatric subjects.

**Table 8.4.2.a** Summary of Adverse Events-Adult Subjects

	MK-7243		Placebo	
	2800 BAU		n=1645	
	n	%	n	%
<b>SUBJECTS REPORTING ANY ADVERSE EVENT</b>	1383	(82.9)	1118	(68.0)
<b>EAR AND LABYRINTH DISORDERS</b>				
EAR PRURITUS	210	(12.6)	19	(1.2)
<b>EYE DISORDERS</b>				
EYE PRURITUS	67	(4.0)	43	(2.6)
<b>GASTROINTESTINAL DISORDERS</b>				
DYSPEPSIA	57	(3.4)	12	(0.7)
LIP SWELLING	68	(4.1)	4	(0.2)
NAUSEA	56	(3.4)	34	(2.1)
OEDEMA MOUTH	186	(11.1)	13	(0.8)
ORAL PRURITUS	448	(26.8)	59	(3.6)
PARAESTHESIA ORAL	168	(10.1)	33	(2.0)
TONGUE PRURITUS	95	(5.7)	8	(0.5)
<b>INFECTIONS AND INFESTATIONS</b>				
INFLUENZA	46	(2.8)	52	(3.2)
NASOPHARYNGITIS	242	(14.5)	276	(16.8)
SINUSITIS	55	(3.3)	55	(3.3)
UPPER RESPIRATORY TRACT INFECTION	138	(8.3)	126	(7.7)
<b>NERVOUS SYSTEM DISORDERS</b>				
HEADACHE	170	(10.2)	164	(10.0)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>				
COUGH	89	(5.3)	64	(3.9)
OROPHARYNGEAL PAIN	90	(5.4)	66	(4.0)
PHARYNGEAL OEDEMA	59	(3.5)	2	(0.1)
RHINORRHOEA	56	(3.4)	48	(2.9)
SNEEZING	54	(3.2)	45	(2.7)
THROAT IRRITATION	386	(23.1)	53	(3.2)

Source: Original BLA 125473/000 Summary of Clinical Safety page 85

**Table 8.4.2.a** Summary of Adverse Events-Adult Subjects

	MK-7243 2800 BAU n=447 n %	Placebo n=434 n %
<b>SUBJECTS REPORTING ANY ADVERSE EVENT</b>	367 (82.1)	343 (79.0)
<b>EAR AND LABYRINTH DISORDERS</b>		
EAR PRURITUS	33 (7.4)	2 (0.5)
<b>EYE DISORDERS</b>		
EYE PRURITUS	23 (5.1)	16 (3.7)
<b>GASTROINTESTINAL DISORDERS</b>		
ABDOMINAL PAIN UPPER	12 (2.7)	14 (3.2)
LIP SWELLING	32 (7.2)	2 (0.5)
NAUSEA	14 (3.1)	5 (1.2)
OEDEMA MOUTH	45 (10.1)	1 (0.2)
ORAL MUCOSAL ERYTHEMA	22 (4.9)	4 (0.9)
ORAL PRURITUS	109 (24.4)	9 (2.1)
PARAESTHESIA ORAL	24 (5.4)	6 (1.4)
TONGUE PRURITUS	41 (9.2)	4 (0.9)
VOMITING	21 (4.7)	18 (4.1)
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>		
PYREXIA	16 (3.6)	24 (5.5)
<b>INFECTIONS AND INFESTATIONS</b>		
BRONCHITIS	10 (2.2)	14 (3.2)
INFLUENZA	18 (4.0)	18 (4.1)
NASOPHARYNGITIS	80 (17.9)	72 (16.6)
PHARYNGITIS STREPTOCOCCAL	11 (2.5)	14 (3.2)
SINUSITIS	11 (2.5)	16 (3.7)
UPPER RESPIRATORY TRACT INFECTION	48 (10.7)	49 (11.3)
VIRAL INFECTION	25 (5.6)	13 (3.0)
VIRAL UPPER RESPIRATORY TRACT INFECTION	9 (2.0)	17 (3.9)
<b>NERVOUS SYSTEM DISORDERS</b>		
HEADACHE	38 (8.5)	39 (9.0)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>		
ASTHMA	13 (2.9)	17 (3.9)
COUGH	35 (7.8)	45 (10.4)
DYSPNOEA	15 (3.4)	7 (1.6)
EPISTAXIS	9 (2.0)	14 (3.2)
NASAL CONGESTION	20 (4.5)	12 (2.8)
OROPHARYNGEAL PAIN	34 (7.6)	31 (7.1)
PHARYNGEAL ERYTHEMA	17 (3.8)	3 (0.7)
RHINORRHOEA	9 (2.0)	14 (3.2)
THROAT IRRITATION	96 (21.5)	11 (2.5)
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>		
URTICARIA	17 (3.8)	11 (2.5)

Source: Original BLA 125473/000 Summary of Clinical Safety page 86

Additional comments related to global AEs for the pooled results can be seen in the medical officer's and epidemiologist's reviews.

#### 8.4.1 Deaths

One death was reported by the applicant; however, this death was caused by a multiple drug overdose several months after study drug was discontinued and was deemed by the medical officer as unlikely to be related to treatment. Further details regarding this patient and their medical history can be found in the medical officer's review.

#### 8.4.2 Nonfatal Serious Adverse Events

Limited non-fatal serious Adverse Events were reported. Within the adult studies, there were 20 (1.2%) serious adverse events in the treated group, while there were 20 (1.2%) serious adverse events in the placebo group. Within the pediatric studies, there were 3 (0.7%) serious adverse events in the treated group and 4 (0.9%) serious adverse events in

the placebo group. All serious adverse events were noted to be self-limiting and resolved. Additional details can be found in the medical officer's and epidemiologist's review.

#### 8.4.3 Study Dropouts/Discontinuations

Within all studies submitted by the applicant, approximately 16% of treated subjects and approximately 13% of placebo treated subjects discontinued treatment. The reason for discontinuation varied, but the predominant reason for dropping out was local side effects, including swelling and irritation in the mouth/tongue and oral region. A detailed discussion related to dropouts and discontinuations is deferred to the medical officer and epidemiologist.

#### 8.4.4 Common Adverse Events

The majority of adverse events that were observed and noted within the various studies were related to allergies (i.e., rhinoconjunctivitis symptoms) for both active treated and placebo treated patients. Overall, approximately 70-80% and 60-70% of subjects in the treatment and placebo groups, respectively, experienced adverse events. The majority of these adverse events were local reactions that involved the throat, nasal, and oral regions as well as the GI tract, which is to be expected when considering grass allergic individuals with symptoms noted at baseline. Further discussion and details related to common adverse events is deferred to the medical officer and epidemiologist.

#### 8.4.5 Clinical Test Results

Clinical test results varied between and within the studies. However, endpoints including IgG, IgE, and other tests performed had results that were expected and not considered outside of normal ranges.

#### 8.4.6 Systemic Adverse Events

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

#### 8.4.7 Local Reactogenicity

There were local reactions noted in both the treated and placebo treated individuals, up to 80% and up to 70%, respectively, depending on the study. The majority of these adverse reactions were either gastro-intestinal or were irritation located in the administration site: the throat. The majority of these events were mild or moderate and all were self-limiting. Additional details related to systemic adverse events can be found in the medical officer's review.

#### 8.4.8 Adverse Events of Special Interest

No adverse events of special interest were noted in the submitted studies.

### 8.5 Additional Safety Evaluations

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

### 8.6 Safety Conclusions

Based on the observed safety data including AEs, this product frequently causes local AEs in the oral region that are known to be associated with SLIT (since it is administered by mouth) in both adult and pediatric subjects. The data reviewed support the general conclusion that the incidence of severe or serious AE associated with SLIT is non-life-threatening and self-limiting. Additional details can be seen in the medical officer's and epidemiologist's reviews.

## 9. ADDITIONAL STATISTICAL ISSUES

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

### 9.1 Special Populations

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

#### 9.1.1 Human Reproduction and Pregnancy Data

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

#### 9.1.2 Use During Lactation

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

#### 9.1.3 Pediatric Use and PREA Considerations

This submission included a North American study designed exclusively to examine pediatric subjects (P05239) as well as a study that included both pediatric and adult subjects in Canada and the US. Safety and efficacy data from these studies were similar to the efficacy data acquired in the adult studies.

#### 9.1.4 Immunocompromised Patients

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

#### 9.1.5 Geriatric Use

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

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

The reviewer has no additional comments.

### 10. CONCLUSIONS

#### **10.1 Statistical Issues and Collective Evidence**

The data from the studies provided in this submission appear to support the applicant's conjecture that the Grastek® 2800 BAU product is safe and effective in the treatment of allergic rhinoconjunctivitis, using CBER's pre-specified criterion for efficacy based on the Combined Symptom score that incorporates both rescue medication and symptom scores.

#### **10.2 Conclusions and Recommendations**

Based on the data submitted and reviewed, Grastek® 2800 BAU per dose, appears to be safe and effective for immunotherapy of allergic rhinoconjunctivitis due to sensitivity to any combination of the five grass pollens included in the product. The product appears to be safe and effective for pediatric subjects 5-18 years of age and adults 18-65 years of age. The statistical analyses performed and examined by the reviewing statistician support the safety and efficacy of this product.