MK-7243

Timothy Grass Pollen Extract Tablets

Advisory Committee Meeting Briefing Document

Timothy Grass Pollen Extract Tablets

Indicated For Treatment of Allergic Rhinitis, with or without Conjunctivitis

BLA 125473

Allergenic Products Advisory Committee Meeting

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Merck Sharp & Dohme Corporation

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Table 1: List of Abbreviations

AE	Adverse Event
ALK	ALK-Abelló A/S
ANOVA	Analysis of Variance
AR	Allergic rhinitis
AR/ARC	Allergic rhinitis/rhinoconjunctivitis
ASR	Application site reaction
BAU	Bioequivalent Allergy Unit
BLA	Biological Licensing Application
BP	Blood pressure
CBER	Center for Biologics Evaluation and Research
CD4+	Positive Cluster of differentiation 4
CI	Confidence Interval
CMC	Chemistry, Manufacturing and Controls
CT	Computed tomography
DMS	Daily Medication Score
DSS	Daily Symptom Score
ECI	Event of Clinical Interest
e-diary	Electronic diary
EMA	European Medicines Agency
ER	Emergency Room
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPS	Grass Pollen Season
GRAZAX®	Registered trade name of MK-7243 in Europe. Trademark is registered to ALK-Abelló A/S
FAS	Full Analysis Set
FcεRI	High-affinity IgE receptor
FDA	United States Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IL-4	Interleukin 4
IL-5	Interleukin 5
IL-10	Interleukin 10
IL-13	Interleukin 13
IND	Investigational New Drug
IM	Intramuscular
IV	Intravenous
LABA	Long acting $beta_2$ agonist
LDA	Longitudinal Data Analysis
LLT	Lower Level Term in MedDRA dictionary
LTRA	Leukotriene receptor antagonists
MCG	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimal important difference
MK-7243	*Phleum pratense* grass pollen extract tablet for sublingual administration
NIAID/FAAN	National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network
NHANES	National Health and Nutrition Examination Survey
PEF	Peak Expiratory Flow
PFT	Pulmonary function test
p.o.	Per os (by mouth)
PRO	Patient Reported Outcome

PRQLQ	Pediatric Rhinoconjunctivitis Quality of Life Questionnaire
PT	Preferred Term in MedDRA dictionary
PV	Pharmacovigilance
RCT	Randomized Controlled Trial
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RQLQ(s)	Rhinoconjunctivitis Quality of Life Questionnaire with standardized activities
SAE	Serious Adverse Event
SC	Subcutaneous
SCIT	Subcutaneous Allergen Immunotherapy
SLIT	Sublingual Allergen Immunotherapy
SmPC	Summary of Product Characteristics
SOC	System organ class in MedDRA dictionary
Sponsor	Merck Sharp & Dohme, Corp.
SPT	Skin Prick Test
SQ	Standardized Quality
TCS	Total Combined Symptoms-Medication Score
TGF-β	Transforming growth factor beta
Th1	Type 1 helper T-cell
Th2	Type 2 helper T-cell
Treg	T-regulatory cell
US	United States
WAO	World Allergy Organization
WHO	World Health Organization

1 EXECUTIVE SUMMARY/OVERVIEW

Health Burden of Allergic Rhinitis and Conjunctivitis

Allergic rhinitis and conjunctivitis (AR/ARC) is one of the most common conditions affecting both children and adults and remains a significant medical problem despite the availability of a number of medical treatments. AR/ARC patients suffer with nasal symptoms of repetitive sneezing, nasal itching, runny nose, and nasal congestion. Ocular symptoms include itchy and watery eyes. The symptoms of rhinoconjunctivitis can have a negative impact on patients' health-related quality of life; affecting sleep quality, work/school performance, and often precedes the development of asthma. [1; 2; 3; 4] Allergic rhinitis (AR) affects up to 25% of the population in the United States (US) with its frequency continuing to increase, especially in the younger population. [5] Due to the large number of people with allergic rhinitis, the condition accounts for a significant proportion of overall health care costs in industrialized countries. [6] In 2005, the estimated total direct US costs of AR exceeded $11 billion ($14 billion in 2011), with 60% of expenditures for prescription medications. [7; 8; 9; 10] Indirect costs of AR include 3.5 million lost work days and 2 million missed school days.

AR/ARC is typically induced by inhalant allergens such as dander, dust mites, and pollens. In North America, grass pollen is one of the most common seasonal allergens to cause allergy symptoms. [11] The most prevalent grass is Timothy (*Phleum pratense*), which pollenates extensively throughout North America with varying intensity based on regional distribution. [11; 12; 13] Data from the third National Health and Nutrition Examination Survey (NHANES), conducted in a cross-sectional sample of the US population, revealed that almost half (44.2%) of the subjects who had allergic rhinitis were sensitized to grass pollen. [12]

Current Management of Allergic Rhinitis

The most common treatments for allergic rhinitis typically consist of allergen avoidance and pharmacotherapy. Allergen avoidance is important to the management of rhinitis induced by pets and house dust mites. However, limiting exposure to pollen can be difficult. Pharmacotherapies most frequently used include anti-histamines, leukotriene antagonists, and intranasal corticosteroids. Based on two recent meta-analyses conducted by Benninger, et. al. and Wilson et.al. [14; 15] the symptomatic treatment effect of seasonal allergic rhinitis was for leukotriene antagonists 5%, antihistamines 7-9%, and for intranasal corticosteroids 17-26% difference from placebo. Thus, pharmacotherapy may not effectively control all symptoms which reduces satisfaction with these therapies. Additionally, patients will discontinue these types of therapies for side effects. Based on the results of two recent large AR patient population surveys conducted in adults and children, it appears that health care providers (physicians, nurse practitioners, physician assistants) overestimate patients' and parents' satisfaction with pharmacotherapy.[16] It was reported that up to 34% of patients ask their doctor to change their pharmacotherapy and the most common reasons cited for dissatisfaction were ineffectiveness (66%) , bothersome side effects (21%) , effectiveness wearing off over time (12%), and incomplete 24-hour symptom relief (10%).

Given the high prevalence, chronic nature, significant clinical and economic consequences, and the limitations of current pharmacotherapy, new treatments that address the underlying cause

of AR with an acceptable safety profile are an important unmet need that could have significant medical and societal benefits.

Allergen Specific Subcutaneous Immunotherapy

Immunotherapy provides an alternative option for patients who have a history of allergy symptoms and evidence of specific immunoglobulin E (IgE) antibodies to clinically relevant allergens. Considerations for initiating allergen immunotherapy include: patient preference and disease severity, lack of efficacy of pharmacotherapy, side effects of pharmacotherapy, and co-morbidities such as asthma. [17] Unlike pharmacotherapy, allergen immunotherapy modulates the basic immunologic mechanism of the allergic disease. It is the only treatment known to provide long-term benefit and alter the course of respiratory allergic disease. [18; 19; 20; 21; 22; 23; 24]

Subcutaneous allergen immunotherapy (SCIT) is the most common form of administration of immunotherapy in North America. The clinical effects of SCIT include reduction in symptoms and need for pharmacologic treatment. Studies have also indicated that SCIT may prevent development of new allergen sensitizations and prevent development of asthma in AR patients. SCIT is associated with a risk of systemic allergic reactions and the rate with non-accelerated schedules (single dose increase per visit) has been reported to range between 0.05 to 7% of injections and 0.8 to 46.7% of patients (mean, 12.92%). [25] There have also been published accounts of both fatal and near-fatal allergic events with subcutaneous immunotherapy. [26; 27] As a result of the risks of serious systemic allergic reactions associated with subcutaneous allergen immunotherapy, it must be administered in a healthcare setting by trained personnel weekly during up-dosing and for maintenance treatment every 4-8 weeks for several years. The requirement for regular office visits in order for a patient to receive a full course of immunotherapy has been cited by patients as a prime reason for either not accepting or discontinuing this form of therapy. [28; 29] In fact, only a minority (2-9%) of US AR patients initiates SCIT and studies indicate a preponderance of patients who initiate treatment discontinue therapy prematurely. Older studies have reported rates ranging from less than 25% to 67%. [30] The most recent study showed that ~53% complete less than 1 year of treatment and 84% completed less than 3 years of treatment. [30]New immunotherapy formulations that are simple to administer and well-tolerated will provide broader options to patients for whom immunotherapy is indicated.

Sublingual Immunotherapy with Timothy Grass Tablet

MK-7243 is a novel delivery and formulation of immunotherapy being developed for daily sublingual administration, which reduces symptoms, requirements for anti-inflammatory and symptomatic medications, and has a potential for a long-term disease-modifying effect. The tablet is a fast-dissolving (less than 10 seconds) oral lyophilisate and contains a biologically standardized Timothy grass allergen extract derived from the extraction and purification of the natural source material, *Phleum pratense* pollen.

It is an important alternative or complementary treatment to pharmacotherapy with a distinct mechanism of action, which induces a sustained long-term effect. The adverse event profile of MK-7243 supports patient self-administration of immunotherapy after the first dose is initiated

under physician supervision. The requirement to administer only the first dose under supervision may simplify immunotherapy for appropriately selected patients and may reduce the overall health care costs of AR.

The efficacy and safety/tolerability profile of MK-7243 was first studied in Europe in multiple randomized, double-blind, placebo-controlled trials, including adults or children. Eligible subjects had a clinical history of significant allergic rhinoconjunctivitis to grass (with or without intermittent and stable asthma) diagnosed by a physician and had received treatment with symptom relieving medication for their disease during the previous grass pollen season(s). IgE sensitivity to Timothy grass was demonstrated by serum specific IgE and skin prick test to *Phleum pratense*. In phase 1 dose-escalating trials with grass allergic subjects, a broad dose range from 900 Bioequivalent Allergy Units (BAU) to 37,000 BAU was evaluated. The 2800 BAU was the highest dose that was well tolerated with a broad safety margin considering that no treatment related serious adverse events were reported within this dose range. A large Phase 2 adult trial evaluating three doses of MK-7243 (93, 933, and 2800 BAU) was conducted to establish a dose-response relationship for clinical efficacy and to confirm the adverse event profile. This trial demonstrated a dose dependent reduction in rhinoconjunctivitis symptoms compared to placebo with the most pronounced reduction for the 2800 BAU dose. In addition, the rescue medication use was reduced in a dose-dependent manner with the greatest reduction demonstrated for the 2800 BAU dose. The trial confirmed that 2800 BAU was well tolerated. Since allergic rhinitis patients often have concomitant asthma and therefore may be more susceptible to severe or serious allergic events, another phase 2 trial evaluated the adverse event (AE) profile of 2800 BAU compared to placebo in subjects with mild to moderate grass pollen induced asthma and rhinoconjunctivitis. The AE profile was similar to the AE profile in non-asthma grass allergy subjects. These results guided the selection of 2800 BAU for evaluation in Phase 3 trials. Two Phase I safety trials in children showed a similar tolerability profile compared to adults and thus the same dose of 2800 BAU was selected for the Phase 3 pediatric trials. Selection of the same maintenance dose for immunotherapy for children and adults is consistent with current immunotherapy practice.

In the European Phase 3 program conducted by the Sponsor's Joint Venture partner ALK-Abelló A/S (herein referred to as ALK), one adult (GT-08) and one pediatric (GT-12) double-blind, placebo-controlled randomized trial was conducted in ARC subjects with and without asthma. The adult trial evaluated the effect of 2800 BAU on co-primary endpoints including symptom improvement and use of rescue pharmacotherapy during the first grass season. The trial maintained its blinded design and was extended to include 2 additional years of daily treatment followed by 2 years of observation after treatment cessation to evaluate the long-term efficacy and safety. The results demonstrated that MK-7243 is an effective form of immunotherapy with a clinically relevant effect on grass induced allergic rhinitis and conjunctivitis in the first season, maintains a sustained treatment effect over 3 years while on therapy and demonstrates a persistent (disease-modifying) treatment effect for at least 2 years after therapy is stopped. The first European pediatric trial (GT-12) was a single season trial. The trial included children between 5-16 years of age with grass induced ARC with and without asthma and evaluated the same co-primary endpoint. The results confirmed the tolerability and efficacy of MK-7243 in children. Based on the results of these trials, MK-7243 was approved by the Mutual Recognition Procedure in Europe for the disease modifying

treatment of grass pollen-induced rhinitis and conjunctivitis in European adults and children (5 years or older).

MK-7243 has been marketed in Europe since 2006 under the trade name GRAZAX®. As of 30April2013, approximately 49 million doses of MK-7243 have been dispensed in Europe with an estimated 134,000 patient years of exposure.

North American Clinical Development Program of MK-7243

To demonstrate the efficacy and tolerability of MK-7243 in American subjects, the North American Phase 3 trial program was initiated by ALK in 2006 with one trial (GT-14) in adults. The primary endpoint of the trial was not met although there was a non-significant trend in favor of MK-7243. No firm conclusions can be made regarding why the trial did not meet its primary endpoint.

Merck subsequently took responsibility for the North American trial program and conducted one additional adult (P05238) and one pediatric trial (P05239). It was proposed to the Food and Drug Administration (FDA) that each trial include efficacy measurements over one grass season and a combined primary endpoint of daily symptoms and rescue medication. FDA confirmed the acceptability to combine two-co-primary endpoint scores to a single variable (sum of two co-primary endpoints). These were the first two Phase 3 trials to incorporate symptoms and medication into one combined endpoint, reflecting the contribution of both parameters to the overall efficacy assessment. The results demonstrated that MK-7243 was efficacious in North American adults and children with both trials meeting their primary endpoint. Due to variability in overall magnitude of treatment effect from trial to trial and based on further consultations with Center for Biologics Evaluation and Research (CBER), it was recommended to power a final confirmatory Phase 3 trial (P08067) based on the lower 95% confidence limit of the difference in scores between placebo and MK-7243 groups relative to the score in placebo group to be no less than 10%. Results of this large trial, including 1501 children and adults, demonstrated that for the total combined symptom and medication (TCS) endpoint, the use of MK-7243 improved the TCS more than placebo during the entire grass pollen season (treatment difference relative to placebo -23%, 95% CI: -36% to -13%, $p < 0.001$) and met the statistical criterion set by the FDA. The magnitude of the treatment effect of MK-7243 in most of the clinical trials is considered clinically relevant as proposed by the World Allergy Organization (WAO) immunotherapy Position Paper that proposes 20% treatment effect as clinically meaningful. [18] Based on indirect comparisons the treatment effect is comparable to data published for Timothy grass SCIT therapy (Frew et al [31]) and supported by a recent systematic review of SCIT and SLIT trials that showed superiority of one administration over the other could not be consistently demonstrated through indirect comparison. [32]

The totality of the Phase 3 trial data from six European and North American trials in children and adults supports the efficacy of MK-7243 in the target population. Consistent efficacy was demonstrated across the trials for the primary endpoint(s) and secondary endpoints including TCS, the individual components of the TCS which are daily symptom score (DSS) and daily medication score (DMS), and quality of life scores (Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ]). The magnitude of efficacy did vary among individual trials. This is

not unexpected given the variable nature of patient reported symptom scoring and differences in pollen exposure between regions and study year. Indeed, the accumulated data across the Phase 2/3 program for MK-7243 demonstrate that the treatment effect is highly associated with the pollen exposure during the grass pollen season, and that high grass pollen levels are associated with higher treatment effect observed in the trials.

Safety Profile of MK-7243

MK-7243 was administered to 2116 grass allergic rhinoconjunctivitis subjects with and without asthma in Phase 2/3 trials for up to 3 years. The tolerability and adverse event profile was favorable in both adults and children. The trials have been conducted with introduction of the therapy under supervision followed by a 30 minute observation period to monitor whether subjects tolerate the treatment. The most common adverse events associated with MK-7243 were local allergic reactions such as oral pruritus occurring in and around the mouth, shortly after tablet administration. Local allergic adverse events typically resolved with continued treatment over the first weeks of dosing and in the vast majority of instances, they did not result in discontinuation of therapy. The incidence of serious adverse events (SAEs) was low and similar between MK-7243 and placebo in both adults and children. No treatment related SAEs were reported for MK-7243 2800 BAU. There was no pattern for specific events beyond allergic reactions, which suggested a MK-7243-associated effect.

In the Phase 2/3 program additional systematic safety assessments of Events of Clinical Interests (ECIs) were performed to evaluate the potential for safety concerns associated with the use of sublingual immunotherapy. The ECIs for MK-7243 included systemic allergic reactions (including anaphylactic shock), local allergic swellings with the potential to compromise the upper airway, and acute asthma related events. Within the clinical program of MK-7243 2800 BAU, there were no serious treatment related systemic allergic reactions or anaphylactic shock, no serious local allergic swellings and no serious asthma related events.

For the non-serious ECIs, there were 10 systemic allergic reactions in 9 subjects: 8 of these subjects were treated with MK-7243 2800 BAU. The MK-7243 2800 BAU events were assessed as mild (n= 5) or moderate (n=4) in intensity by the investigators. The events were characterized by predominantly local symptoms and dyspnea. Six of the 8 MK-7243 treated subjects experienced the events on Day 1 of treatment. The other 2 subjects experienced mild-moderate events on day 2 and 42, respectively; however, neither subject required medication to treat the event nor did they seek medical attention. Thus, based on the clinical trial results the overall incidence rate of systemic allergic reactions observed with MK-7243 is 0.4% (9 events in 8 subjects/2116 pts. treated).

There were no reported local swellings leading to upper airway obstruction in the MK-7243. The local swellings that have occurred self-resolved or were managed by pharmacotherapy.

The safety profile of MK-7243 in subjects with reported asthma from the Phase 2/3 program was similar to those subjects who did not report a history of asthma. The occurrence of asthma-related events in the asthma subgroups was numerically lower in the MK-7243 group, compared with that in the placebo group. There were no reports of treatment related serious or severe asthma related events with MK-7243 2800 BAU.

The findings of ECI assessments in the Phase 2/3 program support the favorable safety profile of MK-7243 across multiple categories known to be of potential concern when administering immunotherapy.

Based on the observational studies systemic allergic reactions are uncommon in real world use as demonstrated by only 6 reports in ~8,500 patients, for an incidence rate of 0.07%. Systemic allergic reactions with clinically important hemodynamic changes observed in post-marketing are rare as none have been observed in the observation trials of approximately 8,500 patients. A review of ALK's MK-7243 global safety database for all serious spontaneous adverse event reports received in Europe post-approval up to 30Apr2013 showed that, in general, the type of adverse events observed in the spontaneous reports were similar to those observed in the clinical program. There wereno fatal allergic events; however, there were cases of systemic allergic reactions with clinically important hypotension, including one case reported as anaphylactic shock at first tablet administration and under medical supervision, indicating that MK-7243 may induce anaphylaxis/anaphylactic shock, a known class effect of allergen immunotherapy. These serious systemic allergic reactions have generally occurred on the first day of exposure to MK-7243 during the 30 minutes of observation in a health care setting. The few events that occurred later than the first day were readily detected and readily managed by standard care. Other allergic type reactions were also uncommon, readily detected and readily managed. [26] The European data for MK-7243 suggest that patients are aware of the onset of allergic reactions and, with or without self-treatment, are able to obtain medical care to successfully manage the events when occurring outside of the health care setting. Given the post-marketing patient population of allergic individuals, in conjunction with the increased exposure to the tablet (~49 million tablets dispensed) during the post-marketing experience, the observed allergic adverse events are not unexpected and are considered manageable.

Conclusions

The data provided in the Biologics License Application (BLA) demonstrate that MK-7243 is a first in class sublingual immunotherapy tablet that meaningfully expands the treatment options available to patients who suffer chronically from grass pollen induced allergic rhinoconjunctivitis. Evidence provided by the clinical development program reveals that MK-7243 prevents the symptoms of allergic rhinoconjunctivitis in the first grass season, with a clinically relevant treatment effect, which is generally similar to or better than first line allergic rhinoconjunctivitis medications and with efficacy comparable to subcutaneous immunotherapy. Unlike pharmacotherapy, which only treats symptoms temporarily, MK-7243 has a long-term and disease modifying effect similar to subcutaneous immunotherapy. MK-7243 provides a more convenient treatment option compared to subcutaneous immunotherapy. Once initial dosing is tolerated under medical supervision, MK-7243 offers the convenience of home immunotherapy without the need of frequent office visits and injections and with a safety profile predominately characterized by oral allergic reactions. The adverse events were usually of mild, short-lived intensity without need of treatment, and diminished over time. Hence, an unmet medical need of a novel, simple, tolerable and effective immunotherapy option will be available to patients with grass pollen induced allergic rhinitis and for whom existing subcutaneous immunotherapy is appropriate but impractical or not preferable. Overall, these comprehensive assessments demonstrate that MK-7243 offers patients an important alternative

to existing therapies through a novel approach to the administration of allergen immunotherapy. MK-7243 works by altering the underlying immunologic mechanism of the allergic disease and provide a long-term disease-modifying effect, with a favorable tolerability and safety profile.

The clinical data support the conclusions that MK-7243:

- Fulfills an unmet medical need as a novel immunotherapy formulation for treatment of grass induced allergic rhinitis with and without conjunctivitis which allows for the convenience of at home dosing once tolerance is demonstrated in the health care setting
- Has clinically relevant efficacy in preventing symptoms of grass allergy and reduces the need for pharmacotherapy after a short induction period prior to the first grass pollen season
- Has clinically relevant long-term, sustained efficacy during 3 years of treatment
- Has a disease-modifying effect shown by a maintained treatment effect for at least 2 years after therapy is stopped.
- Improves rhinitis quality of life parameters
- Is both efficacious and generally well tolerated in a diverse group of patients representing different age groups (children and adults), genders, races, geographic regions, and asthma status
- Is associated with a low risk of systemic allergic reactions, which generally occur immediately after dosing on the first day
- In indirect, cross study comparisons, the efficacy of MK-7243 appears comparable to grass SCIT, and the data suggest MK-7243 may have a lower risk of systemic allergic reactions
- Has an overall favorable risk/benefit profile

The proposed prescribing indication and dosing recommendation for GRASTEK, the proposed trade name for MK-7243, is as follows:

<u>INDICATION AND USAGE:</u>

GRASTEK is an immunotherapy indicated in adults and children 5 years of age and older for:

- the seasonal treatment of diagnosed Timothy and cross-reactive grass pollen induced allergic rhinitis, with or without conjunctivitis.
- the sustained and disease modifying treatment of diagnosed Timothy and cross-reactive grass pollen induced allergic rhinitis, with or without conjunctivitis.

<u>DOSAGE AND ADMINISTRATION:</u>

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 a severe local allergic reaction.

GRASTEK should only be administered to children under adult supervision.

One sublingual tablet to be taken daily.

2 SCIENTIFIC RATIONALE

2.1 Burden of Allergic Rhinitis and Prevalence of Grass Allergy in North America

The prevalence of allergic disease is increasing in most countries throughout the world. Respiratory allergy, in some countries, is estimated to affect up to 50% of the population with an estimated 500 million affected worldwide. [33] Allergic rhinitis/rhinoconjunctivitis (AR/ARC) affects between 10-25% of the population in the United States (US), with over 40 million AR/ARC sufferers. [11; 12] The symptoms of rhinoconjunctivitis can have a pronounced negative impact on patients' health-related quality of life; it affects sleep quality, work/school performance, and social activities. [1; 2; 3]

Allergic diseases are chronic conditions that account for a significant proportion of overall health care costs in industrialized countries. [6] In the US alone, AR/ARC has a significant pharmacoeconomic impact. In 2011, the estimated total direct US costs of allergic rhinitis (AR) were $14 billion. [7; 8; 9; 10]

AR/ARC is caused by exposure to allergens, which result in nasal and ocular allergy symptoms. In North America, Northen Pasture grasses, such as Timothy (*Phleum pratense*) grass pollen, are one of the most common seasonal allergens to cause allergy symptoms. [11] Timothy grass is prevalent extensively throughout North America with varying intensity based on regional distribution. [13; 34] Furthermore, data from the third National Health and Nutrition Examination Survey (NHANES, 2005-2006) demonstrated that 27% of the US population (ages 6 to 59 years) had atopic sensitization to perennial rye grass, a northern pasture grass with high cross-reactivity to *Phleum pratense*. [12] The NHANES 2005-2006 survey revealed that almost half (44.2%) of those with current hay fever or allergies were sensitized to grass pollen. [12] In Canada sensitization to Timothy grass has been reported to occur in up to 29% of the population. [35]

2.2 Allergic Rhinitis Treatments

The treatment for allergic rhinitis typically consists of: 1) allergen avoidance, 2) pharmacotherapy, and 3) may also include subcutaneous allergen immunotherapy. [36] Pharmacotherapies most frequently utilized include anti-histamines, leukotriene antagonists, and intranasal corticosteroids. Based on two recent meta-analyses conducted by Benninger, et. al. and Wilson et.al. [14; 15], the symptomatic treatment effect of seasonal allergic rhinitis was for leukotriene antagonists 5%, antihistamines 7-9%, and for intranasal corticosteroids 17-26% difference from placebo. Published surveys have shown more than 60% of US patients characterize current pharmacotherapy as "not at all" or "moderately" effective. [16] Immunotherapy provides an alternative to pharmacotherapy for patients for whom the efficacy of symptomatic medications is not sufficient or who are dissatisfied with such treatments because of side effects.

Unlike pharmacotherapy, specific allergen immunotherapy has the potential for the treatment effect to persist when treatment is discontinued (i.e. disease modification). Allergen immunotherapy modulates the basic immunologic mechanism of the allergic disease, and, therefore has the potential for long-term efficacy and disease-modifying effect. [18; 19; 20; 21; 22; 23; 24]

Subcutaneous allergen immunotherapy (SCIT) represents the main approach of allergen immunotherapy in North America. Allergen immunotherapy is considered for patients who have a history of allergy symptoms and evidence of specific immunoglobulin E (IgE) antibodies to clinically relevant allergens. A choice to start allergen immunotherapy for AR/ARC depends on several variables, which include the following: patient's preference; disease severity; efficacy and side effects of pharmacotherapy; response to avoidance measures; and co-morbidities such as asthma. [17] About 2-9% of US patients with an AR/ARC diagnosis receive SCIT and grass is estimated to be one of the most frequent allergens used. [7] Older studies have reported rates ranging from less than 25% to 67%. [30] The most recent study showed that a preponderance of patients who initiate treatment discontinue therapy prematurely (~53% complete less than1 year of treatment and 84% complete less than 3 years of treatment). [30]

SCIT is associated with a risk of systemic allergic reactions and the rate with non-accelerated schedules (single dose increase per visit) has been reported to range between 0.05 to 7% of injections and 0.8 to 46.7% of patients (mean, 12.92 %). [25] There have also been published accounts of both fatal and near-fatal allergic events with subcutaneous immunotherapy. [37; 27; 26; 25] As a result of the risks of serious systemic allergic reactions associated with subcutaneous allergen immunotherapy must be administered in a healthcare setting by trained personnel weekly during up-dosing and for maintenance treatment every 4-8 weeks for several years. [17] The requirement for regular office visits in order for a patient to receive a full course of immunotherapy has been cited by patients as a prime reason for either not accepting or discontinuing this form of therapy. [28; 29]

Current subcutaneous allergen immunotherapy requires careful physician oversight and monitoring in a healthcare setting. For example, subcutaneous immunotherapy requires up-titration during initiation and typically down-titration during allergy season or when allergen

administration from a newly opened vial is initiated. Although specific maintenance doses are targeted, the amount of allergen in SCIT administered to patients is variable, in part, dependent on an individual patient's tolerability, and therefore requires physician involvement throughout the course of treatment.

2.3 Rationale for Sublingual Immunotherapy

Immune Mechanism of Allergy

In the upper part of Figure 1 the immunologic mechanisms driving the allergic response is depicted and the lower part describes the inhibitory effects of immunotherapy on the allergic response. Natural allergen exposure stimulates naïve CD4+ T-lymphocytes to differentiate into T-helper cells 2 (Th2), which produce interleukin 4 (IL-4), interleukin 5 (IL-5), and interleukin 13 (IL-13). IL-4 and IL-13 induces antibody class switching to IgE in immature B-cells and stimulates the production of allergen-specific IgE by IgE-producing plasma cells. Allergen cross-linking of IgE antibodies on mast cells result in allergic mediator release and subsequent early clinical manifestations of allergic diseases. IL-5 induces influx of eosinophils to the site of inflammation as well as activation of the eosinophils leading to an enhancement of the allergic inflammation in mucosal tissues of the affected target organ. The consequence of an elevated level of Th2 cells is thus compatible with the distinctive clinical feature of the allergic immune response, namely an elevated level of allergen-specific IgE combined with a chronic eosinophil-driven inflammation in the affected target organ (Figure 1).

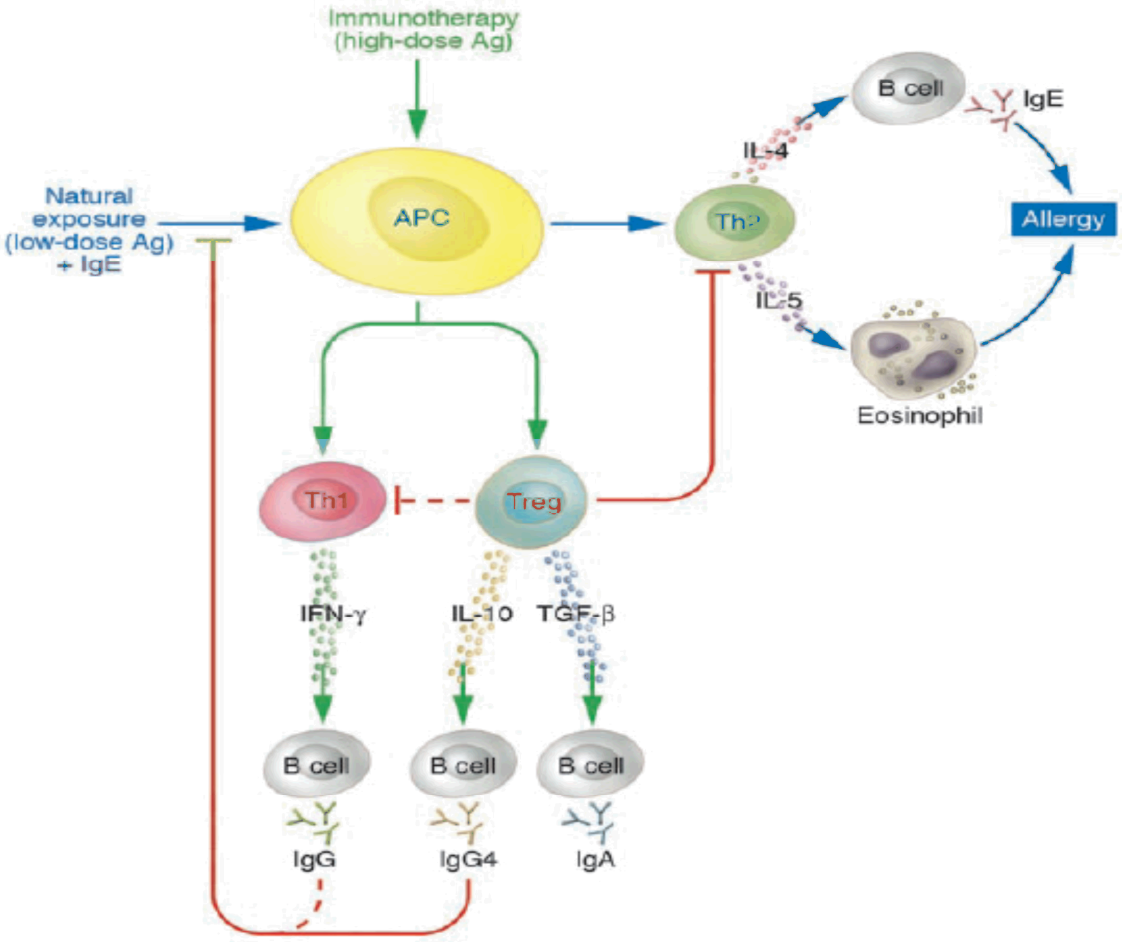


Figure 1: Immunological Mechanism of Allergy and Specific Immunotherapy

Data Source: [38]

Mechanism of Allergen Immunotherapy

The objective of allergen specific immunotherapy is to increase immunological tolerance by exposing allergic patients to repeated high allergen loads to ameliorate symptoms following subsequent allergen exposure. Applying allergens to the local environment in the mouth is regarded as a simple approach to elicit natural immune tolerance with the potential to reduce the risk of eliciting serious allergic reactions due to limited systemic exposure.

Research has shown that the effect of subcutaneous allergen immunotherapy is mediated through the interaction of antigen presenting cells, and T-cells within the tissue site or in the regional lymph nodes, Figure 1. [39; 40; 41] The high allergen exposure through immunotherapy will result in a desensitization of the mast cells and basophils initially followed by the induction of T cell tolerance shown by changes in the Th2 to type 1 helper T

cell (Th1) polarization of allergen-specific CD4+ T cells and related cytokine profiles. [42; 43] The immunomodulatory mechanisms include changes in allergen specific antibodies and regulatory T-cells (Treg) leading to long-term tolerance development (i.e., immune deviation). Immunological changes such as increased allergen specific immunoglobulin G4 (IgG4) antibody titers and induction of T regulatory cells occur within the first month of treatment, and clinical symptom reduction appears after 8 to 12 weeks of treatment, [44] followed by a sustained clinical effect during 2 to 3 treatment years. Long-term tolerance induction may result in reduced symptoms also after immunotherapy has been stopped.

Recent research also provides evidence that the oral/lingual immune system is prone to induce tolerance, as a default response to unharmful antigens. [45] The proposed pathway of allergen uptake and mechanisms of sublingual immunotherapy within the oral mucosa and local lymph nodes are as follows:

- Allergen is taken up by oral Langerhans' cells within the sublingual epithelium, possibly mediated by the high-affinity IgE receptor, FcεRI.
- Following allergen uptake, oral Langerhans' cells migrate across the submucosa to draining lymphatic vessels.
- Within the regional lymph nodes Langerhans' cells present allergen to T cells. Oral Langerhans' cells may produce interleukin 10 (IL-10) and transforming growth factor beta (TGF-β) during interaction with T cells. This production may lead to the development of regulatory T cells and inhibition of TH2 cells.
- Regulatory T cells subsequently stimulate B cell immunoglobulin class switching to IgG4 and immunoglobulin A (IgA), likely via the secretion of IL-10 and TGF-β, respectively. Regulatory T cells may subsequently migrate to allergen exposed mucosae. [46; 47; 48]

Thus, similar to subcutaneous immunotherapy, sublingual immunotherapy has been shown to reduce recruitment and activation of inflammatory cells, affect antibody regulation, and produce a T cell immunoregulatory effect. [44; 49; 46; 47; 50; 48] In the Clinical Program, Pharmacodynamics of MK-7243, Sec. 3.2, the results characterizing the effect of MK-7243 on the immune system are summarized.

2.4 Rationale for MK-7243 as a Novel Form of Immunotherapy

MK-7243 is an oral pharmaceutical formulation of the allergen extract from Timothy grass pollen (*Phleum pratense*) in tablet form. The starting dose of MK-7243 is the maintenance dose. The treatment requires no dose adjustments by up or down titration. MK-7243 has been developed to provide a convenient and safe approach to repeated high allergen dose exposure through continuous daily treatment without interruption over several years. The principle behind the continuous dosing regimen is similar to subcutaneous immunotherapy, which has shown that repeated constant exposure to grass pollen allergen results in development of long-term immunologic tolerance. [19]

The formulation of MK-7243 is intended to provide a simple, oral, at-home delivery (following the administration of the first dose in office) of an effective, well-defined dose of allergen immunotherapy with a favorable safety profile. The tablet contains a quality controlled, well-

characterized, biologically standardized Timothy grass allergen formulation with a potency of 2800 bioequivalent allergy unit (BAU). This will also be one of the first regulated US allergen immunotherapy products that has been rigorously evaluated and approved according to current standards of good clinical practice (GCP) and good manufacturing practices (GMP).

Timothy grass was selected because, as a member of the Pooideae subfamily, it demonstrates extensive cross-reactivity with other Pooideae members such as perennial rye (lolium), meadow fescue (festuca), bluegrass/june (poa), orchard/cocksfoot (dactylis), sweet vernal (anthoxanthum), and redtop/bent/velvet (agrostis) and is partially cross-reactive with Johnson grass. All of these grasses are major aeroallergens in North America. [44; 51; 52; 53; 54]

Immunotherapy guidelines and publications support that there is high cross-reactivity amongst grasses from the Pooideae subfamily. [17; 55] As stated in the Immunotherapy Practice Parameter [17], many temperate pasture grasses share major allergens; therefore, treatment with a representative member generally also provides treatment for the group. [56] Patients with a demonstrated Timothy allergy who are also allergic to related grasses (i.e., within the Pooideae subfamily) are expected to benefit from treatment with the Timothy grass tablet. Supporting evidence is based on others as well as the Sponsor's research on amino acid sequence homology, IgE-inhibition experiments, and clinical data from our pivotal trials, which have demonstrated direct cross-reactivity between Timothy and the closely related grass species. [44; 51] Data from one of the pivotal trials (GT-12) showed that treatment with the Timothy grass tablet, MK-7243, induced treatment- specific IgG_4 to other Pooideae species and inhibited the binding of specific IgE to the other Pooideae allergens. In addition, data from the North American P08067 trial showed that 100% of Timothy grass sensitized subjects were also IgE-sensitized to the cross-reactive grasses: perennial rye grass, redtop grass, Kentucky blue grass, orchard grass, and sweet vernal grass and 88% were sensitized to Johnson grass. This concept of treatment with only one member of the cross-reacting allergens (i.e., "allergen families" or "homologous groups") is also supported by the European Medicines Agency (EMA) immunotherapy guideline [21] and draft guidance ("Guideline on Allergen Products: Production and Quality Issues" (CPMP/BWP/304831/07) [57], which state that efficacy proven for one representative allergen is sufficient to prove the efficacy for the "homologous group".

2.5 Regulatory History

MK-7243 is currently marketed in Europe under the trade name GRAZAX® by ALK. A Marketing Authorization Application for GRAZAX® was filed by ALK via the Mutual Recognition Procedure in the European Union (EU) and ALK received its first approval in 2006. The trials supporting the original approval included the pivotal Phase 3 trial (GT-08) which was supported by the Phase 1 trials (GT-01, GT-03 and GT-04) and Phase 2 trials (GT-02 and GT-07). GRAZAX® is indicated in the EU for the disease modifying treatment of grass pollen-induced rhinitis and conjunctivitis in adults and children (5 years or older) with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test to grass pollen. GRAZAX® is currently marketed in 20 countries.

To address requirements for licensure of MK-7243 in the US, a pre-investigational new drug application (pre-IND) meeting was held with US FDA by ALK in 2001 to clarify

manufacturing and pre-clinical testing requirements. At that time FDA indicated that demonstration of efficacy of MK-7243 in the North American population would be required for licensure. The IND for MK-7243 was initiated by ALK in 2006 with the Phase 3 trial GT-14. In 2007, Merck (then Schering-Plough) and ALK initiated the partnership. At this time the GT-14 trial concluded; however, the primary endpoint of the trial was not met. After consultation with FDA, Merck initiated two additional North American Phase 3 trials, P05238 (adult) and P05239 (pediatric). These trials concluded in 2009 and met their primary endpoint of statistically significant reduction in TCS compared to placebo. These trial results were shared with FDA, and Merck was advised that an additional trial would be required for licensure to fulfill FDA's criterion that the 95% confidence interval of the relative treatment effect for the primary endpoint demonstrate at least a 10% improvement compared to placebo. Therefore, Merck conducted the Phase 3 trial P08067, which concluded in 2012.

A pre-BLA meeting was held with the FDA in January of 2013. The BLA for MK-7243 was submitted on January 25, 2013. The BLA was accepted for review on March 19, 2013 with a target review date of January 25, 2014.

Extensive scientific advice was sought between 2008 and 2012 regarding Chemistry, Manufacturing and Controls (CMC) and clinical topics. Over this time, concurrence was reached with the FDA on the extent of the North American clinical population required for licensure, the use of the Total Combined Score (TCS) as the primary clinical endpoint and clarification of specific statistical criteria required to adequately demonstrate efficacy.

Following the above guidance from FDA, clinical trials were conducted to evaluate efficacy in a grass pollen allergic North American population. The designs of the trials supporting the US biological licensing application (BLA) incorporated recommendations from the FDA and the EMA Committee for Medicinal Products for Human Use for AR clinical trials and guidance from the World Health Organization (WHO) and WAO position papers for development of sublingual immunotherapy. [58; 59; 18; 60; 21; 61; 62]

3 DEVELOPMENT PROGRAM FOR MK-7243

The development and formulation of MK-7243 is based on the extensive clinical and nonclinical experience with MK-7243 and with similar Timothy grass extracts for subcutaneous administration that are manufactured by ALK and commercially available in both Europe and the United States for immunotherapy of grass allergy.

3.1 Nonclinical Summary

Nonclinical studies conducted to support registration consist of single-dose sublingual and intravenous studies in mice, multiple-dose sublingual toxicology studies in mice up to 6-months and in dogs up to 12 months in duration, genetic toxicology studies, and sublingual reproductive toxicology studies in mice.

The nonclinical program was designed to take into account the extensive clinical and nonclinical experience with similar Timothy grass extracts for subcutaneous administration that is manufactured by ALK and available in both Europe and the United States and to incorporate feedback from the FDA. Further, the MK-7243 tablet is the same tablet formulation that was

approved for use in the EU in 2006 and continues to be marketed by ALK under the trade name GRAZAX®. To date, there are no reports or any indication that the active substance (i.e. grass pollen extract) has direct effects on organ systems other than the immune system. No animal studies regarding secondary pharmacodynamics, safety pharmacology, pharmacodynamic drug interactions, pharmacokinetics, metabolism and carcinogenicity were performed since the immune-modulating effect from sublingual immunotherapy is related to exposure of specific allergens to local antigen presenting cells in the oral submucosa and biodistribution studies in humans with allergens (not MK-7243) have shown that the systemic absorption of allergen through the oral mucosa is absent or negligible. [63; 64; 65] The absence of detectable systemic exposure of intact allergens explains in part the safety profile of SLIT, with mostly local and rare systemic adverse events.

Results of the nonclinical toxicology program for MK-7243 indicate no toxicological findings, mutagenic potential, or effects on reproduction and fetal development.

3.2 Clinical Program

The clinical program was designed to evaluate the efficacy, safety and tolerability of MK-7243 in subjects diagnosed with grass induced AR/ARC across multiple safety and single-season efficacy trials and in one multi-season trial of 5 years duration. The clinical program encompassed extensive subject exposure, duration of treatment, and subject diversity to provide a robust assessment of the efficacy and safety profile of MK-7243 in Timothy grass sensitized subjects with grass allergy symptoms. Potential safety issues associated with allergen immunotherapy were thoroughly assessed via systematic collection (i.e. terms and events fulfilling the Sampson criteria [66]) of adverse events of local or systemic nature both in Phase 1 trials and in the Phase 2/3 program.

The MK-7243 clinical program is comprised of the following:

1) In ***Phase 1***, 5 trials of approximately 28-days duration were conducted outside the grass season in grass allergic subjects (GT-01, GT-03 and GT-04 in adults; GT-09 and GT-11 in children) to assess initial tolerability and pharmacodynamics based on levels of *Phleum pratense* specific immunoglobulin IgE, IgG4 and IgE-blocking factor[1]. [67]

[1] The IgE-blocking factor relates the amount of specific IgE bound to allergen in the presence of other components (competitive sIgE) to the total amount of IgE specific for that allergen (ordinary sIgE). The IgE-blocking factor is a dimensionless number which varies theoretically from 0 (no presence of IgE-blocking components) to 1 (all IgE blocked from binding to allergen).

$$\text{IgE-blocking factor} = 1 - \frac{\text{competitive sIgE}}{\text{ordinary sIgE}}$$

2) In ***Phase 2***,

   - 1 dose-ranging clinical adult trial (GT-02) was a single season treatment trial conducted in adult AR/ARC grass allergic subjects to establish proof-of-concept for the efficacy and safety of MK-7243 and to identify the dose for further evaluation in Phase 3.
   - 1 safety trial (GT-07) was conducted in adult AR/ARC subjects with concomitant grass induced mild to moderate asthma, who are potentially at higher risk of adverse events, to assess tolerability of 2800 BAU in AR/ARC subjects with this co-morbidity to assess if seasonal allergic asthma subjects were at risk to be included in Phase 3.

3) In ***Phase 3***, the efficacy and safety of MK-7243 in AR/ARC subjects with and without asthma were confirmed by conducting 6 placebo-controlled, parallel group, multi-center/multi-national trials with treatment 8-12 weeks prior to and throughout the entire grass pollen season. Initial dosing of study medication (first 1-3 days depending on the trial) occurred under supervision at the investigative site followed by at-home dosing for the remainder of the trial. The GT-08 trial and its extension included continuous daily treatment for 3 years and 2 years without treatment

   - 2 one-season adult efficacy and safety trials (GT-14, P05238)
   - 1 five-year adult efficacy and safety trial (GT-08)
   - 2 one-season pediatric efficacy and safety trials (GT-12 and P05239)
   - 1 one-season adult/pediatric efficacy and safety trial (P08067)

Overview of Clinical Trials

Clinical Phase 1-3 adult and pediatric trials included in the development program are presented in Table 2.

Table 2: Overview of Randomized, Placebo-Controlled Phase 1, 2 and 3 North American and European Trials in the MK-7243 Clinical Program

Trial ID/ Objective	Trial Phase	Dose (QD) and Control & Regimen	Randomized (n)	Approximate Treatment Duration
Adults				
GT-01 Dose-Escalation Clinical Safety in grass pollen allergic subjects	1	Period 1: Dose escalation: doses included 93 BAU, 933 BAU, 2800 BAU, 4,699 BAU, 14,097 BAU and Placebo Period 2, 3 & 4: 93 BAU 933 BAU 2800 BAU Placebo	Period 1: 39 active[a], 8 placebo Period 2, 3 and 4: 36 active[a] (12 on 2800 BAU) 11 placebo	Period 1: 7-14 days Period 2: 8 wks. Period 3: 15 wks. (~4 wks. prior to and during GPS); extension following 6 wk. treatment interruption Period 4: follow-up visit (off treatment) ~3 months after completion of period 3

Trial ID/ Objective	Trial Phase	Dose (QD) and Control & Regimen	Randomized (n)	Approximate Treatment Duration
GT-03 Dose-escalation Safety of MK-7243 in subjects with seasonal rhinoconjunctivitis caused by grass pollen allergy	1	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	28 days
GT-04 Dose-escalation Safety of MK-7243 in subjects with seasonal grass pollen induced rhinoconjunctivitis and mild to moderate asthma	1	2800 BAU 5600 BAU 11,200 BAU 18,666 BAU Placebo	9 9 9 5 11	28 days
GT-02 Dose-finding trial	2	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	2	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	3	2800 BAU Placebo (Years 1-3)[bc] and no treatment (Years 4 and 5)	316 318	Year 1: 4 to 6 months prior to the GPS and during the 2005 GPS. Year 2: Extension of GT-08 to the end of the 2006 GPS. Year 3: Extension of GT-08 to the end of the 2007 GPS.
GT-14 Efficacy and safety	3	2800 BAU Placebo	163 166	24 weeks (approximately 8 to 16 weeks prior to and during the 2007 GPS)
P05238 Efficacy and safety	3	2800 BAU Placebo	213 226	24 weeks (approximately 16 weeks prior to and during the 2009 GPS)
Pediatrics				
GT-9 Safety in Children Aged 5-12 years with Grass Pollen Induced Rhinoconjunctivitis (with/without asthma)	1	2800 BAU Placebo	23 7	28 days (outside of GPS)
GT-11 Safety in children aged 5-12 years with grass pollen induced rhinoconjunctivitis (with/without asthma)	1	2800 BAU Placebo	22 8	28 days (outside of GPS)
GT-12 Efficacy and Safety	3	2800 BAU Placebo	126 127	24 weeks (approximately 16 weeks prior to and during the 2007 GPS)
P05239 Efficacy and Safety	3	2800 BAU Placebo	176 169	24 weeks (approximately 16 weeks prior to and during the 2009 GPS)

Trial ID/ Objective	Trial Phase	Dose (QD) and Control & Regimen	Randomized (n)	Approximate Treatment Duration
Adults and Pediatrics				
P08067 Efficacy and safety	3	2800 BAU Placebo	752 749	24 weeks (approximately 12 weeks prior to and during the 2012 GPS)

GPS = grass pollen season; QD = once daily
Note: Trials GT-08 and GT-12 were conducted in Europe; whereas, trials GT-14, P05238, P05239, and P08067 were conducted in North America.
a: The number of active subjects in GT-01 combine all subjects that received any active dose of MK7243.
b: Each subject was followed for 2 years post-treatment for total trial duration of 5 years.
c: In trial GT-08, blinded treatment continued daily throughout the year during Years 1-3.

In summary, a total of 13 clinical trials comprise the clinical program, including 2077 adults (18 to 66 years of age) and 491 pediatric (5 to 17 years of age) subjects treated with MK-7243 in both North America (>65% of the trial population) and Europe, Table 3.

Table 3: Number of Subjects Included in the 13 Trials Comprising the MK-7243 Clinical Development Program by Trial and Age Range (All Randomized as Randomized)

Trial Number	Trial Phase	Number of Subjects			Trial Region	Age Range (Years)
		Total	Active	Placebo		
Clinical Trials in Adult Subjects						
GT-01	1	47	39	8	Europe	20 to 57
GT-03	1	84	63	21	Europe	20 to 61
GT-04	1	43	32	11	Europe	18 to 42
GT-02	2	855	569	286	Europe	18 to 66
GT-07	2	114	74	40	Europe	18 to 64
GT-08 Year 1	3	634	316	318	Europe	18 to 65[a]
Year 2		351	189	162		18 to 63[a]
Year 3		308	170	138		18 to 63[a]
Year 4		283	157	126		18 to 63[a]
Year 5		258	145	113		18 to 63[a]
GT-14	3	329	163	166	North America	18 to 65
P05238	3	439	213	226	North America	18 to 63
P08067[b]	3	1218	608	610	North America	18 to ≥65
Total Number of Adult Subjects Enrolled/Treated		**3763**	**2077**	**1686**		**18 to 66**

Trial Number	Trial Phase	Number of Subjects			Trial Region	Age Range (Years)
		Total	Active	Placebo		
Clinical Trials in Pediatric Subjects						
GT-09	1	30	23	7	Europe	5 to 12
GT-11	1	30	22	8	Europe	5 to 12
GT-12	3	253	126	127	Europe	5 to 16
P05239 [a]	3	345	176	169	North America	5 to 17
P08067[b]	3	283	144	139	North America	5 to 17
Total Number of Pediatric Subjects Enrolled/Treated		**941**	**491**	**450**		**5 to 17**

a. Age ranges represent age at screening.
b. P08067 enrolled children and adults

Pharmacodynamics of MK-7243

During the MK-7243 trials, serum samples from children and adults were collected to evaluate allergen-specific immunologic parameters. Changes over time in *Phleum pratense* specific-IgE, IgG4, and IgE-blocking factor levels (footnote 1)were assessed in the majority of clinical trials.

Treatment with MK-7243 led to time- and dose dependent increases of allergen specific IgG, IgG4, IgA, IgE and IgE-blocking factor confirming the immunological effect on the allergic immune response. Figure 2, Figure 3, and Figure 4 provide the mean change from baseline and its associated 95% confidence interval for the *Phleum pratense* specific IgE, IgG4, and blocking IgE factor based on the available data from the GT-08 trial.

In the 5-year trial (GT-08) it was observed that an initial increase in allergen specific IgE was followed by a decrease, which returned to levels similar to those observed for placebo treated subjects. During the first season, there was a blunting effect on the seasonal specific IgE rise in the MK-7243 group compared to the placebo group. This trend was also noted in the following treatment years. The level of specific IgE in the MK-7243 group was, by the end of the third treatment year, close to the level in the placebo group and remained low during the 2 years after the end of treatment (Figure 2). The blunting effect and decrease in specific IgE response is expected due to the down regulation of the allergic response and has also been demonstrated in trials of subcutaneous immunotherapy. [68] Yearly increases in IgE are seen in both the MK-7243 group and the placebo group. This is due to environmental grass exposure during the yearly grass pollen seasons.

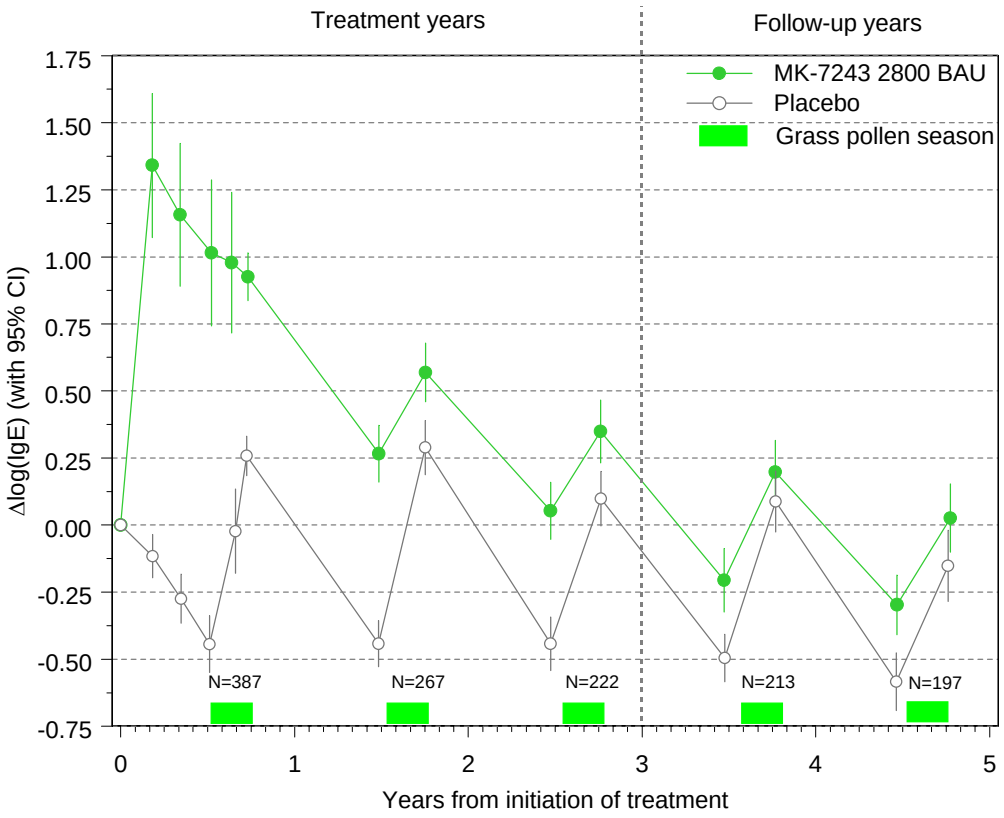


Figure 2: Change from Baseline in logarithm of *Phleum pratense* Specific IgE – GT-08 Trial (Full Analysis Set)

Within the first weeks of treatment a significant increase in mean levels of allergen-specific IgG4 and IgE-blocking activity was also detectable. Results of the GT-08 long-term trial showed that in the MK-7243 treated subjects, the immunologic changes in *Phleum pratense* specific IgG4 and IgE-blocking factor were sustained during the entire 3-year treatment period. The increased levels of IgG4 (Figure 3) and IgE-blocking factor (Figure 4) with MK-7243 compared to placebo persisted post-treatment, although the difference was of lower magnitude in the post-treatment years than that observed during the treatment years.

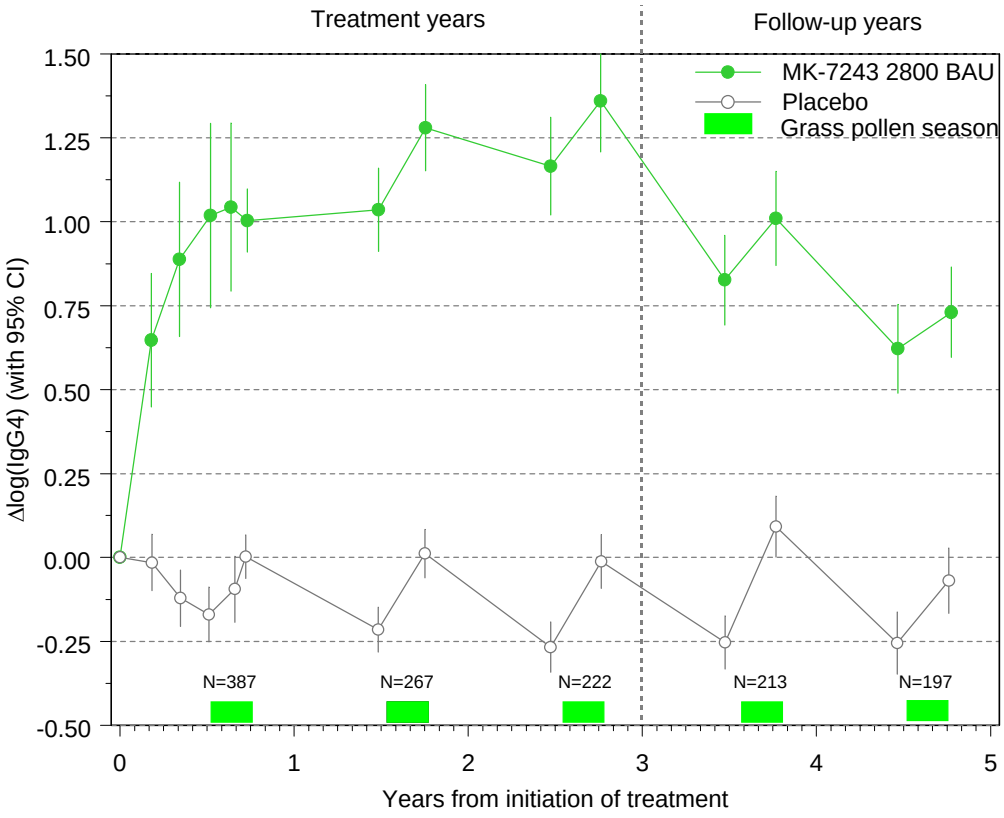


Figure 3: Change from Baseline in logarithm of *Phleum pratense* Specific IgG4 – GT-08 Trial (Full Analysis Set)

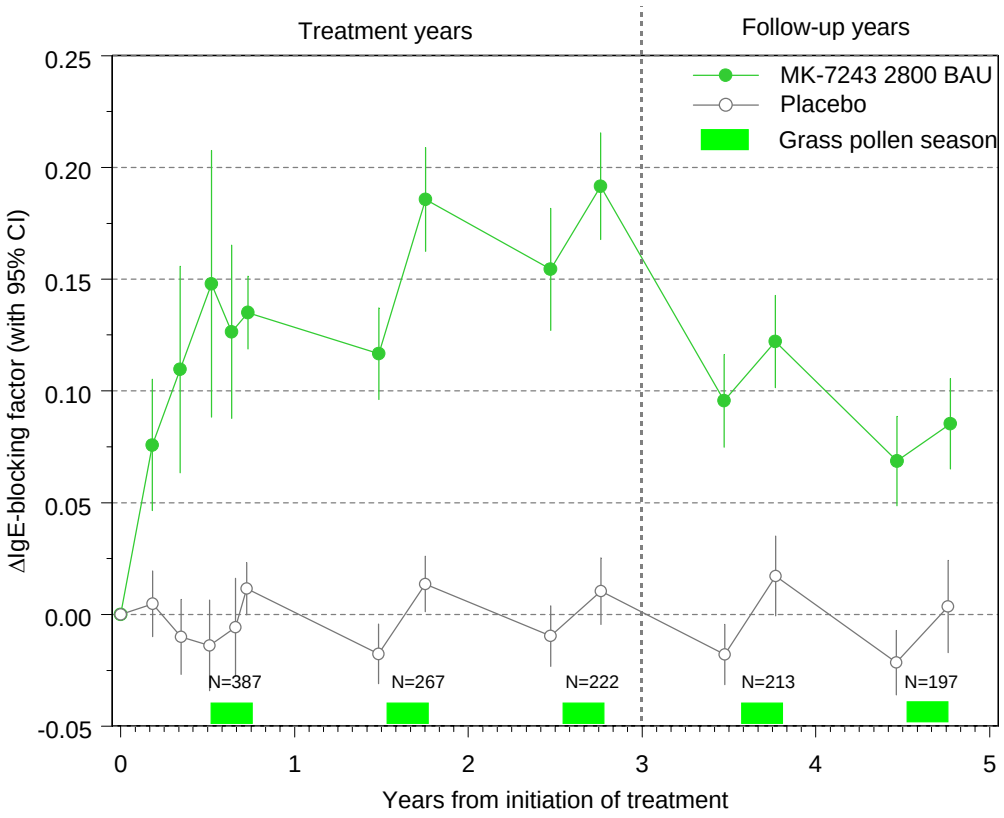


Figure 4: Change from Baseline in *Phleum pratense* specific IgE Blocking Factor – GT-08 Trial (Full Analysis Set)

The early immunologic changes observed in the single season trials in children and adults were similar (data not shown) suggesting that the dose and treatment regimen induces the same immunological changes in children and adults. There are no long-term or post-treatment immunologic data available for children.

4 OVERVIEW OF EFFICACY

4.1 Features of Efficacy Trials

The clinical effect and assessment of immunotherapy in clinical trials is influenced by four important factors: 1) the selection of appropriately allergic subjects; 2) the duration of the induction period required to attain efficacy during the first pollen season; 3) the duration of the pollen season; and 4) the level of pollen exposure. [69] Clinical trial design can address factors 1 and 2; however, factors 3 and 4 are beyond the scope of the protocol or control of the investigator and potentially lead to greater variability in any given trial, or between trials.

For all of the MK 7243 efficacy and safety trials, adults and/or children with grass pollen induced allergic rhinoconjunctivitis with or without asthma were recruited. Specific inclusion/exclusion criteria were applied to promote subject safety and to minimize potential confounders that would interfere with the interpretation of the efficacy and safety data and to increase the potential to randomize subjects with clinically relevant grass pollen allergy.

4.2 Duration of Induction (Pre-seasonal Treatment) with MK-7243

The rationale for an induction period is to allow for sufficient time to induce immunomodulatory changes to obtain meaningful clinical efficacy during the first seasonal exposure. While immunologic changes can be demonstrated with as little as 4 weeks of dosing, it is important to establish the appropriate induction period by demonstrating clinical efficacy. The GT-02 trial, which included an induction period of ~7 to ~11 weeks, supports the relationship between efficacy and duration of induction dosing (pre-seasonal treatment) with MK-7243. This trial demonstrated statistically significant and clinically relevant reductions in rhinoconjunctivitis symptom scores only for those subjects who received at least 8 weeks of pre-seasonal treatment with MK-7243 2800 BAU. Based on the results from GT-02, subsequent trials were designed to ensure that pre-seasonal treatment was at least 8 weeks in duration.

Based on further subgroup analyses using data pooled from the eight Phase 2 and Phase 3 trials (GT-02, GT-07, GT-08(year 1), GT-12, GT-14, P05238, P05239, P08067, Figure 5), it was concluded that efficacy could be demonstrated following induction periods less than 12 weeks; however, optimal efficacy required at least 12 weeks of dosing prior to season.

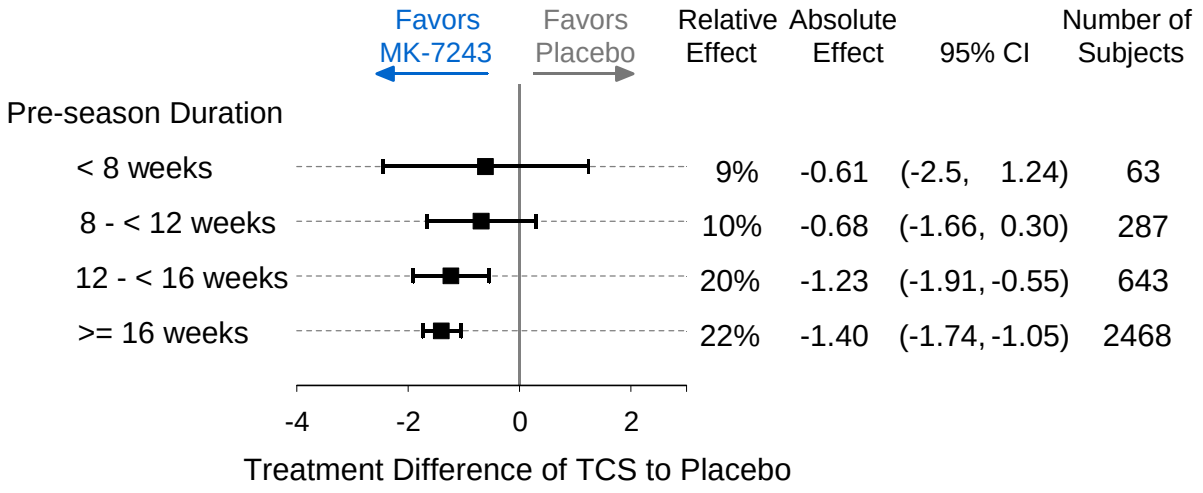


Figure 5: Average TCS during Grass Pollen Season by Pre-season Duration Sub-Group Pool All Phase 2 and 3 Populations (Full Analysis Set)

4.3 Duration of Treatment Period

MK-7243 is intended for use daily during the course of treatment without interruption. Continuous dosing year-round is consistent with current practice set forth for subcutaneous immunotherapy. [17] It appears that chronic allergen exposure drives the immune-modulatory changes induced by T regulatory cells, resulting in decreased allergen specific T cell proliferation, and leading to increased specific IgG4 antibody levels, ultimately culminating in a maintained clinical effect and disease modification. [70] It is unknown if non-continuous immunotherapy (e.g. pre-and co-season) treatment for multiple years will induce disease-modification. A number of studies with continuous treatment have investigated and demonstrated the long-term benefit of subcutaneous immunotherapy and the persistence of benefit after discontinuation of a long–term treatment schedule. [19; 20; 22; 23; 24] For subcutaneous immunotherapy, therefore, it is recommended that immunotherapy maintenance treatment be given continuously for 3 to 5 years. [58; 17] A similar approach was taken for MK-7243.

4.4 Relevant Features of the Subject Population

Trial subjects included patients with a history of grass pollen allergy, prior need for pharmacotherapy during grass pollen season, and specific IgE sensitization to Timothy grass pollen. All subjects demonstrated Timothy grass sensitivity by skin prick test (SPT) and serum specific IgE, and reported a history of grass allergic rhinoconjunctivitis symptoms. The criteria to include subjects with a history of allergic rhinoconjunctivitis, who required previous pharmacotherapy for their allergic symptoms, helped the selection of a moderate to severe AR/ARC population. Although the majority of subjects were sensitized to other allergens in addition to grass pollen, as a means to reduce bias due to other symptomatic allergies during the grass pollen season, subjects with clinically significant allergies which overlap the grass season were excluded from enrollment into the trials. However, subjects

with clinically important allergy to non-grass allergens were allowed as long as the season(s) or exposure was separated from the grass pollen season.

Subjects with a History of Asthma

All trials included a notable percentage of subjects with concomitant asthma, consistent with the natural demographics of allergic disease; however, subjects were excluded if they had severe or unstable asthma or if they had a forced expiratory volume in 1 second (FEV_1) of < 70% of predicted. Subjects requiring year-round maintenance inhaled corticosteroids (ICS) or long-acting $beta_2$-agonists (LABA) treatment were generally excluded. Thus, the majority of enrolled subjects with a diagnosis of asthma suffered from intermittent or mild persistent perennial or seasonal asthma. In one of the adult trials (GT-07 Trial), as per inclusion criteria, all enrolled subjects had mild to moderate grass-pollen induced asthma and had used medication for control of their asthma symptoms during the last two grass pollen seasons (GPSs). The majority of subjects' asthma medication histories included short acting beta-2 agonists, and approximately 34% of the population had previously used ICSs; a small number of subjects had used LABA and combination therapy (LABA plus ICS). However, as with the other trials, subjects requiring year-round maintenance inhaled corticosteroids were excluded; generally, when required, asthma maintenance medications were utilized due to asthma symptoms that developed during the seasonal grass pollen exposures.

4.4.1 Subject Demographics and Baseline Characteristics

Key demographic and baseline characteristic data for the program are presented in Table 4. In general, the adult and pediatric populations were similar across the treatment groups.

Table 4: Subject Demographics and Select Baseline Characteristics for Phase 2/3 Adult and Pediatric Pooled Clinical Trials (As Randomized[a])

	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,%)				

	Adult		Pediatric	
	MK-7243 2800 BAU n=1668	**Placebo n=1646**	**MK-7243 2800 BAU n=446**	**Placebo n=435**
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,%)[b]				
No	332 (20)	321 (20)	61 (14)	50 (11)
Yes	1336 (80)	1325 (80)	385 (86)	385 (89)

[a] All randomized subjects were included, based on treatment they were randomized to, regardless of which treatment they actually received
[b] Sensitization was determined by serum specific IgE to a panel of inhalant allergens

Across all Phase 2/3 adult trials and the Phase 3 pediatric trials, approximately 25% of adult subjects and 31% of pediatric subjects had a history of asthma. All subjects in GT-07 trial were required to have asthma.

Subjects who tested positive to Timothy grass are expected to test positive to the cross-reactive Northern Pasture grasses. As such, the pivotal P08067 trial data showed that 100% of Timothy grass sensitized subjects were also IgE-sensitized to the cross-reactive grasses: perennial rye grass, redtop grass, Kentucky blue grass, orchard grass, and sweet vernal grass and due to partial cross-reactivity 88% were sensitized to Johnson grass. The correlation coefficient based on the allergen specific IgE levels (kU/L) was >0.97 for all of these grasses except Johnson grass (0.77). In addition, the majority of subjects demonstrated sensitization to non-grass (e.g. tree, house dust mite, cat, etc.) allergens (approximately 80% of adults and 86% of children).

4.5 Key Efficacy Endpoints

The clinical development program assessed the efficacy of the MK-7243 in accordance with the EMA and Canadian Immunotherapy Guidelines and recommendations by WAO. [59; 18; 60; 21; 61; 71] The efficacy endpoints were consistent 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. [60; 21; 61] According to these guidelines, an accepted demonstration of efficacy in rhinoconjunctivitis is based on a decrease of symptoms relative to placebo treatment as measured by subject symptom score, reduced use of AR/ARC rescue medication, and change in allergen-specific immunologic in vitro parameters. Thus, in order to be in accordance with these guidelines the efficacy endpoints chosen for the clinical trials included rhinoconjunctivitis daily symptom score (DSS) and daily medication score (DMS). However, recently it was recommended by WAO and EMA [18; 21] to select endpoints that reflect symptoms adjusted by AR/ARC rescue medication usage and for that reason, and in agreement with Center for Biologics Evaluation and Research (CBER), later trials included the total combined symptom and medication score (TCS: the sum of DSS and DMS). The Rhinoconjunctivitis Quality of Life Questionnaire with standardized activities (RQLQ(s)) total score was also a key secondary endpoint.

4.5.1 Daily Symptom Scoring (DSS)

Daily rhinoconjunctivitis symptoms, Table 5, including the four nasal symptoms of runny nose, blocked nose, sneezing, and itchy nose, and the two non-nasal symptoms of gritty feeling/red/itchy eyes and watery eyes, were measured on a scale of 0 (none) to 3 (severe). The maximum achievable symptom score, if all symptoms were rated with intensity as severe, is 18.

The daily symptom score were collected daily before the start of the grass pollen season and through the end of treatment using an electronic diary (e-diary). The daily data collected from each subject required responses for all symptoms. Therefore, if a subject missed a daily entry, all questions would have been missed.

Table 5: Daily Symptom Scale

Individual Symptoms	Symptom Severity/ Intensity Score[a]	Scale Range	Maximum Daily Score
Allergic Rhinitis Symptoms (AR)			
Runny Nose	Absent Mild Moderate Severe	0 1 2 3	3
Blocked Nose			3
Sneezing			3
Itchy Nose			3
Allergic Conjunctivitis Symptoms (ARC)			
Gritty Eyes	Absent Mild Moderate Severe	0 1 2 3	3
Watery Eyes			3
		Symptom Daily Total Score	18

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

The 4-point scale (0 to 3) for each symptom in the DSS is consistent with a well-established methodology for assessment of efficacy in trials of AR/ARC, and is in accordance with regulatory and therapeutic guidance documents. [60; 21; 61] The guidances indicate that the core nasal symptoms of rhinorrhea, sneezing, nasal obstruction and nasal itching and the core eye symptoms of gritty/itching and tearing should be assessed. Symptoms are typically scored

on a scale of 0 to 3 (none, mild, moderate, severe). These symptom rating scales have been used to support registration of major classes of therapy for AR/ARC including antihistamines [72; 73], intranasal steroids [74; 75; 76; 77; 78] and antileukotriene receptor antagonists. [79; 80]

4.5.2 Daily Medication Scoring (DMS)

Unlike allergy trials of pharmacotherapy, seasonal allergy trials evaluating immunotherapy allow use of symptom relieving (AR/ARC rescue) medications to allow appropriate symptom-relieving therapy during lengthy trials. Since optional symptom-relieving medications can improve symptoms, their use in immunotherapy trials must be accounted for and evaluated to appropriately assess the overall treatment effect of the investigational immunotherapy.

In the trials of MK-7243, subjects were provided with open-label AR/ARC rescue medication to be used as needed for treatment of their rhinoconjunctivitis symptoms not controlled by study drug. Predefined values are assigned to each class of medication to represent an estimate of the symptomatic relief provided by the rescue medication. The total score for all medications used by the subject each day are summed for the DMS.

The AR/ARC rescue medication scores for the DMS are listed in Table 6 for the P08067, P05238, and P05239 trials. The maximum achievable medication score, if all available AR/ARC rescue medications were used, is 36.

Table 6: Daily Medication Scale

RHINOCONJUNCTIVITIS			
STEP	**AR/ARC Rescue Medication**	**Score/Dose Unit**	**Maximum Daily Score**
1	Loratadine syrup 1 mg/mL – 5 mL QD (5 to <6 yr.)	6 (per 5 mL)	6
	Loratadine RediTabs tablet 10 mg – 1 tablet QD ≥ 18 yr.); Claritin syrup 1 mg/mL – 10 mL QD (≥6 to <18 yr.)	6 (per tablet or 10 mL)	
	Olopatadine hydrochloride 0.1% ophthalmic solution -1 drop in the affected eye BID	1.5 (per drop)	6
2	Mometasone furoate monohydrate nasal spray 50 micrograms (mcg) – 1 spray in each nostril QD (5 to <12 yrs.)	4 (per spray)	8
	Mometasone furoate monohydrate nasal spray 50 mcg - 2 sprays in each nostril QD (≥12 yr)	2 (per spray)	
3	Prednisone tablet 5 mg (Day 1 - 1 mg/kg/day, Max 50 mg/day)	1.6 (per tablet)	16[a]
	Prednisone tablet 5 mg (Day 2+ - 0.5 mg/kg/day, Max 25 mg/day)	1.6 x 2 (per tablet)	
		Maximum daily rhinoconjunctivitis medication score	36

a. Use of prednisone will be counted in the rhinoconjunctivitis medication score and/or the asthma medication score depending on the symptoms. In the combined score, use of prednisone was counted only once.

For the MK 7243 development program, the rhinoconjunctivitis medication score was adapted from the medication scores developed for use in studies on subcutaneous immunotherapy. [19; 31] The Daily Medications Score (DMS) is based on use of rescue medications for symptoms of allergic rhinitis and conjunctivitis. Rescue medication doses are transformed into the DMS based on a predefined algorithm derived from the estimated clinical benefit in reduction in symptom score that a subject would experience from the use of the rescue medication. [81]

The score for each rescue medication was based on use of the maximum recommended daily dose as specified by the Summary of Product Characteristics (SmPC) for the product, and linked to placebo-adjusted symptom relief observed in placebo-controlled randomized trials of seasonal allergic rhinitis. The assigned score for each rescue medication reflects its effect on rhinoconjunctivitis symptoms supported by the Sponsor's own trials with loratadine and mometasone furoate nasal spray in seasonal allergic rhinitis subjects. The total score from use of the rescue medication was summed each day as the DMS. The DMS was captured in a subject e-diary that was provided by the Sponsor for each trial.

4.5.3 Total Combined Symptom and Medication Scoring (TCS)

Specifically for the most recent trials (P05238, P05239, and P08067), a single endpoint (TCS) which combined DSS and DMS was selected as the primary endpoint to provide a more clinically relevant measurement of the total benefit experienced by the subject as recommended in the guidelines, Table 7. To facilitate the analysis between the pivotal trials for this endpoint and given the similar design of these trials, the TCS was calculated post-hoc for GT-08, GT-12, and GT-14. The TCS will be presented for all trials, in addition to the components of TCS (DSS and DMS), which constituted the primary endpoints for the trials that did not use the combined endpoint.

Table 7: Total Combined Score

	Maximum Score
Daily Symptoms Score: (scale 0-3) runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes	18
Daily Medication Score: Combined use of Step 1, Step 2 and Step 3 medications	36
Maximum daily Total Combined Score[a]:	54

a. The maximum achievable TCS for GT-14 is 30 due to the lower maximum medication score.

4.5.4 Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)

The Rhinoconjunctivitis Quality of Life Questionnaire with standardized activities (RQLQ(s); ≥18 years of age), the Pediatric RQLQ (6 to 12 years), and the Adolescent RQLQ (12 to <18 years) were utilized as a key secondary or secondary efficacy variable in several trials. Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities (RQLQ(s) 12+) was used for P08067 to allow for subjects 12 and older to complete the same questionnaire.

There are no patient reported outcome (PRO) measures of health impact specifically developed and validated in the context of allergen immunotherapies. The RQLQ was developed under the context of treating symptomatic patients e.g., at the peak of an allergy season allowing assessment of a symptomatic baseline. A minimal important difference (MID) for within-treatment group change of 0.5 has been proposed for the RQLQ, based on studies of pharmacotherapy. [82] However, in clinical trials of seasonal allergen immunotherapy, subjects are typically randomized during a preseasonal, relatively asymptomatic period. An MID, as appropriate to the design of clinical trials of allergen

immunotherapy, without a symptomatic baseline, has not been established. The RQLQ was included in trials of MK-7243 to provide additional information and context regarding the potential benefit in patients with AR/ARC. The RQLQ endpoint for the MK-7243 trials was calculated by comparing the average weekly RQLQ total score over the entire grass pollen season for the MK-7243 group and placebo.

Table 8 presents the primary, key secondary and additional secondary efficacy endpoints by trial in the clinical program for MK-7243. Please note that the table does not present a complete list of all secondary endpoints.

Table 8: Primary, Key Secondary, and Additional Secondary† Efficacy Endpoints by Trial in MK-7243 Clinical Program

	Adults					**Pediatrics**		**Adult and Pediatrics**
	Phase 3 Trials			**Phase 2 Trials**		**Phase 3 Trials**		**Phase 3 Trial**
Endpoint	GT-08	P05238	GT-14	GT-02	GT-07	GT-12	P05239	P08067
TCS entire GPS	S[a]	P	S			S	P	P
TCS peak GPS		S	S			S	S	KS
DSS entire GPS	P[b]	KS	P	P[b]	S	P[b]	KS	KS
DSS peak GPS	S	S	S	KS		KS	S	S
DMS entire GPS	P[b]	KS	KS	P[b]	S	P[b]	KS	KS
DMS peak GPS	S	S	S	KS		KS	S	S
RQLQ entire GPS	S	KS	KS				KS	
RQLQ peak GPS (for subjects ≥12 years of age)								KS

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

†: Note that this is not a complete list of all secondary endpoints. Rather the secondary endpoints noted reflect additional evaluations of the primary or key secondary endpoints.

a: In year 1, TCS was done post-hoc. In years 2-5, TCS was analyzed prospectively

b: DSS entire GPS and DMS entire GPS were co-primary endpoints.

4.5.5 Definition of Duration of Entire and Peak Grass Pollen Season

In order to assess the clinical effect of MK-7243 during the pollen season, pollen counts specific to each site were recorded during the entire grass pollen season. The start and stop dates for the entire grass pollen season were pre-defined as follows:

- Start date of grass pollen season: the first day of 3 consecutive recorded days with grass pollen counts greater than or equal to 10 grains/m^3 (cubic meter).
- Stop date of grass pollen season: the last day before 3 consecutive days with grass pollen counts less than 10 grains/m^3 (the GT trials), or the last day of the last occurrence of 3 consecutive recorded days with a grass pollen count ≥10 grains/m^3 (Trials GT-08 year 3,4 and 5, GT-12, P05238, P05239, and P08067).

The rationale for 10 grains/m^3 is that this magnitude of pollen exposure correlates with the expression of symptoms in sensitive subjects, and many subjects with sensitivity to grass pollen will experience symptoms at this threshold level. [83] A requirement of 3 days of 10 grains/m^3 to represent the start of the GPS allows for a persistent level of grass pollen exposure on consecutive days. The disadvantage of this approach compared to using a higher threshold value (e.g., 30 grains/m^3) or using results obtained during peak season only is that the overall treatment signal may be weakened due to a dilution effect since the association between subject symptoms and pollen exposure is quite variable at lower pollen counts. Furthermore, this approach increases the length of the season under trial and includes more days with minimal pollen exposure requiring less rescue medication usage. It may, therefore, bias the results towards smaller average treatment effects. An evaluation of efficacy during peak pollen season assesses the effect of treatment when subjects are expected to be the most symptomatic due to high pollen exposure. Hence, the pollen season was also characterized by a time period of peak pollen counts for which the data were analyzed. While primary efficacy was evaluated over the entire season for all trials, treatment effects over the peak grass pollen season were evaluated as key secondary or secondary endpoints to support the primary endpoint.

Peak Season was defined as follows:

- The 15 consecutive recorded days within grass pollen season with the highest 15-day moving average pollen count for each site.

The highest 15-day moving average was chosen from the period 14 days prior to the start of season through 14 days after the end of grass pollen season. The final peak season, however, only included those days that fell within season. Due to the continuous nature of the moving average measure, there was only one unique peak season for each site.

4.6 Statistical Methods

The key efficacy endpoints of clinical interest in the Phase 2 and 3 trials of MK-7243 included TCS, DSS, and DMS. The daily TCS was computed as the sum of daily DSS and DMS score. TCS was selected as the primary endpoint for the Merck sponsored North American trials P05238, P05239 and P08067. To facilitate the evaluation of efficacy totality across all the Phase 2 and Phase 3 trials given the similar design of these trials, the TCS was calculated post-

hoc for the ALK trials GT-02, GT-07, GT-08, GT-12, and GT-14. The key efficacy endpoints over grass pollen season (GPS) period (entire or peak) were computed as the average of the available daily score over the specified period. Each trial in the clinical development program used the entire season as the primary efficacy evaluation time point.

The key efficacy endpoints were generally analyzed using analysis of variance (ANOVA) models, allowing different variation for different treatment groups. The analysis model adjusted for additional factors such as site/region effect and asthma status, and these details are outlined in each individual study report. The least square 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 percent reduction relative to placebo effect was calculated as (MK-7243-placebo) / placebo x 100% using the within-group least square means for the MK-7243 group and the placebo group. The 2-sided 95% CI for this percent reduction was obtained using the bootstrap sampling percentiles (2.5^{th} and 97.5^{th}) from 10,000 bootstrap samples. The treatment differences were computed during the treatment period; change from baseline could not be computed because of the lack of baseline given the design of these trials.

The normality assumption of the ANOVA model was examined for the key efficacy endpoints. When the normality assumption was severely violated, additional analysis based on appropriate parametric methods (e.g., square root and log transformation of the data, and zero-inflated log-normal model) or nonparametric analysis (e.g., Wilcoxon rank sums test and Hodges-Lehmann analysis of median differences, and percent difference in medians relative to placebo) were performed. The analyses for the primary efficacy assessments were adopted as per the prespecified plan. Further, the interactions of treatment with other model covariates were examined via subgroup analyses by each level of the covariates.

The handling of missing data was generally similar across trials. For all Phase 3 trials, the analyses of TCS and DSS endpoints were based on observed data only. For DMS, the missing daily score was imputed as zero when DSS on that day was non-missing for trials P05238, P05239, and P08067. This convention was considered reasonable as it was considered that subjects who filled in symptom score did not fill in medication diary data because they did not use medication. Note that using the endpoints of average scores during the specified period is intrinsically consistent with imputing any missing day with the average scores. Several sensitivity analyses were performed for the primary endpoint of TCS to examine the robustness of the pre-specified analyses in the presence of missing data. For the North American trials P05238, P05239, and P08067, these included analyses imputing the missing values using the last observation carried forward method for those with available data to carry forward, and the worst case scenario method for all treated subjects regardless of availability of diary data. In the worst case scenario method, missing daily scores were conservatively imputed with the average score from the opposite treatment groups (e.g., missing daily scores of an MK-7243 subject were imputed with the placebo group average score), and all subjects, including those who discontinued prior to the GPS start, were included in this analysis. For all trials, additional sensitivity analyses were performed for the key efficacy endpoints using the longitudinal data analysis (LDA) model, applied to the repeated measurements for the daily scores.

As an important supportive efficacy measure, RQLQ total score was computed (i.e., average score over the specified period) and analyzed in a similar manner as the key efficacy

endpoints. The analysis of RQLQ was based on observed data only, and a sensitivity analysis using LDA model was also conducted.

Multiplicity control on testing multiple endpoints was conducted by using either a gate-keeping step-down testing procedure in which the hypotheses were tested according to a pre-specified hierarchy of ordering, or by adjusting test p-values based on the Benjamini-Hochberg method. [84]

The efficacy analyses were based on the full analysis set (FAS) approach, 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 confirm the results of the primary efficacy endpoints.

In addition to the results of the individual trials, the data were also pooled across the six Phase 3 trials to provide an overall assessment of treatment effect for the key endpoints TCS, DSS, and DMS. The pooling of data across trials was considered appropriate as the trial design, eligibility criteria, demographics, endpoints, and methodology of the measurement tools were generally similar across trials, and the effect of treatment was generally consistent across different populations such as North American and European and pediatric and adult populations. Specifically, five pools of Phase 3 trials were analyzed as follows:

1. All Phase 3 trials (GT-08 [Year 1], P05238, GT-14, GT-12, P05239, and P08067)
2. Adult population (GT-08 [Year 1], P05238, GT-14, and P08067 [age ≥18])
3. Pediatric population (GT-12, P05239, and P08067 [age <18])
4. North American subjects (GT-14, P05238, P05239, and P08067)
5. European subjects (GT-08 [Year 1] and GT-12)

For the pooled analyses, an ANOVA model extracting sources of variation due to trial and treatment was performed. The qualitative trial-by-treatment interaction was examined by the Gail and Simon test [85] to further investigate the consistency across trials. All pooled analyses were performed based on the FAS population.

Subgroup analyses were also performed for the pooled adult and pediatric Phase 3 populations, respectively, on the primary endpoint of TCS for the selected factors. The subgroup analyses were conducted using the same ANOVA model as the pooled analyses.

Further, the relation between efficacy and pollen exposure was investigated in a post-hoc fashion. This included exploration of the relation between the score value of the key efficacy endpoints and the pollen exposure level. Daily TCS and daily pollen counts were pooled for individuals across Phase 2 and 3 trials and the relation was modeled separately by treatment using a generalized additive model with TCS as a dependent variable and pollen count as an independent variable. The predicted (model fitted) values of TCS and the associated point wise 95% prediction intervals were plotted against the corresponding pollen counts. Additionally, the treatment effect in terms of percent reduction relative to placebo for each trial was plotted against the pollen exposure level during the corresponding grass pollen season.

4.7 Efficacy Results

The Phase 2 trial results supporting the Phase 3 dose selection are discussed below. The data presentation for the confirmatory Phase 3 trials that follows is focused first on the total combined symptom-medication score (TCS), daily symptom score (DSS), and daily medication score (DMS) endpoints for the entire season and peak pollen season. The inclusion of the peak pollen results compliments the description of the treatment effect during the part of the season when subjects suffer the most from AR/ARC symptoms. Next, the impact of pollen exposure on the observed magnitude of the treatment effect is discussed, followed by the results from the GT-08 extension trial demonstrating the sustained and disease-modifying effect of MK-7243. Results from rhinitis quality of life assessments (RQLQ), subpopulation analyses and potential unblinding due to local application site reactions are described last. In order to provide perspective on the clinical relevance of the MK-7243 treatment effect the efficacy section is concluded with a presentation of the MK-7243 efficacy results indirectly compared to SCIT and pharmacotherapy.

4.7.1 Rationale for Phase 3 Dose Selection

Dose Selection Adults

The WAO/WHO position papers [58; 18] recommend that the effective therapeutic dose for subcutaneous immunotherapy should be the maximum tolerated maintenance dose.

The Phase 3 dose selection for MK-7243 was based upon the safety results from Phase 1 trials GT-01, GT-03, and GT-04 and safety and efficacy results from the Phase 2 dose-range trial GT-02. In the Phase 1 dose-escalation trials, 2800 BAU was the highest dose that was well tolerated. Doses above 2800 BAU were associated with longer duration and higher incidence of treatment-related AEs as well as AEs of worsening intensity. The data also indicated a broad safety margin as no SAEs were reported with doses up to 37,592 BAU (Table 9).

Table 9: Percentage of Subjects with Treatment-Related AEs in Phase 1 Trials (All Randomized Subjects)

Dose (BAU)	Subjects N	% Subjects with TRAE	AE Max Duration (Days)	% Subjects with TRAEs by Maximum Intensity			% Subjects with Treatment Related Serious AE[a]
				Mild	Moderate	Severe	
933	9	22	4	22	0	0	0
2,800	18	78	21	78	0	0	0
5,600	18	83	**31**	61	**22**	0	0
11,200	18	100	**28**	78	**22**	0	0
18, 666	14	100	**28**	79	**21**	0	0
28,194	9	89	**31**	56	**33**	0	0
37,592	9	100	**22**	89	**11**	0	0
Placebo	32	38	**19**	344	**3**	0	0

TRAE: treatment related adverse events
[a] There were no serious adverse events

Based on the tolerability results from the Phase 1 trials, 3 doses 93, 933 and 2800 BAU were evaluated in the adult Phase 2 dose-finding trial (GT-02).

GT-02 trial demonstrated a dose dependent reduction in the average rhinoconjunctivitis symptom score during the pollen season for MK-7243 2800 BAU (16%; p=0.071) when compared with placebo, as well as lower AR/ARC rescue medication use compared with placebo (28%; p=0.047), (Figure 6).

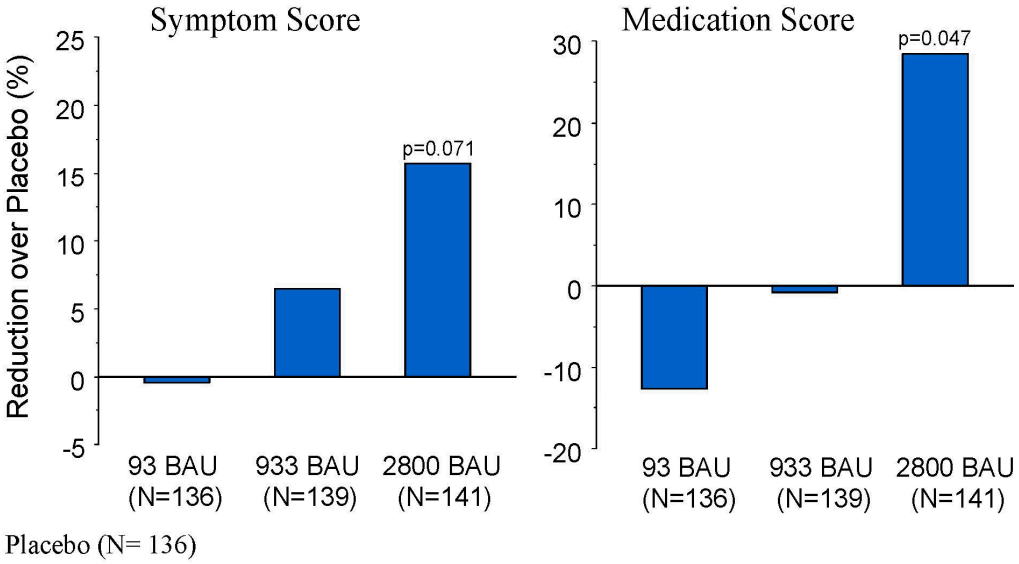


Figure 6: GT-02 Trial Mean Reduction of Rhinoconjunctivitis Symptom Score and Mean Reduction Rhinoconjunctivitis Medication Score Relative to Placebo during the Entire Season (Full Analysis Set)

In addition, the trial confirmed that 2800 BAU was generally well-tolerated (Table 10). One drug related serious adverse event was reported (uvula oedema in the 933 group). The event was upgraded by the Sponsor from non-serious to serious after closure of the database as a conservative approach following evaluation by the trial principal investigator. The subject experienced after intake of the first tablet an itching feeling of the tongue and a localized oedema of the uvula developed. The subject was observed at the clinic for two hours and was thereafter released to his home. No treatment was given and the subject continued in the trial and completed the trial according to protocol. There were no systemic reactions reported in this trial.

Table 10: Percentage of Subjects with Treatment-Related AEs in GT-02 Trial (All Randomized Subjects)

Dose (BAU)	Subjects N	% Subjects with TRAE	AE Max Duration (Days)	% Subjects with TRAEs by Maximum Intensity			% Subjects with Treatment related Serious AE[a]
				Mild	Moderate	Severe	
93	136	32	146	26	6	1	0
933	139	73	148	46	20	7	1[b]
2,800	294	73	164	49	19	5	0
Placebo	286	26	152	17	8	1	0

TRAE: treatment related adverse events
[a] There were seven subjects with 7 serious adverse events assessed as unrelated to treatment.
[b] One event (uvula oedema) was upgraded from non-serious to serious after database lock and was considered related to MK-7243.

The safety assessment was also supported by a Phase 2 safety trial in mild to moderate asthma subjects (GT-07 Trial). The AE profile in asthma subjects was similar to the AE profile in non-asthmatic grass allergy subjects. Therefore, 2800 BAU was the dose selected for further investigation in the adult Phase 3 trials.

Dose Selection in Children

The safety and tolerability of MK-7243 was initially investigated in two Phase 1 dose-escalating pediatric trials (GT-09 and GT 11 trials). In both trials, subjects with grass pollen induced seasonal allergic rhinoconjunctivitis were treated daily with either 2800 BAU or placebo for 28 days (outside the GPS). The percentage of subjects reporting treatment-related AEs in the MK-7243 treatment group (77.8%) was higher than that observed in the placebo group (33.3%). The most common treatment-related AEs were local application reactions. There were no treatment related serious AEs, systemic reactions or epinephrine administrations in these Phase 1 trials. Of the 60 subjects included in the Phase 1 trials, there were a total of 7 subjects (all in the MK-7243 treatment group) with at least 1 severe treatment related AEs. All were local events of the oral cavity and none of the severe events led to airway obstruction or trial discontinuation.

The 2800 BAU dose was chosen for Phase 3 trials and the usage of the same dosage of immunotherapy in adults and children is in accordance with clinical practice since the allergens are not systemically absorbed; rather allergen is bound to epithelial cells and then processed by local allergen presenting cells. [33; 18; 86]

4.8 Efficacy Results Phase 3

Key Findings: Phase 3 Trials

MK-7243 was superior to placebo for the co-primary endpoints (DSS, DMS) or the combined endpoint (TCS) in the first grass pollen season in three (GT-08, P05238, P08067) of the four confirmatory efficacy trials in adults as shown in Table 11. In the first North American trial (GT-14) the primary endpoint of the trial was not met. The results suggest that the symptoms reported by the subjects were not primarily reflective of the effects of grass pollen exposure. Thus, symptom scores were high even before the start of the grass pollen season and showed little relationship to the variations in pollen counts during the grass pollen season. Post-hoc analyses could not confirm that the efficacy of MK-7243 was masked by the allergic responses to other common seasonal (e.g. trees) and perennial allergens. It is conceivable that some subjects were symptomatic due to other unidentified causes, or that some subjects understood poorly the standards by which they were to score their symptoms.

The long-term extension of GT-08 showed that MK-7243 was superior to placebo for the co-primary endpoints DSS and DMS in the second and third grass pollen season. In the first follow-up season without MK-7243 treatment, DSS and DMS were superior to placebo and in the second follow-up season MK-7243 was superior to placebo for DSS only.

In all three (GT-12, P05239, and P08067) confirmatory trials including children, MK-7243 was superior to placebo for the primary endpoint in the first grass pollen season.

Key observations are summarized below to support the MK-7243 treatment indication in subjects with Timothy and related grass pollen-induced rhinitis with or without conjunctivitis.

1. Results from the Phase 2/3 trials demonstrated that MK-7243 (2800 BAU) provided significant clinical benefits (reduction in TCS generally ranging between 21-34%) to subjects with allergic rhinitis with or without conjunctivitis as shown by symptom reduction and reduced need for pharmacotherapy compared to placebo during the entire and peak GPS. MK-7243 is optimally effective with at least 12 weeks of pre-seasonal treatment at reducing rhinoconjunctivitis symptoms and, in general, pharmacotherapy use relative to placebo in children and adults with grass pollen allergy. Some first season efficacy is provided from at least 8 weeks of preseasonal treatment. While the results of individual trials varied, changes in DSS and DMS both contributed to the overall treatment effect demonstrated by the TCS. This evidence is consistent with the current EMA immunotherapy guideline to claim a treatment of allergic symptoms. [21]
2. Treatment with MK-7243 shows a sustained, clinically relevant, long-term, disease-modifying effect relative to placebo during 3 years of treatment and for at least 2 years after discontinuation of therapy. This is consistent with the current EMA immunotherapy guideline to claim a sustained clinical effect and disease-modifying effect. [21] This claim is further corroborated by the maintenance of immunological changes during 3 years of treatment and after discontinuation of therapy.
3. Overall, consistent treatment effect was demonstrated in multiple trials over several seasons with different grass pollen exposure levels. The variation in grass pollen exposure and the difference in the magnitude of efficacy across multiple trials

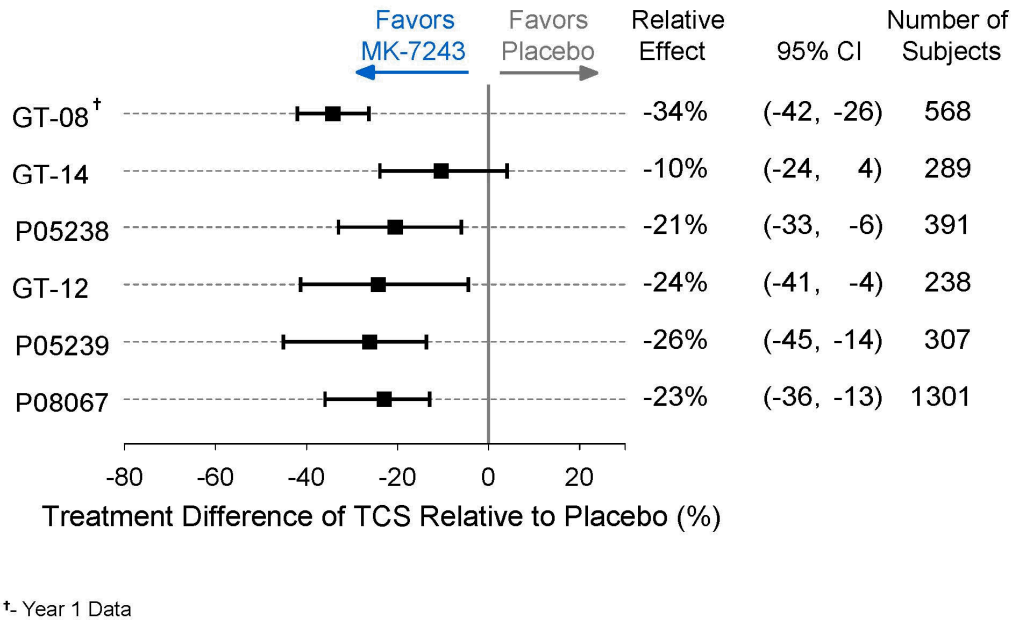
highlighted the significant dependency on pollen exposure. A relationship between pollen exposure and efficacy has been demonstrated. When pollen exposure was similar (e.g., the North American and European pediatric trials), the magnitude of efficacy was comparable.

4. The treatment effect was shown both in children and adults with and without asthma and was generally consistent across subgroups (e.g. race, asthma status, etc.). The treatment effect on grass induced AR/ARC was also apparent whether subjects were sensitized to grass alone or to grass and other non-cross-reacting allergens (e.g. ragweed, trees etc.).

4.8.1 Total Combined Score (TCS), Daily Symptom Score (DSS) and Daily Medication Score (DMS) for Entire Grass Pollen Season

Figure 7, Figure 8, and Figure 9, and Table 11, provide a summary of the primary results from the six pivotal Phase 3 trials, including individual trial results analyses from the TCS, DSS, and DMS, respectively, for the entire grass season. The treatment difference relative to placebo was presented with the associated 95% confidence interval and sample size entailing the precision of the estimated treatment effect. For Figure 7, Figure 8 and Figure 9, treatment nt differences towards the left of the zero line indicate a treatment benefit with MK-7243.

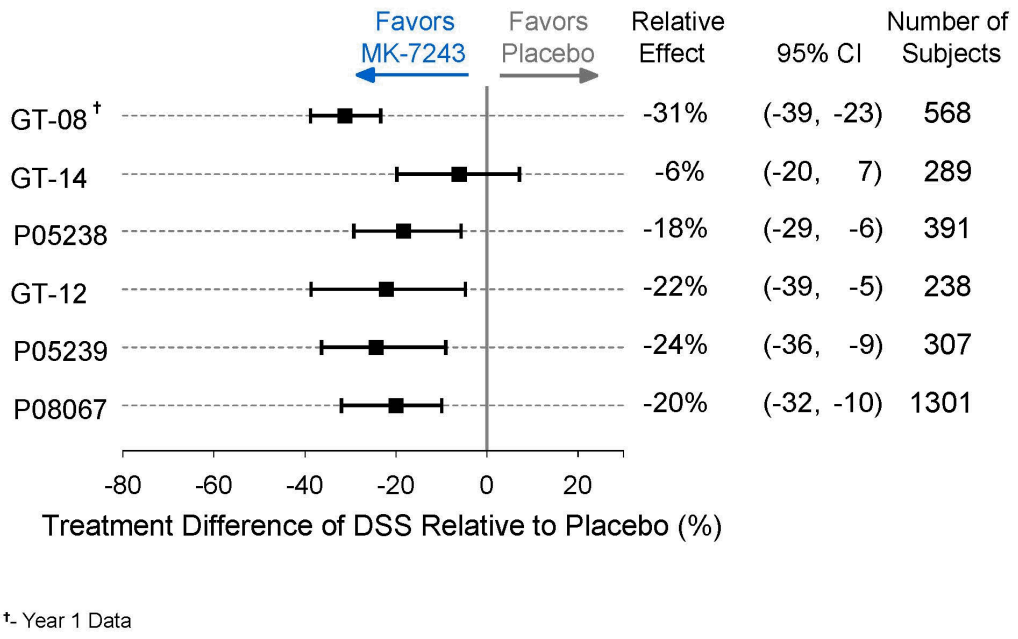
MK-7243 demonstrated efficacy in symptoms reduction and reduced need for rescue pharmacotherapy as shown by lower TCS, DSS, and DMS scores both in the adult and pediatric trials. Across the trials a consistent trend in favor of MK-7243 was observed with some variation in overall magnitude of effect as expected in season 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 MK-7243. As a consequence (explained in Sec. 2.5) Merck conducted three additional trials (P05238, P05239, and P08067) in North America and per FDA request the last trial was powered based on the lower 95% confidence limit of the difference in scores between placebo and MK-7243 groups relative to the score in placebo group to be no less than 10%. Results of the first two trials were statistically significant and although not powered as such the pediatric trial (P05239) met the FDA's statistical criterion based on the 95% CI. The last trial, including 1501 children and adults, demonstrated that MK-7243 improved the TCS more than placebo during the entire grass pollen season (treatment difference relative to placebo -23%, 95% CI: -36% to -13%, $p < 0.001$). Therefore, the results of three out of 6 confirmatory trials also met the statistical criterion based on 95% confidence limit, set by the FDA.



†- Year 1 Data

Figure 7: Analysis of TCS for the Entire Grass Pollen Season across the MK-7243 Individual Phase 3 Trials (Full Analysis Set).

Adult trials (GT-08, GT-14, P05238)
Pediatric trials (GT-12, P05239)
Combined adult/pediatric trial (P08067)



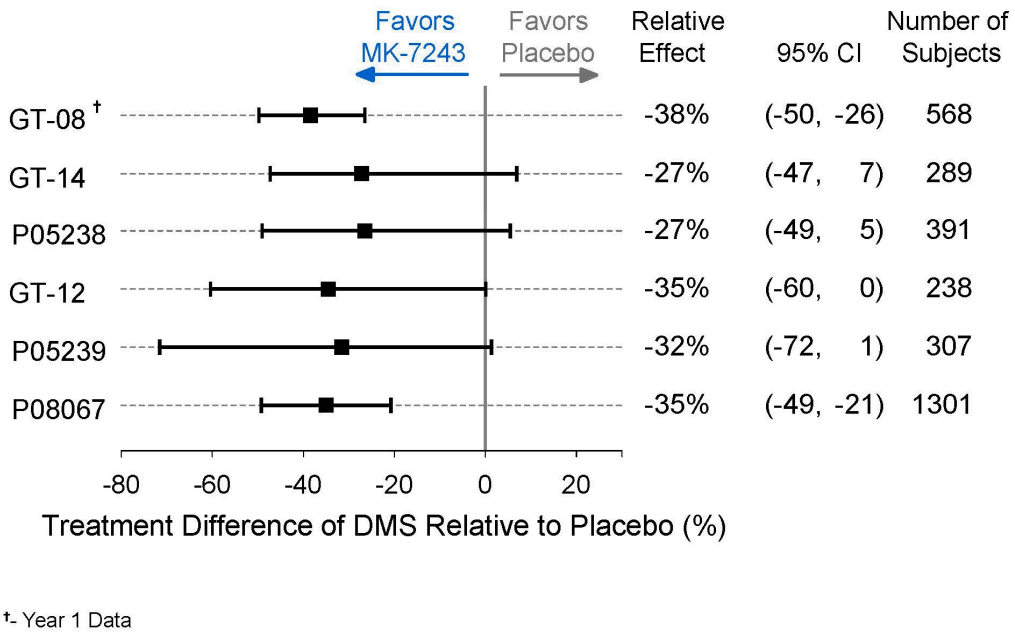
†- Year 1 Data

Figure 8: Analysis of DSS for the Entire Grass Pollen Season across the MK-7243 Individual Phase 3 Trials (Full Analysis Set)

Adult trials (GT-08, GT-14, P05238)
Pediatric trials (GT-12, P05239)
Combined adult/pediatric trial (P08067)

One of the objectives of immunotherapy is to decrease the need for daily medications during the allergy season; however, with one caveat that the need for pharmacotherapy may be highly dependent on the strength of the pollen season.

In all of the trials, there was a statistically significant reduction or a numerical reduction over the grass pollen season in DMS for subjects treated with MK-7243, compared with placebo (Figure 9).



†- Year 1 Data

Figure 9: Analysis of DMS for the Entire Grass Pollen Season across the MK-7243 Individual Phase 3 Trials (Full Analysis Set)

Adult trials (GT-08, GT-14, P05238)
Pediatric trials (GT-12, P05239)
Combined adult/pediatric trial (P08067)

Table 11: Analysis Results of Entire Grass Pollen Season TCS, DSS, DMS across the MK 7243 Phase 3 Individual Trials (Full Analysis Set)

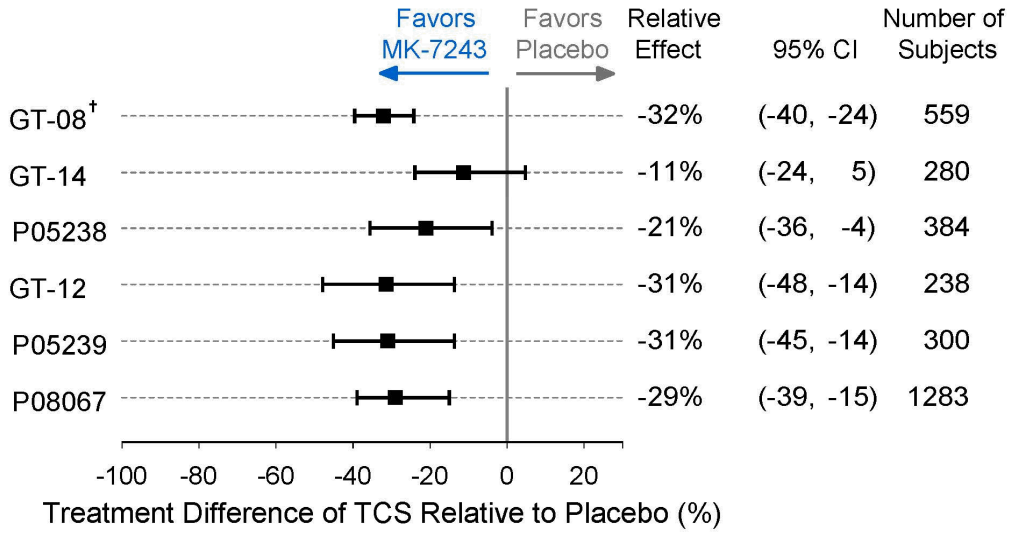
Trial/ Endpoint	MK-7243 Mean (N)	Placebo Mean (N)	Treatment Difference (MK-7243 – Placebo)			Difference Relative to Placebo (%)[a]	
			Estimate	95% CI	p-value	Estimate	95% CI
GT-08 Year 1							
TCS	(N=282) 4.46	(N=286) 6.78	-2.32	(-2.98, -1.67)	<0.001	-34.2	(-42.0, -26.3)
DSS	(N=282) 2.85	(N=286) 4.14	-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)
Trial GT-14							
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)

Trial/ Endpoint	MK-7243 Mean (N)	Placebo Mean (N)	Treatment Difference (MK-7243 – Placebo)			Difference Relative to Placebo (%)[a]	
			Estimate	95% CI	p-value	Estimate	95% CI
Trial P05238							
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[e]	-18.3	(-29.4, -5.7)
DMS	(N=184) 1.25	(N=207) 1.70	-0.45	(-0.96, +0.06)	0.084[e]	-26.5	(-49.1, 5.4)
Trial GT-12							
TCS[b]	(N=117) 3.70	(N=121) 4.87	-1.18	(-2.17, -0.19)	0.022	-24.2	(-41.3, -4.5)
DSS[b]	(N=117) 2.18	(N=121) 2.80	-0.62	(-1.15, -0.10)	0.022	-22.1	(-38.7, -4.8)
DMS[c]	(N=117) 0.78	(N=121) 1.19	-0.41	(-0.68, -0.01)	0.016	-34.5	(-60.4, 0.1)
Trial P05239							
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[e]	-24.4	(-36.4, -9.1)
DMS	(N=149) 0.91	(N=158) 1.33	-0.42	(-0.88, +0.03)	0.066[e]	-31.6	(-57.7, 4.0)
Trial P08067							
TCS[c]	(N=629) 3.24	(N=672) 4.22	-0.98	(-1.2, -0.4)	<0.001	-23.0	(-36.0, -13.0)
DSS[c]	(N=629) 2.49	(N=672) 3.13	-0.64	(-0.7, -0.2)	0.001	-20.0	(-32.0, -10.0)
DMS[d]	(N=629) 0.88	(N=672) 1.36	-0.48	(-0.73, -0.22)	0.0003	-35.0	(-49.3, -20.8)

TCS = Total combined score (DSS + DMS); DSS = Rhinoconjunctivitis Daily Symptom Score; DMS = Rhinoconjunctivitis Daily Medication Score; CI = Confidence Interval.
Note: All trials compared MK-7243 (2800 BAU) with placebo; all scores presented are for the entire GPS.
a: Percent reduction in the MK-7243 (2800 BAU) group compared to placebo: (MK-7243-placebo)/ placebo X 100%. Confidence intervals were obtained using the bootstrap method.
b: Parametric analysis (square-root-transformed data), treatment difference and that relative to placebo of back-transformed adjusted means.
c: Non-parametric analysis: Wilcoxon rank sum test with associated Hodges-Lehmann CI for median difference, the group medians are reported, treatment difference and that relative to placebo of group medians.
d: Parametric analysis (zero-inflated lognormal model), treatment difference and that relative to placebo of estimated means .
e: Adjusted p-value based on Benjamini and Hochberg method.

4.8.2 Total Combined Score (TCS), Daily Symptom Score (DSS) and Daily Medication Score (DMS) for Peak Grass Pollen Season

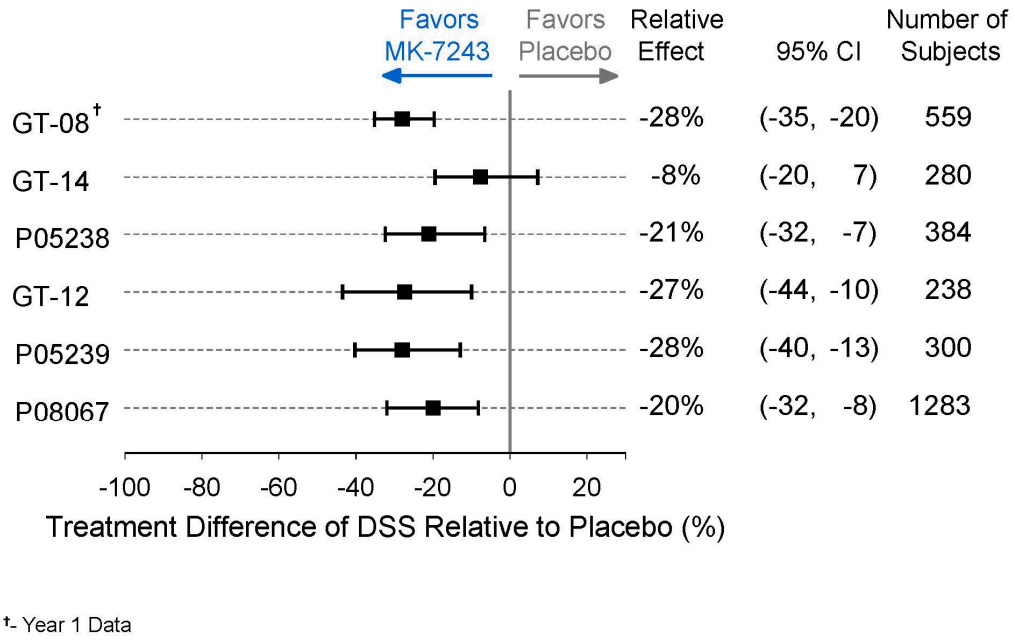
The results for the peak grass pollen season (including the seasonal trials as well as the peak season from GT-08 Yr. 1) are similar to the results for the entire grass pollen season. The treatment effect in all six Phase 3 trials favored treatment with MK-7243 for TCS, DSS, and DMS for the peak grass pollen season, during which subjects may suffer the most symptoms, Figure 10, Figure 11, and Figure 12, respectively. The table containing the analysis results for the peak grass pollen season of TCS, DSS, and DMS across the MK 7243 phase 3 individual trials is located in Appendix 1.



†- Year 1 Data

Figure 10: Analysis of TCS for the Peak GPS across the MK-7243 Individual Phase 3 Trials (Full Analysis Set)

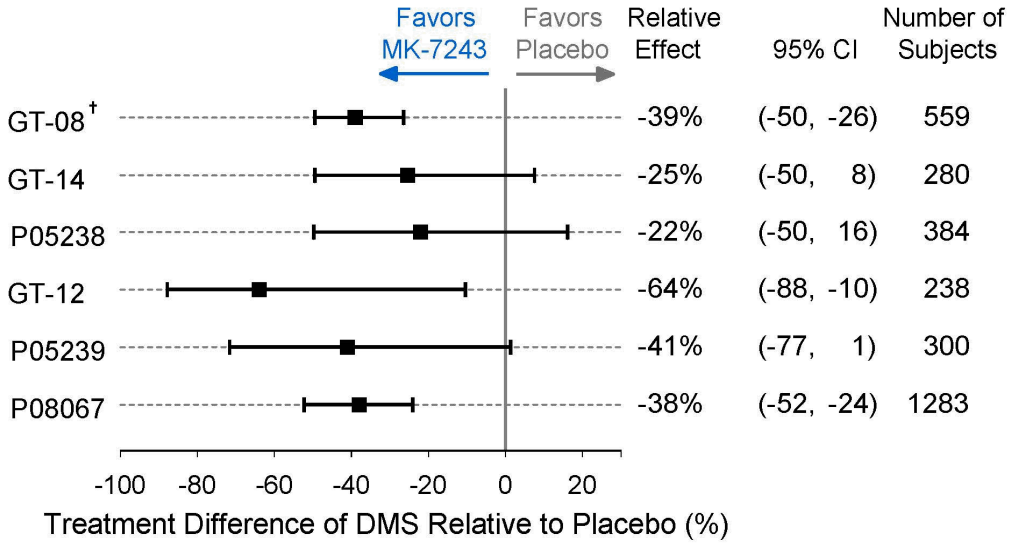
Adult trials (GT-08, GT-14, P05238)
Pediatric trials (GT-12, P05239)
Combined adult/pediatric trial (P08067)



†- Year 1 Data

Figure 11: Analysis of DSS for the Peak GPS across the MK-7243 Individual Phase 3 Trials (Full Analysis Set)

Adult trials (GT-08, GT-14, P05238)
Pediatric trials (GT-12, P05239)
Combined adult/pediatric trial (P08067)



†- Year 1 Data

Figure 12: Analysis of DMS for the Peak GPS across the MK-7243 Individual Phase 3 Trials (Full Analysis Set)

Adult trials (GT-08, GT-14, P05238)
Pediatric trials (GT-12, P05239)
Combined adult/pediatric trial (P08067)

4.8.3 Total Combined Score (TCS), Daily Symptom Score (DSS) and Daily Medication Score (DMS) for Phase 3 Trials Pooled

For an overall assessment of efficacy, integrated efficacy analysis was conducted by pooling individual data from all 6 Phase 3 trials. Section 4.6 provides detailed analyses method for the pooled analyses. Figure 13 and Table 12 present the results from the pooled analysis for the key efficacy endpoints during both the entire GPS and peak GPS. Note that the pooled analysis utilized individual-level data and thus differs from other integrated efficacy analysis approaches such as a meta-analysis which utilizes trial-level results. The overall robustness of the clinical trial data are supported by these pooled results, which consistently demonstrated a >10% difference relative to placebo based on the 95% CI for all the endpoints.

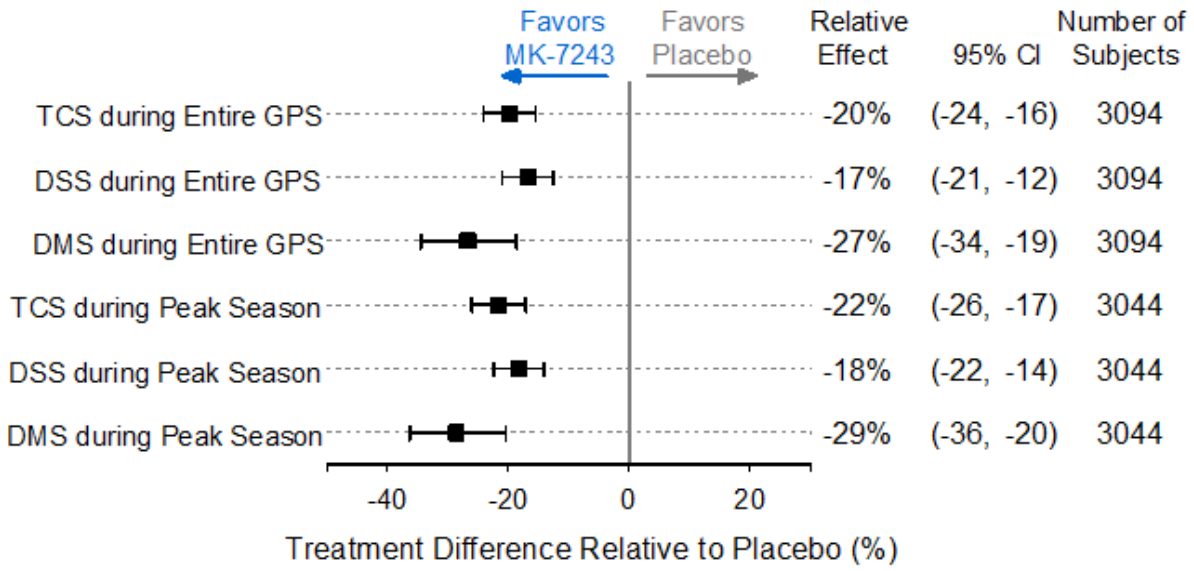


Figure 13: Pooled Analysis Results for the Entire and Peak Grass Pollen Season TCS, DMS, DSS across the MK-7243 Phase 3 Trials (Full Analysis Set)

Table 12: Pooled Analysis Results for the Entire and Peak Grass Pollen Season TCS, DSS, DMS across the MK 7243 Phase 3 Trials (Full Analysis Set)

Endpoint	MK-7243 Mean (N)	Placebo Mean (N)	Treatment Difference (MK-7243 – Placebo)			Difference Relative to Placebo (%)[a]	
			Estimate	95% CI	p-value	Estimate	95% CI
Entire Grass Pollen Season							
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)
Peak Grass Pollen Season							
TCS	(N=1482) 6.04	(N=1562) 7.71	-1.67	(-2.05, -1.29)	<0.001	-21.6	(-26.0, -17.1)
DSS	(N=1482) 4.25	(N=1562) 5.20	-0.95	(-1.19, -0.71)	<0.001	-18.2	(-22.3, -14.0)
DMS	(N=1482) 1.79	(N=1562) 2.51	-0.72	(-0.95, -0.49)	<0.001	-28.6	(-36.3, -20.4)

TCS = Total combined score (DSS + DMS); DSS = Rhinoconjunctivitis Daily Symptom Score; DMS = Rhinoconjunctivitis Daily Medication Score; CI = Confidence Interval.
Note: All trials compared MK-7243 (2800 BAU) with placebo.
The qualitative treatment-by-trial interaction based on Gail & Simon is 0.969.
a: Percent reduction in the MK-7243 (2800 BAU) group compared to placebo: (MK-7243-placebo)/ placebo X 100%. Confidence intervals were obtained using the bootstrap method.

4.8.4 Treatment Effect across the Season and Over Multiple Grass Pollen Seasons

The results from the first 3 treatment years of the long-term trial (GT-08) illustrate the difference in TCS values for the MK 7243 and placebo groups during the grass pollen season across multiple seasons in relation with the pollen counts (green area) on a daily basis (Figure 14). The graphic summary is based on all available data. All pollen regions are aligned with the start of the pollen season and for all subjects with diary data, the mean pollen count and the mean TCS is calculated for each day in the pollen season. The MK-7243 group (blue line) demonstrates lower overall TCS compared to placebo (magenta line) from the beginning and throughout the grass season with a consistent effect during peak pollen periods. The treatment effect persists across the entire season and over subsequent pollen seasons with continuing treatment (Yr. 2 and 3) confirming the sustained effect of MK-7243.

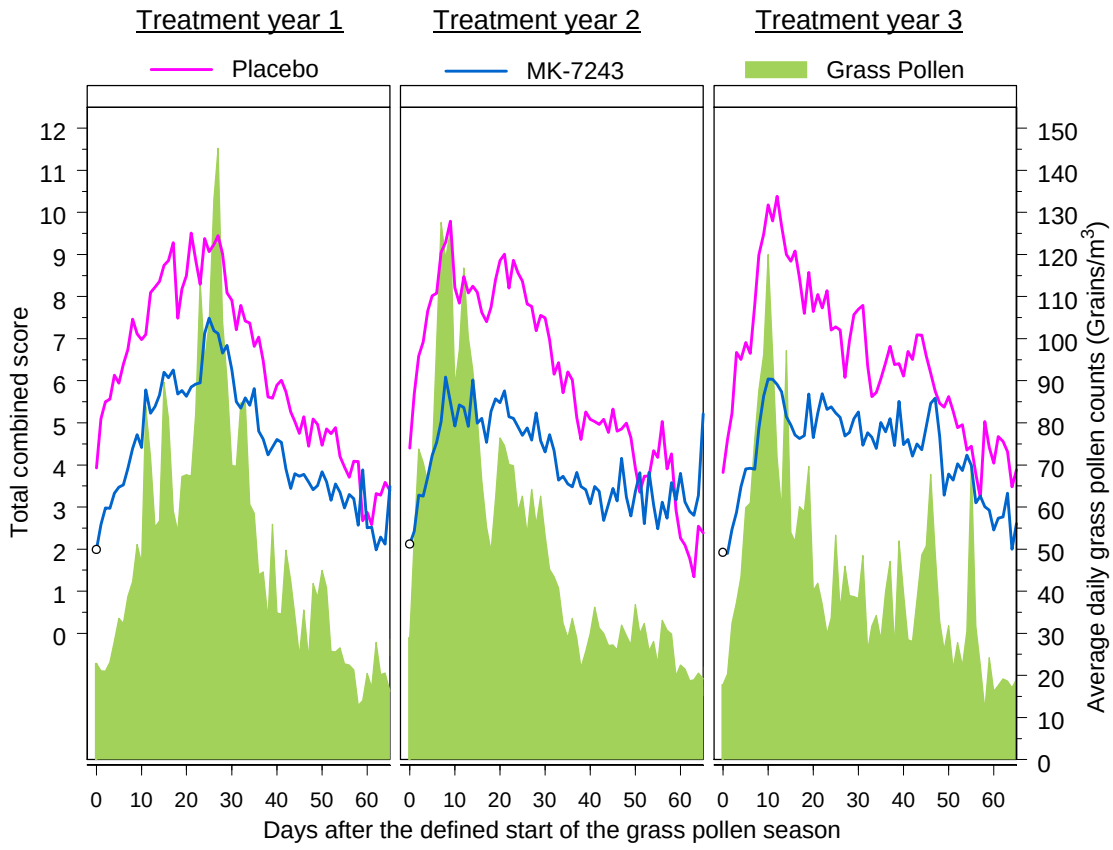


Figure 14: Average Total Combined Score for the Entire Grass Pollen Season for MK-7243 Compared to Placebo – GT-08 Trial (Full Analysis Set)

4.8.5 Treatment Effect Related to Pollen Exposure

Recently published data indicate that there is a relationship between pollen exposure and allergy symptoms and this relationship is not linear. [87] This observation is corroborated by the results from the MK-7243 pooled dataset, as shown in Figure 15 which presents the relationship between the predicted TCS and pollen levels for subjects treated with placebo and MK-7243 in Phase 2 and 3 trials. As observed from Figure 15, the score value increases with higher pollen counts in a non-linear fashion, where the dependency of efficacy measurements on pollen exposure is steeper for daily pollen counts below 90-100 grains/m^3 than for higher pollen counts. Similar relationships were found for the DSS and DMS.

The magnitude of the clinical effect of immunotherapy may be influenced by the level of pollen exposure in a given trial year and may explain the variability in treatment effect observed between trials conducted across multiple pollen seasons. [88]

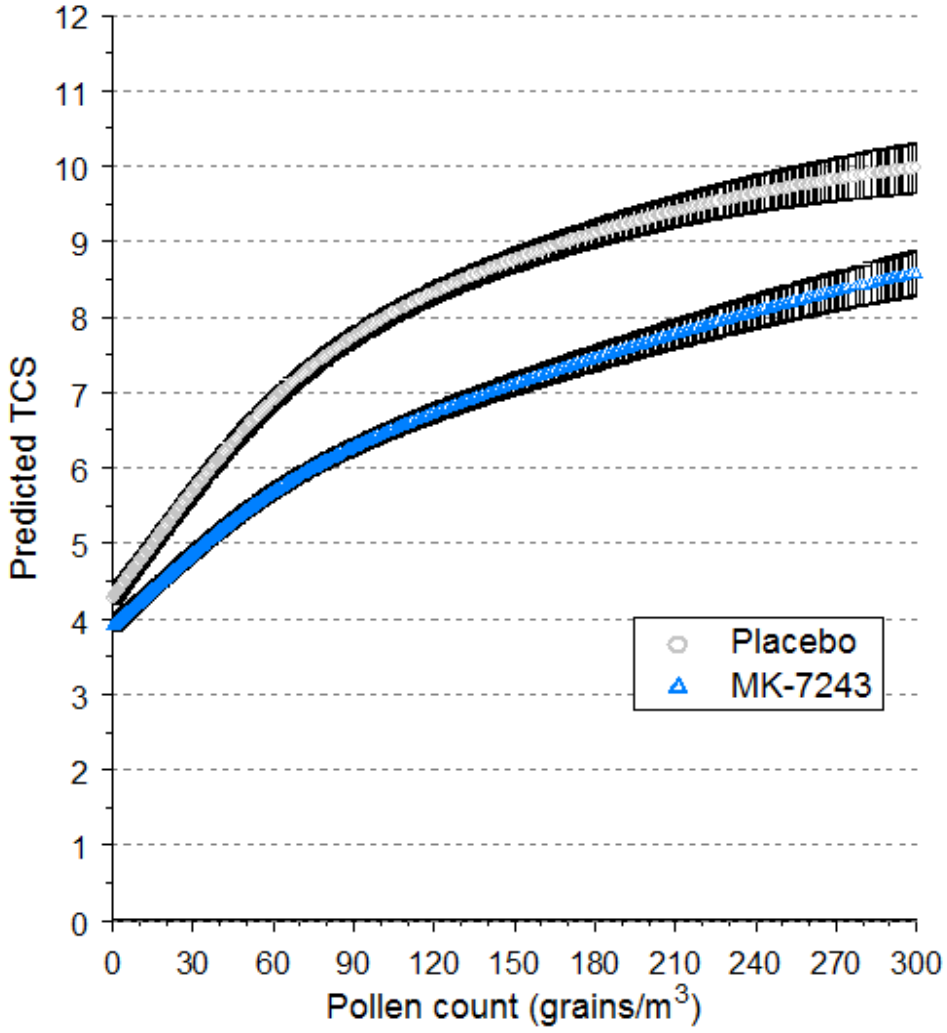


Figure 15: Treatment Group-specific Predicted Daily Total Combined Symptom (TCS) Score as a Function of Daily Pollen Count (GT-02, GT-07, GT-08 (All 5 Years), GT-12, GT-14, P05238, P05239, and P08067 Trials) (Full Analysis Set)

Bands represent 95% confidence band on the treatment group-specific non-linear model of predicted TCS on pollen count.

The relationship between MK-7243 treatment effects as a function of grass pollen counts over the first 20 days of the season was evaluated. The first 20 days was selected for this analysis because at the beginning and during the mid-part of the season the pollen counts are generally higher and more consistent (Figure 14) and since symptoms are driven by pollen counts at least >5-10 grains/m^3 the correlation will be better in the beginning and mid portion of the season. Considering the average season length is typically 60 days of duration the first 20 days covers approximately 30% days of the season. At the end of the season the pollen counts are lower

and many subjects will have few if any symptoms. Relative treatment effect on TCS in each trial (or each year of a trial) was related to the average grass pollen exposure during the grass pollen season (Figure 16). In comparison to the European trials pollen seasons, the North American trials grass pollen seasons were characterized by lower pollen counts and relatively lower magnitude of treatment effects. When the European pollen season was low (e.g. the European pediatric trial GT-12) the treatment effect was similar to the North American pediatric trial P05239. GT-14 did not achieve its primary endpoint and appears to be an outlier despite a pollen count similar to the other North American trials.

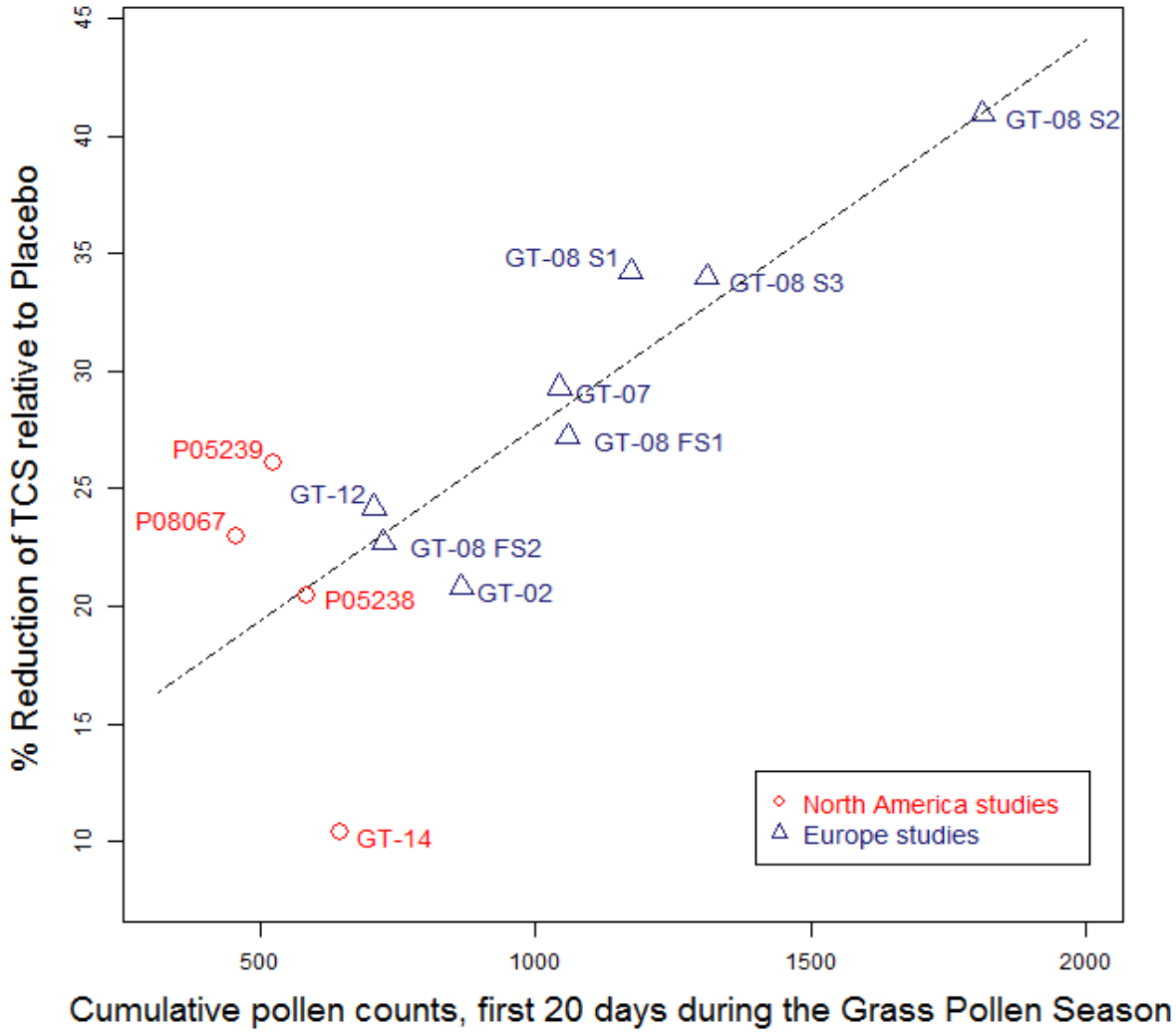


Figure 16: Relationship of Percent Reduction in TCS and Pollen Exposure During the First 20 Days from Phase 2 and Phase 3 Clinical Trials (Full Analysis Set)

Triangles mark the European trials and circles mark the North American trials.
Units for grass pollen counts on the x-axis are grains/m^3

4.8.6 Disease Modifying Effect of MK-7243 in GT-08 Trial

GT-08 trial was amended to include two additional years of daily treatment, to evaluate long term efficacy during 3 years of treatment with an additional 2 follow-up years to assess the disease modifying effect post-treatment. Due to closure of some trial centers after the first grass season, only 472 subjects (out of 568 subjects completing year one) were offered continuation in the extension trial and of these, 351 subjects accepted to participate and continued double-blind treatment after the first season. The baseline characteristics as well as the treatment effects between subjects who were originally in the first year of the trial and those who did not continue beyond year 1 were similar indicating no differential drop-out due to disease severity or other demographic factors. The baseline, other demographic factors and efficacy results can be found in Appendix 2. The majority of the subjects who consented to enter the Year 2 extension continued in Year 3 up to Year 5. The dropout rates during Year 2 and Year 3 through Year 5 were low and similar across the two treatment arms. The GT-08 trial demonstrated the following (Table 13):

- Efficacy in the first season based on reduction of symptom and medication use relative to placebo
- Sustained efficacy during active treatment Years 2 and 3
- Disease modification as evidenced by a clinically relevant treatment effect that persisted during post-treatment follow-up Years 4 and 5 when treatment had been discontinued

Table 13: Summary of Analysis Results of Rhinoconjunctivitis Daily Symptom, Daily Medication and Total Combined Scores Over the Entire GPS for Years 1 to 5 for GT-08 Trial (Full Analysis Set)

Trial Endpoint	MK-7243 (N) Mean	Placebo (N) Mean	Treatment Difference (MK-7243 – Placebo)			Difference Relative to Placebo (%)[a]	
			Estimate	95% CI	p-value	Estimate	95% CI
GT08 (Year 1)							
TCS	(282) 4.46	(286) 6.78	-2.32	(-2.98, -1.67)	<0.0010	-34.2	(-42.0, -26.3)
DSS	(282) 2.85	(286) 4.14	-1.29	(-1.68, -0.90)	<0.0001	-31.2	(-38.8, -23.4)
DMS	(282) 1.65	(286) 2.68	-1.03	(-1.44, -0.63)	<0.0001	-38.4	(-49.8, -26.5)
GT08 (Year 2)							
TCS	(172) 4.10	(144) 6.94	-2.84	(-3.88, -1.79)	<0.0001	-40.9	(-51.8, -29.5)
DSS	(172) 2.40	(144) 3.76	-1.36	(-1.86, -0.86)	<0.0001	-36.2	(-46.5, -26.2)
DMS	(172) 1.74	(144) 3.19	-1.45	(-2.16, -0.75)	<0.0001	-45.5	(-60.4, -28.2)
GT08 (Year 3)							
TCS	(160) 4.39	(127) 6.64	-2.26	(-3.26, -1.25)	<0.0001	-34.0	(-45.5, -21.4)
DSS	(160) 2.56	(127) 3.59	-1.04	(-1.56, -0.52)	0.0001	-29.0	(-40.3, -16.3)
DMS	(160) 1.82	(127) 3.04	-1.22	(-1.92, -0.52)	0.0007	-40.1	(-55.4, -21.2)
GT08 (Year 4)							
TCS	(142) 4.96	(115) 6.81	-1.85	(-2.97, -0.73)	0.0014	-27.2	(-39.9, -12.4)
DSS	(142) 2.68	(115) 3.63	-0.95	(-1.50, -0.40)	0.0007	-26.2	(-37.6, -12.2)
DMS	(142) 2.32	(115) 3.25	-0.93	(-1.72, -0.14)	0.0215	-28.6	(-46.3, -6.0)
GT08 (Year 5)							
TCS	(137)4.96	(104) 6.42	-1.46	(-2.61, -0.31)	0.0128	-22.7	(-37.1, -6.3)
DSS	(137) 2.56	(104) 3.40	-0.84	(-1.41, -0.28)	0.0037	-24.7	(-37.7, -9.7)
DMS	(137) 2.42	(104) 3.04	-0.62	(-1.38, 0.15)	0.1136	-20.4	(-39.8, 4.3)

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

Note: All trials compared MK-7243 (2800 BAU) with placebo; all scores presented are for the entire GPS.

a: Percent reduction in the MK-7243 (2800 BAU) group compared to placebo: (MK-7243 -placebo)/placebo X 100%. Confidence intervals were obtained using the bootstrap method.

Of note, the treatment effect of MK-7243 varied across the grass season and the year, with the lowest effect being observed during Year 5, Figure 17. However, the relative treatment effect for the total combined symptom and medication score (TCS) during the 5 seasons covered by the trial was highly correlated to the pollen exposure in the beginning of the season. During the trial, there was a trend towards lower pollen counts in the follow-up years compared to the treatment years, with the lowest pollen counts in year 5, the second follow-up year. The peak of the average daily pollen counts reached 75 grains/m^3 in year 5 whereas it exceeded 100 grains/m^3 in the treatment years.

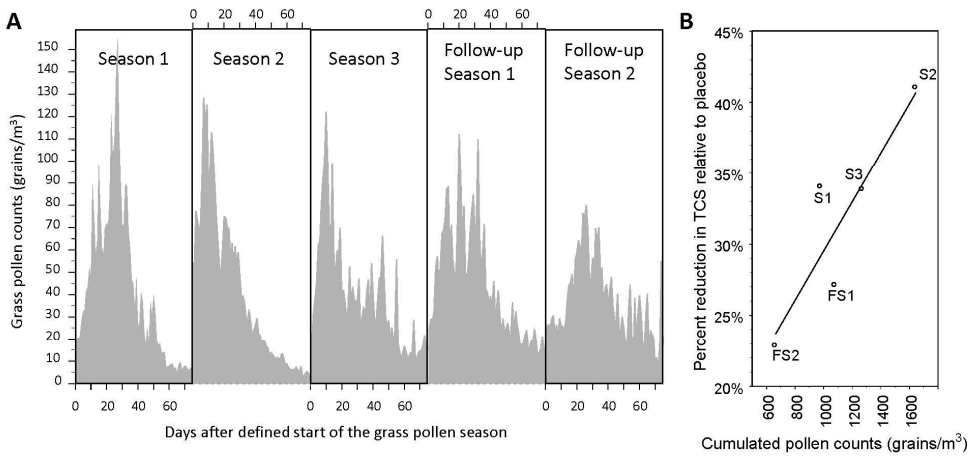


Figure 17: Grass Pollen Exposure and Relationship to Treatment Effect for GT-08 Trial (Full Analysis Set)

A: Average grass pollen exposures, for subjects with diary data on the given day, during the 5 grass pollen seasons of the GT-08 trial (2005-2009)

B: Relationship between relative difference in the total combined score (TCS) and cumulative grass pollen counts (grains/m3) in the initial 3 weeks of the grass pollen season (S: season, FS: Follow-up season). The lowest cumulative counts were observed during the second follow up season (FS2).

The immunological endpoints were supportive of the disease-modifying effect of MK-7243 with raised levels of IgG_4 (Figure 3) and IgE-blocking factor (Figure 4), and changes in IgE levels during 3 years of treatment and continuing through 2 years after treatment (Figure 2). These results are consistent with the published changes observed following long-term subcutaneous immunotherapy and are in accordance with the EMA recommendation to provide immunological evidence to support a disease-modifying claim. [18; 21]

4.8.7 Rhinoconjunctivitis Quality of Life and Effect of MK-7243

In the GT-14, P05238, P05239, and P08067 Trials, RQLQ Total Score was a key secondary endpoint. In GT-08 and GT-02, RQLQ(S) was an additional secondary endpoint. Results for the mean total RQLQ score for the primary GPS analysis demonstrated that treatment with 2800 BAU of MK-7243 also provided benefit in improving quality of life, as summarized in Table 14.

Table 14: Treatment Differences and Percent Reductions Relative to Placebo Mean Scores in RQLQ from the MK-7243 Adult and Pediatric Trials (Full Analysis Set)

	RQLQ[a]		
Trial	**Difference (95% CI)**	**% Reduction Relative to Placebo**	**p-Value**
Phase 3 Trials			
GT-08 Yr. 1	-0.37 (-0.50, -0.23)	26%	p<0.0001
GT-14	-0.08 (-0.32, 0.16)	5%	p=0.5293
P05238	-0.27 (-0.48, -0.05)	17%	p=0.022[b]
P05239	-0.32 (-0.60, -0.03)	18%	p=0.042[b]
P08067[c]	-0.13 (-0.2, -0.0)[d]	12%	p=0.027
GT-12	NA	NA	NA
Phase 2 Trials			
GT-02[e]	-0.21 (-0.384, -0.033)	20%	p=0.020
GT-07	NA	NA	NA

NA = Not available; Yr. = Year; RQLQ = Rhinoconjunctivitis quality of life questionnaire score; CI = Confidence Interval.

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

a Results are between group comparisons.

b: Adjusted p-value, based on Benjamini and Hochberg method.

c: Trial included approximately 20% pediatric subjects (<18 years of age)

d: Difference between two group medians and Hodges-Lehmann confidence interval for median difference.

e: (p-values), Group 1 and 4 comparison from GT-02 Trial.

4.8.8 Effects of Important Demographic and Prognostic Factors on Efficacy

Effect of MK-7243 treatment for the TCS endpoint was investigated for subgroups based on age, race, asthma status, allergy sensitization type, and geographic region. The subgroups were summarized for the pooled adult (i.e., Trials GT-08, P05238, P08067, and GT-14) and pooled pediatric (Trials GT-12, P05239, and P08067) trials. The point estimate of the treatment effect and their 95% CIs were used to examine consistency of the effect. While smaller sample sizes in some subgroups introduce caveats to interpretation, in general there was a consistent treatment effect for these subgroups with treatment differences in all subgroups directionally similar to the results for the overall population, indicating that MK-7243 improved TCS in the subpopulations, Figure 18 and Figure 19, for the adult phase 2/3 and pediatric phase 3 pooled populations, respectively.

There is a greater observed treatment effect in the European adult trials compared to the North American trials. As discussed above (Sec.4.8.5), this is likely due to higher pollen exposure during the European trial seasons.

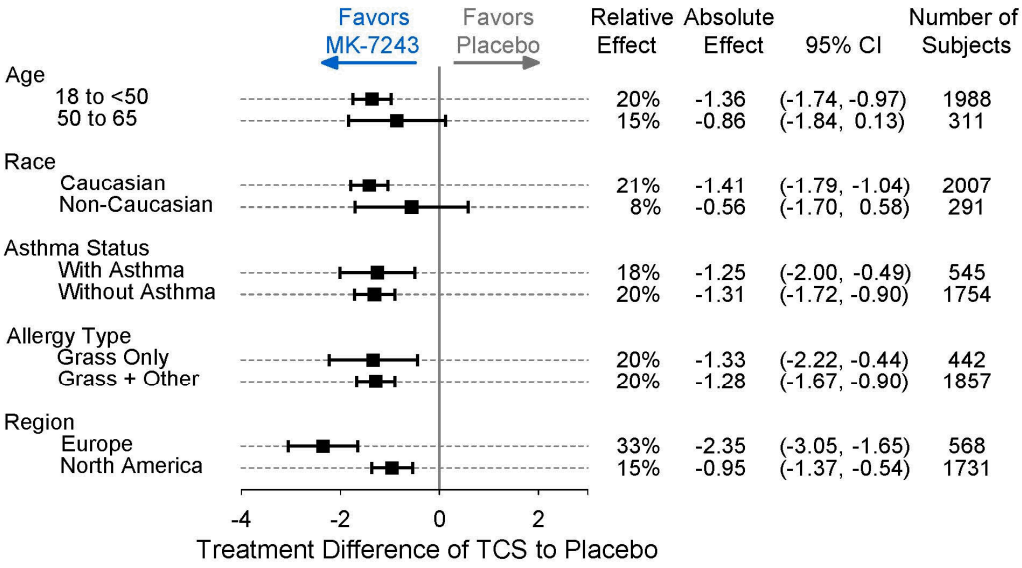


Figure 18: Sub-Population Analyses using Total Combined Score (TCS) for the Entire Grass Pollen Season (GPS) by Age, Race, Asthma Status, Allergy Sensitization Type, and Geographic Region for the Adult Phase 3 Pooled Trials (Full Analysis Set)

Overall similar findings in the subpopulations were noted for the pooled pediatric population (Figure 19). Unlike the adult phase 3 pooled population, the treatment difference between the two regions in the pediatric phase 3 pooled population revealed that North American pediatric subjects had a numerically higher treatment effect than European pediatric subjects. However the regional treatment difference for MK-7243 as compared to placebo was less pronounced in the children population and supported by the fact the pollen exposure in the North American and European pediatric trials were similar.

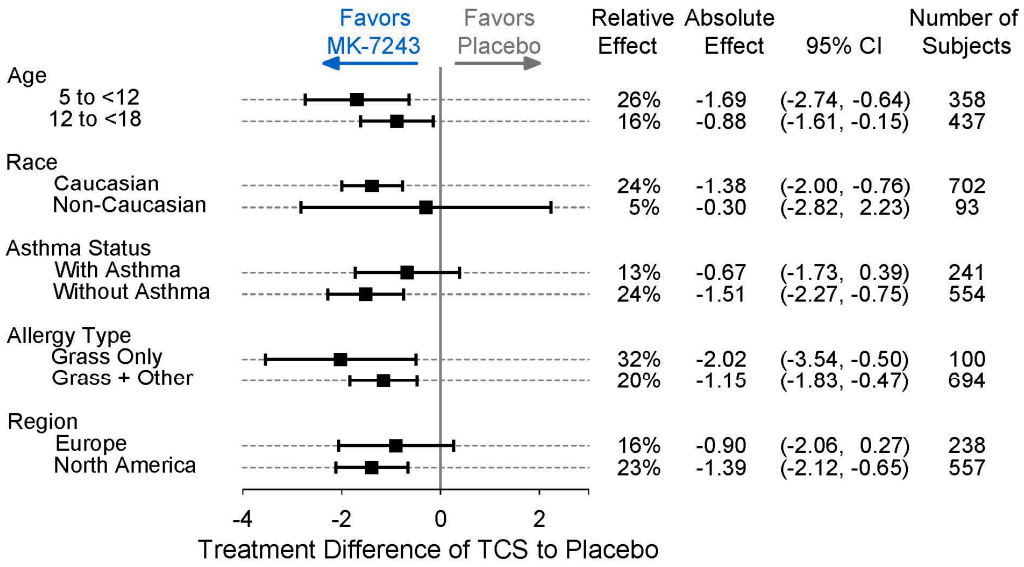


Figure 19: Sub-Population Analyses using Total Combined Score (TCS) for the Entire Grass Pollen Season (GPS) by Age, Race, Asthma Status, Allergy Sensitization Type, and Geographic Region for the Pediatric Phase 3 Pooled Trials (Full Analysis Set)

4.8.9 Potential Unblinding from Local Application Site Reactions (ASR)

Placebo and MK-7243 tablets were similar as regards appearance, smell, taste and method of administration.

Due to the higher frequency of local application site reactions (ASRs) in subjects treated with MK-7243 compared to placebo, additional analyses of the efficacy results were performed in order to evaluate if the blinding was compromised. The TCS values for the subgroups of subjects with and without local ASRs in the pooled adult and pediatric Phase 3 trials were examined with the acknowledgement that this subgroup analysis is confounded by treatment.

Theoretically, if placebo-treated subjects with local ASRs thought they were receiving MK-7243 because of the local ASRs they would be expected to report a lower TCS than subjects without local ASRs. Likewise, if subjects treated with MK-7243 and with local ASRs were guessing their treatment assignment, they would be expected to report a greater treatment response, i.e., lower TCS, than MK-7243 treated subjects without local ASRs.

The results of the TCS during the entire GPS in subjects with and without local ASRs are presented in Table 15. Placebo treated subjects with local ASRs reported a higher TCS than placebo-treated subjects without local ASRs. Adult subjects treated with MK-7243 and with local ASRs reported a higher TCS than MK-7243 treated subjects without local ASRs as opposed to the pediatric subpopulation treated with MK-7243 and reporting local ASRs where the TCS was slightly lower than for subjects without local ASRs.

The additional analyses of TCS in subjects with and without local ASRs do not indicate compromised blinding.

Table 15: Summary and Analysis of Average Total Combined Rhinoconjunctivitis Score (TCS) during the Entire GPS for the Adult Phase 3 and Pediatric Phase 3 Population: Local Application Site Reactions Sub-Group (FAS)

Parameter	Phase 3 Adult Population		Phase 3 Pediatric Population	
	MK-7243 (2800 BAU) (N=1289)	Placebo (N=1316)	MK-7243 (2800 BAU) (N=441)	Placebo (N=431)
With Local ASRs				
n	619	140	183	31
Adjusted Mean(SE)	5.43 (0.19)	8.14 (0.45)	4.42 (0.32)	6.37(0.87)
Without Local ASRs				
n	492	1048	206	375
Adjusted Mean(SE)	5.19 (0.20)	6.39 (0.15)	4.83 (0.33)	5.83 (0.23)

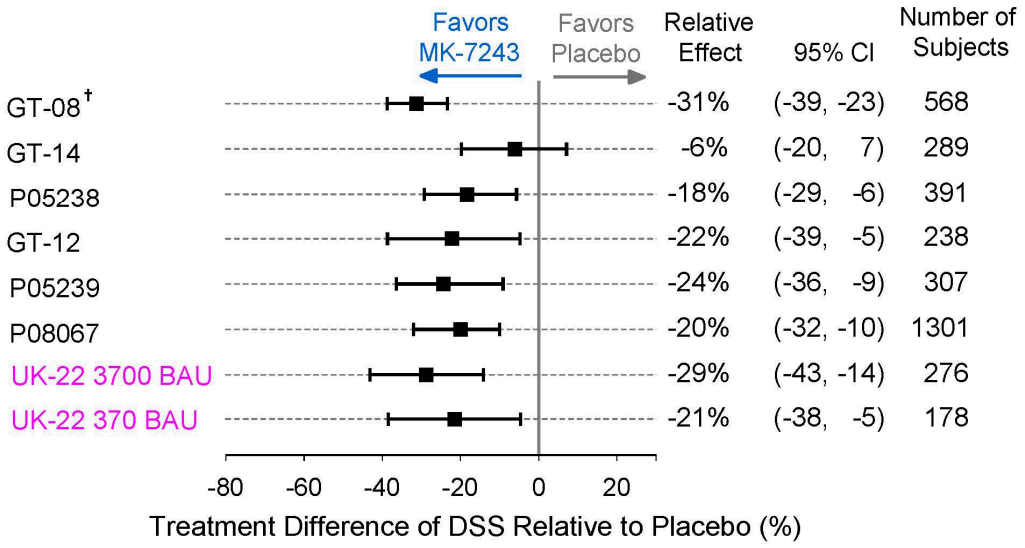
N=number of subjects in the FAS population; n: number of subjects with diary data and for analysis; SE = Standard Error
Adjusted mean calculated via ANOVA with treatment group and trial as fixed effects and adjusting for different error variation for each treatment group
Note: Local Application Site Reactions include: ORAL PRURITUS, THROAT IRRITATION, LIP SWELLING, HYPOAESTHESIA ORAL, HYPOAESTHESIA ORAL NOS, ORAL DISCOMFORT, PALATAL OEDEMA, DYSPHAGIA, DYSPHAGIA AGGRAVATED,TONGUE OEDEMA, TONGUE EDEMA, PARAESTHESIA ORAL, PARAESTHESIA ORAL NOS, SWOLLEN TONGUE, STOMATITIS, LIP OEDEMA, LIP EDEMA, LARYNX IRRITATION, GLOSSODYNIA, EDEMA MOUTH, OEDEMA MOUTH, PHARYNGEAL EDEMA, PHARYNGEAL OEDEMA, SWELLING FACE and EAR PRURITUS

4.8.10 Conclusions of Clinical Efficacy of MK-7243

1. In a large clinical development program including children ages 5-17 years and adults with grass allergic rhinoconjunctivitis, dosing with MK-7243 when initiated 8-12 weeks prior to the onset of the grass pollen season demonstrated clinically relevant first-season efficacy for the pre-specified primary endpoints measuring daily rhinoconjunctivitis symptoms and allergy medication use over the entire season.
2. Efficacy was also consistently demonstrated in replicate trials across additional key secondary endpoints such as symptoms, rescue medication use and patient quality of life measures during peak and over the entire grass pollen season.
3. Based on the totality of the data, clinically relevant efficacy has been consistently demonstrated. The effect size with MK-7243 was similar to subcutaneous grass immunotherapy and similar to or greater than effect sizes that have been historically reported for antihistamines or topical corticosteroids in the target population (discussed in Sec. 4.9).
4. Sustained efficacy and changes in immunologic parameters over three years of continuous dosing followed by persistent, clinically relevant effects as well as immunologic changes for two years post-treatment have been demonstrated supporting a “disease modifying” immunotherapeutic effect.
5. Efficacy was consistently demonstrated when assessed by age, race, asthma status (subject population included those with stable asthma), allergen sensitization pattern (poly vs. mono) and region (North America and Europe).

4.9 MK-7243 Treatment Effect Compared to Subcutaneous Immunotherapy

There are no direct comparisons of MK-7243 with subcutaneous immunotherapy. The best evidence is indirect evidence from an ALK sponsored clinical trial (UK-22) evaluating a similar Timothy grass pollen extract administered as subcutaneous injection therapy. The UK-22 trial including 410 adults, one of the largest SCIT trial ever conducted, compared two doses of subcutaneous Timothy grass extract (3700 BAU, the maximum recommended dose (100,000 standardized quality unit (SQ); 20 mcg of major allergen (Phl p 5)) and 370 BAU (10,000 SQ; 2 mcg of major allergen (Phl p 5))), to placebo. [31] The subject population was similar to the GT-08 MK-7243 trial population and efficacy based on daily symptom scoring was evaluated over an entire pollen season with mean grass pollen counts of 67 grains/m^3. The grass pollen count was somewhat higher than GT-08 Year 1 where mean counts were 45 grains/m^3. The reduction in daily symptom scores with 3700 BAU subcutaneously administered in the UK 22 trial and 2800 BAU sublingually administered in GT-08 were similar (Figure 20). The medication scoring algorithm in UK-22 and GT-08 differed and therefore DMS and TCS cannot be compared.



†- Year 1Data

Figure 20: Analysis Comparing the Daily Symptom Scores during the Entire Grass Pollen Season from MK-7243 Trials and UK-22 using a Similar Timothy Grass Extract for Subcutaneous Therapy in Grass Allergic Subjects (Full Analysis Set)

Adult trials (GT-08, GT-14, P05238)
Pediatric trials (GT-12, P05239)
Combined adult/pediatric trial (P08067)

These results indirectly comparing UK-22 and MK-7243 Phase 3 trials support the notion that sublingual and subcutaneous immunotherapy provide similar efficacy.

This outcome is further supported by a clinical trial directly comparing sublingual and subcutaneous birch allergen immunotherapy although the trial included a different allergen than Timothy grass and was not powered to show equivalence. [89] This small placebo-controlled trial (N=71) evaluating birch immunotherapy revealed that birch sublingual immunotherapy (SLIT) diminished the median disease severity to one-half and SCIT to one-third of placebo treatment. No statistically significant difference between the two groups was observed. Both for symptoms and medication scores actively treated subjects showed statistically significant and clinically relevant efficacy compared with placebo. SLIT treatment only resulted in local mild side-effects, while SCIT resulted in few serious systemic side-effects.

In addition, a recent systematic review of double blind randomized clinical SCIT and SLIT trials with predominantly pollen allergens (updated from previous Cochrane Reviews) was conducted. The meta-analysis showed that both SCIT and SLIT are statistically significantly more effective than placebo based on the combined symptom-medication scores (SCIT standardized mean difference: -0.48; 95% CI, -0.67 to -0.29; P < .00001; 8 trials: trees(n=1), grass(n=5), weed allergen(n=2)) and (SLIT standardized mean difference, -0.40; 95% CI, -0.55 to -0.25; P <.00001; 6 trials: (grass(n=4), weed(n=1), Alternaria(n=1))), Figure 21. However, superiority of SCIT over SLIT could not be consistently demonstrated through indirect comparison. [32] Thus, based on the indirect comparison of grass SCIT and SLIT, direct comparison of birch SCIT and SLIT, and the systematic review of SLIT and SCIT trials the data suggest that the sublingual method of immunotherapy administration does not overall alter the efficacy profile relative to injection based therapy. [32]

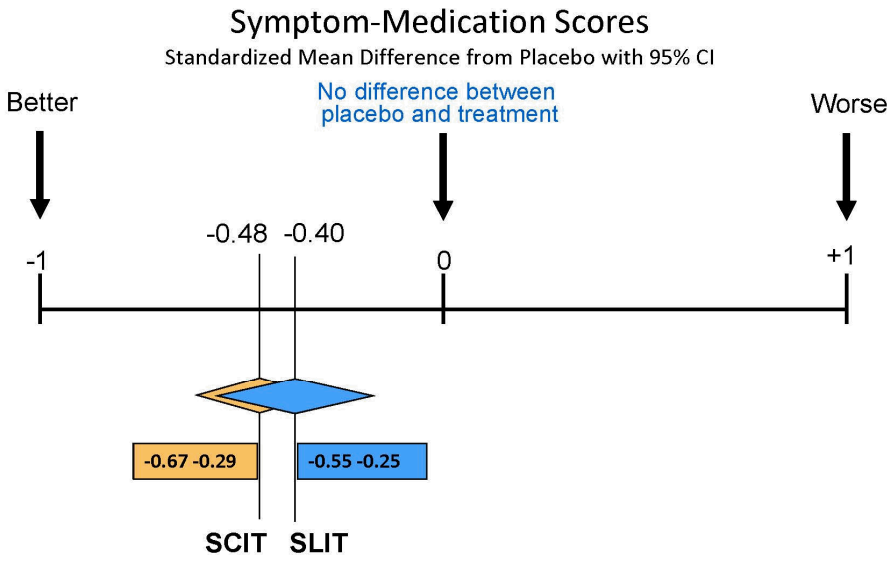


Figure 21: Standard Mean Difference of SCIT versus SLIT: Combined Symptom-Medication Score

4.10 MK-7243 Treatment Effect Compared to Pharmacotherapies

There are no direct comparisons of MK-7243 with pharmacotherapy and generally, differences in trial designs would largely preclude head-to-head comparisons. The pharmacotherapy trial designs typically include a 2 week observation period during the pollen season when subjects are pre-selected to be highly symptomatic and subjects are not allowed any rescue medication ("true placebo") in the efficacy evaluation period. For that reason the MK-7243 pooled analysis presented in Table 16 shows the TCS during the peak pollen season, which adjust the symptom score for the use of pharmacotherapy. The treatment effect observed for MK-7243 (22% difference from placebo) compares favorably or is similar to that observed with currently approved symptom-relieving pharmacotherapies (e.g., antihistamines, leukotriene inhibitors, nasal steroids).

Two recent meta-analyses were conducted by Benninger, et. al. and Wilson et.al. [15; 14] The meta-analysis by Benninger, et. al. on approved medications to treat allergic rhinitis searched the databases MEDLINE (1966 onward), EMBASE (1974 onward) and Cochrane Library (2007) to conduct a systematic review to determine the comparative efficacies of currently used classes of medications to treat the nasal symptoms of allergic rhinitis. [14] The criteria for the systematic review were defined at a panel chaired by Benninger and included: randomized controlled trials, at least 2-weeks in duration, and approved indication and dosages in the US. [14]

The meta-analysis by Wilison, et. al. searched the databases MEDLINE (1966 to February 2003), EMBASE (1980 to Feb 2003) and Cumulated Index to Nursing and Allied Health (CINAHL) (1956 to February 2003) to conduct a systematic review of leukotriene receptor antagonists for allergic rhinitis. [15] Potentially relevant articles were independently reviewed for inclusion, where reviewers assessed methodological quality using the scale described by Jadad et. al. [90] Each article was rated on a scale from 0-5 based upon randomization, blinding, allocation concealment, withdrawals and dropouts. [15]

Results from the two recent meta-analyses estimated the effect for leukotriene antagonists (5%) and antihistamines (7-9%) compared to placebo, which are substantially smaller than the effect produced by MK-7243 (Table 16). Although an intranasal corticosteroid effect may be comparable showing 17-26% difference from placebo, such medications are not typically as effective on non-nasal symptoms such as the gritty, itchy, red or watery eyes that often accompany seasonal environmental allergen exposure. [91] Furthermore, intranasal corticosteroids offer no potential for disease modification.

Table 16: Meta-Analyses of Pharmacotherapies and Pooled Analysis of MK-7243 for Treatment of Allergic Rhinitis based on 2 week Evaluation Periods (Peak Symptom Period)

	No. of Trials	No. of patients	Type of SAR treatment	Symptoms Evaluated	Improvement vs. placebo (95% CI)
Pooled Analysis MK-7243[a]	6	3,501	MK-7243	Nasal/ocular adjusted for medication use	22 % (17%, 26%)
Meta-analysis[b] [14]	38	12,926	antihistamine	Nasal/ocular	9 % (-24%, 23%)†
			nasal corticosteroid	Nasal	26 % (-16%, 43%)†
Meta-analysis[c] [15]	11	3,924	antihistamine	Nasal/ocular	7 % (2%, 9%)
			nasal corticosteroid	Nasal	17 % (7%, 23%)
			leukotriene receptor antagonist	Nasal	5 % (3%, 7%)

SAR=seasonal allergic rhinitis
† Range (min, max) is provided due to lack of information in the publication
a Percent relative improvement vs. placebo in TCS during peak GPS
b Difference vs. placebo in percent change from baseline
c Composite Nasal Symptom Score, expressed as the percentage of maximum possible symptom score (higher score indicating worse symptoms.

The symptom scoring system (grading of nasal and non-nasal symptoms on a scale from 0 to 3) was similar in the montelukast and loratadine/desloratadine trials. In the mometasone trials, only nasal symptoms were included. Although the trials are not directly comparable, they do provide a reference point for an estimation of general treatment effect observed with pharmaceutical therapy approved for the relief of AR symptoms.

5 OVERVIEW OF SAFETY IN THE CLINICAL DEVELOPMENT PROGRAM

The MK-7243 development program was designed to enable a comprehensive evaluation of safety and tolerability in a grass allergic adult and pediatric population with allergic rhinoconjunctivitis with and without asthma. The results of this extensive evaluation showed that MK-7243 is generally safe and well tolerated. The adverse event profile is consistent with the known allergic reactions associated with allergen immunotherapy with no unexpected safety findings. Local adverse events of allergic nature were experienced by the majority of actively treated subjects. The discontinuation rate due to adverse events was low and similar across age groups. The adverse events were generally mild to moderate in intensity and resolved over time with repeated administration. There were no reports of anaphylactic shock or of treatment-related death during the clinical development program. Systemic adverse events were few, non-serious and of mild to moderate intensity. The observed safety profile of MK-7243 was similar in adults and children.

The clinical safety from the development program is described below and is followed by a section summarizing adverse events of interest from post-approval trials, observational surveillance studies and spontaneously reported adverse events collected in the global pharmacovigilance (PV) database up to 30Apr2013. The results from the post-approval safety data are consistent with the overall safety profile observed in the clinical development program and the expectation that serious allergic reactions can occur with any form of allergen immunotherapy. The data revealed that uncommon serious systemic allergic reactions (including one case reported as anaphylactic shock occurring at first administration and under supervision), local allergic reactions, and asthma related events were reported. Serious systemic allergic reactions generally occurred on the first day of exposure to MK-7243 during the 30 minutes of observation in a health care setting. The few events that occurred later than the first day were readily detected and readily managed by standard pharmacological care. Other allergic type reactions were also readily detected and readily managed. In order to provide additional perspective on the safety profile of MK-7243 treatment, the safety section is concluded with a summary of information from datasets that describe what has been published regarding the safety profile of SCIT for both grass and other inhalant allergens.

Safety Database

The safety assessment of MK-7243 is supported by a total of 13 phase 1-3 clinical trials involving approximately 4700 Timothy grass allergic subjects ranging in age from 5 to 66 years of whom ~2570 subjects were treated with 2800 BAU for up to three years. Overviews of the clinical trials are located in Table 2.

Long-term safety/tolerability of treatment is available from GT-08 (Phase 3) trial years 2-5. Subjects were exposed to blinded therapy for 3 years and then followed off treatment for an additional 2 years.

The assessment of the overall safety was mainly based on 4 different pooled data sets (adult phase 1, pediatric phase 1, adult phase 2/3 and pediatric phase 3), outlined in Table 17. For this safety summary, the exposure data, and AE summary data focuses on the adult Phase 2/3

and pediatric Phase 3 pooled safety datasets, in which subjects were treated with MK7243 2800 BAU or placebo. The trials included in the respective adult Phase 2/3 and pediatric Phase 3 pooled datasets had similar trial designs, trial duration, and subject populations. The reasons for the focus on these two pools include: the large number of subjects in the Phase 2/3 adult and Phase 3 pediatric pools and the longer duration of exposure. Long-term safety data, in which subjects received 3 years of treatment, is reviewed separately to support the long-term tolerability profile of MK-7243.

Table 17: Clinical Trial Safety Database Analysis Pools

Safety Data Pools	Trials Included
Initial Phase 1 Adults†	GT-01
Adult Phase 1 Pool	GT-03, GT-04
Pediatric Phase 1 Pool	GT-09, GT-11
Adult Phase 2/3 Pool	P05238, GT-02, GT-07, GT 08 (1st year), GT-14, and adults from P08067
Pediatric Phase 3 Pool	P05039, GT 12, and children from P08067
Long Term Safety/Tolerability	2-5-years GT-08

†GT-01 was not pooled with GT-03 and GT-04 due to a different trial design and increased length of exposure.

The safety analyses pooled data across trials, separately for the adult and pediatric population, to provide an integrated summary of safety profile of MK-7243 treatment. All the pooled 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).

5.1 Extent of Exposure by Dose and Duration

The duration of treatment for the Phase 2/3 adult pool and Phase 3 pediatric pool is shown in Table 18, and Table 19, respectively.

Table 18: Extent of Exposure to MK-7243 by Treatment –Adult Phase 2/3 Pooled Clinical Trials (All Randomized Subjects)

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)
Statistics (day)		
N	1669	1640
Mean	175	182.6
SD	67	59.1
Median	184	188
Min	1	1
Max	317	317

Table 19: Extent of Exposure to MK-7243 by Treatment –Pediatric Phase 3 pooled Clinical Trials (All Randomized Subjects)

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
Statistics (day)		
N	442	433
Mean	176.9	185.2
SD	59.2	45.8
Median	194	196
Min	1	1
Max	258	258

5.2 Approaches for Collection and Evaluation of Safety Data

In the clinical program, safety assessments were based on review of adverse events, change from baseline in safety laboratory analyses, pulmonary function test results (PFTs) and vital signs. Adverse events, including treatment-related AEs, events of clinical interest (ECIs), serious adverse events (SAEs), and AEs that led to discontinuation of study medication, were identified and summarized. Subject demographics, medical history, trial disposition, and exposure also contributed to the evaluation of safety in the trial populations.

Because of the lack of systemic absorption and mechanism of action, there is no perceived risk of drug abuse with MK-7243. As such, no AEs associated with potential for abuse were assessed. Withdrawal and rebound effects were not formally studied by the Sponsor. However, data from GT-08 Yr. 4 and GT-08 Yr. 5 were evaluated since data from these years were following cessation of therapy. Detailed information is found in Sec. 5.11.

Additional safety parameters evaluated and specific features of safety monitoring in the clinical development program are described in Sec. 5.2.4 and Sec. 5.2.5.

5.2.1 Adverse Event Definitions

Definitions related to adverse events were consistent among the 13 trials. An Adverse Event (AE) was defined as:

- Any untoward medical occurrence in a subject administered a pharmaceutical or biologic product (at any dose), or medical device, which does not necessarily have a causal relationship with the treatment. Adverse events may include the onset of new illness and the exacerbation of pre-existing conditions. Additionally, any event that is associated with, or observed in conjunction with, a product overdose (whether accidental or intentional) or a product abuse and/or withdrawal is also considered an AE.

A **serious adverse event (SAE)** was any adverse drug event that resulted in any of the following outcomes:

- Death
- Life-threatening event (i.e., adverse event that places the patient, in view of the initial reporter at immediate risk of death from the event as it occurs)
- Persistent or significant disability/incapacity
- Required prolonged hospitalization
- Congenital anomaly or birth defect
- Medically important event as determined by investigator/reporter (one may require medical or surgical intervention to prevent one of the outcomes previously listed)

5.2.2 Intensity/Severity of Adverse Events

Grading the intensity of an AE was conducted by the investigator. The following definitions were used for grading the severity of AEs:

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

For most of the summary tables presented in this document, an AE is listed only once (at its most severe intensity), regardless of the number of times it occurred for a given subject.

5.2.3 Relationship of Adverse Event to Study Medication

Relationship of any AE to the use of study drug, based on available information, was assessed by the investigator. The relationship of an AE to treatment included one of the following:

- **Unlikely related**: no temporal association, or the cause of the event has been identified, or the IMP, biological, or device could not be implicated;
- **Possibly related**: temporal association, but other etiologies were likely to be the cause; however, involvement of the IMP, biological, or device could not be excluded;
- **Probably related**: temporal association, other etiologies were possible, but unlikely.

In the presentation of safety results, 'treatment-related' refers to any AE that was considered either 'possibly' or 'probably'-related to study therapy by the investigator[2].

5.2.4 Events of Clinical Interest

The most common adverse events seen with immunotherapy, regardless of the allergen and route of administration, are local allergic reactions. Since the route of administration for sublingual immunotherapy is the oral cavity, local allergic reactions may result in mouth/throat itching or mucosal swelling. Local swelling in the throat has the theoretical risk of upper airway obstruction; hence, local allergic swellings with the potential to obstruct the upper airway is a key event of clinical interest for MK-7243. In addition to local allergic swellings, systemic allergic reactions (including anaphylactic shock) and asthma related events are experiences that have been identified as potential risks with any formulation of immunotherapy.

[2] Treatment related adverse event tables also include two records where the relationship to study medication was not captured.

Therefore, the Events of Clinical Interest for the MK-7243 program are as follows:

- Systemic allergic reactions
  - Including Anaphylactic shock
- Local Allergic Swellings with the potential to obstruct the upper airway
- Asthma Related Events

5.2.5 Definitions of Adverse Events Pertinent to Safety Concerns of Immunotherapy

Table 20 reviews the definitions for the adverse events of interest for MK-7243, as well as the MedDRA terminology associated with these events.

Education regarding the criteria required for systemic allergic reactions and local allergic reactions were reviewed in detail during the training sessions for the North American trials (P05238, P05239, and P08067). Key safety adverse events were designated a priori as Adverse Events of Clinical Interest within the North American trials (P05238, P05239 and P08067) and post-hoc to the remainder of the clinical trial program.

All investigator reported adverse events were collected for the trials; however, specific adverse event terms were used by Sponsor (Merck Sharp & Dohme, Corp.) when reviewing the database for defining systemic allergic reactions, which included the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PT): anaphylactic reactions, hypersensitivity reactions, drug hypersensitivity and lower level terms (LLTs) systemic allergic reaction, anaphylaxis, and allergic reactions. For reporting purposes anaphylactic shock represents the most critical subset of the category systemic allergic reaction. As such, it appears separately in the tables summarizing the data.

The local allergic swellings with the potential to compromise the airway included swellings affecting the inside of the oral cavity, tongue or throat. The PT terms utilized to identify such events included the following: Oedema mouth, Oropharyngeal swelling, Palatal oedema, Pharyngeal oedema, Tongue oedema, Swollen tongue, Throat tightness, Laryngeal edema.

Epinephrine was supplied to all subjects as an emergency medication in 3 of the 4 North American trials (P05238, P05239, and P08067). In the first US trial (GT-14), epinephrine was not supplied, nor was it supplied to subjects enrolled in the European trials. As an additional measure to identify potential systemic allergic reactions or significant local allergic reactions, all epinephrine administrations were evaluated. Similarly, identification of subjects with potential anaphylaxis according to the diagnostic criteria proposed by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) and published by Sampson et al was conducted. A search of the clinical database was conducted to identify subjects with a constellation of symptoms which could indicate a potential case of anaphylaxis. This entailed a review of all adverse events to determine if a subject had more than one adverse events affecting more than one organ system on the same day. [66]

Table 20: Definitions of Hypersensitivity Events Used in the Clinical Trial Program

Hypersensitivity Event Type	Clinical definition	Applied MedDRA Preferred and Lower Level Terms
Systemic allergic reaction	An allergic event that affects an organ system, which is distant from the site of allergen application. Clinical terms used to denote a systemic allergic reaction includes anaphylaxis, anaphylactic reaction, anaphylactic shock and hypersensitivity reaction. For sublingual immunotherapy, the term will include signs or symptoms distant from the mouth and/or throat. ***Note that clinicians may report local allergic reactions as "anaphylaxis" or "anaphylactic" without any systemic signs and symptoms of anaphylaxis or degree of severity as defined by the NIAID/FAAN.**	Anaphylactic reaction; Hypersensitivity; Drug Hypersensitivity Systemic allergic reaction; Anaphylaxis; Allergic reactions
Anaphylactic shock	Anaphylactic shock is the most severe form of a systemic allergic reaction. Anaphylactic shock is characterized by systemic symptoms in conjunction with hypotension 1. systolic blood pressure <90 mmHg or 2. >30% decrease from baseline blood pressure	Anaphylactic Shock
Local allergic reaction	An allergic event that occurs in a region located in close proximity to where the allergen was placed. For sublingual immunotherapy, a local allergic reaction may affect the mouth, pharynx, and larynx. Lower gastro-intestinal symptoms are considered distant from the upper gastro-intestinal tract and therefore not included in this definition.	Oral pruritus, Throat irritation, Lip swelling, Hypoaesthesia oral, Oral discomfort, Palatal oedema, Dysphagia, Tongue oedema, Paraesthesia oral, Swollen tongue, Stomatitis, Lip oedema, Lip edema, Larynx irritation, Glossodynia, Oedema mouth, Pharyngeal oedema, Swelling face, Laryngeal edema, Throat tightness, Oropharyngeal swelling, and Ear pruritus
Local allergic swelling	A local allergic reaction that results in swelling in and around the mouth or throat. The following terms are considered local allergic swellings by the Sponsor: oedema mouth, tongue swelling, oedema tongue, palatal oedema, pharyngeal oedema, throat tightness, laryngeal edema.	Oedema mouth, Oropharyngeal swelling, Palatal oedema, Pharyngeal oedema, Tongue oedema, Swollen tongue, Throat tightness, Laryngeal edema

5.3 Subject Disposition

The subject disposition for the adult Phase 2/3 and pediatric Phase 3 pooled populations are presented in Table 21 and Table 22, respectively. More subjects on MK-7243 discontinued due to an adverse event as compared to placebo in both the adult and pediatric populations.

Table 21: Disposition of Subjects – Adult Phase 2/3 Pooled Clinical Trials (All Randomized Subjects)

Subject Disposition	Number (%) of Subjects			
	MK-7243 2800 BAU		Placebo	
Randomized	1669	(100)	1645	(100)
Discontinued Treatment Phase	267	(16)	217	(13)
Adverse Event[a]	99	(6)	45	(3)
Treatment Failure	0		1	(<1)
Lost To Follow-Up	31	(2)	36	(2)
Subject Did Not Wish To Continue For Reasons Unrelated To Assigned Study Treatment	9	(1)	9	(1)
Subject Did Not Wish To Continue For Reasons Related To Assigned Study Treatment	0		3	(<1)
Subject Withdrew Consent	66	(4)	48	(3)
Non-Compliance With Protocol	39	(2)	46	(3)
Did Not Meet Protocol Eligibility	3	(<1)	1	(<1)
Other	20	(1)	27	(2)
Death	2	(<1)	1	(<1)
Completed Treatment Phase	1402	(84)	1428	(87)

[a] Numbers of subject that discontinued due to an Adverse Event are determined from the disposition data

Table 22: Disposition of Subjects – Pediatric Phase 3 Clinical Trials (All Randomized Subjects)

Subject Disposition	Number (%) of Subjects			
	MK-7243 2800 BAU		Placebo	
Randomized	447	(100)	434	(100)
Discontinued Treatment Phase	70	(16)	47	(11)
Adverse Event[a]	29	(6)	8	(2)
Treatment Failure	0		1	(<1)
Lost To Follow-Up	8	(2)	1	(<1)
Subject Did Not Wish To Continue For Reasons Unrelated To Assigned Study Treatment	11	(2)	8	(2)
Subject Withdrew Consent	5	(1)	5	(1)
Non-Compliance With Protocol	12	(3)	21	(5)
Did Not Meet Protocol Eligibility	2	(<1)	1	(<1)
Other	3	(1)	2	(<1)
Completed Treatment Phase	377	(84)	387	(89)

[a] Numbers of subject that discontinued due to an Adverse Event are determined from the disposition data

5.4 Analysis of Adverse Events

The following summarizes the key safety findings for MK-7243 in the Phase 2/3 development program:

- The safety profile of MK-7243 was generally similar in adults and children.
- Treatment-related AEs occurred in approximately 67% adult subjects and 58% pediatric subjects who were treated with MK-7243 as compared to ~24% of subjects treated with placebo. No serious treatment-related AEs were observed in subjects treated with MK-7243 2800 BAU. One drug related serious adverse event was

reported on MK-7243 933 BAU (uvula oedema following first intake of the tablet; the event self-resolved and the subject completed the trial). Events with the highest incidence were local allergic reactions such as oral pruritus, with approximately 96% of events being mild or moderate in intensity. Generally, the recurrence of AEs diminished with continued daily treatment.

- In the adult Phase 2/3 and pediatric Phase 3 trials, there were a total of 10 systemic allergic reactions in 9 subjects; nine reactions occurred in 8 subjects treated with 2800 BAU. The MK-7243 2800 BAU events were all non-serious and were assessed as either mild (n= 5) or moderate (n=4) in intensity by the investigators. The events were characterized by predominantly local symptoms and dyspnea. One of the 9 subjects was classified as having an anaphylactic reaction, although the symptoms were all local in nature.
    - Six of the 8 subjects on MK-7243 2800 BAU experienced the events on Day 1 of treatment. The other 2 subjects experienced events on day 2 and 42, respectively; however, neither subject required medication to treat the event nor did they seek medical attention.
    - There were no reports of anaphylactic shock in clinical trials.
    - No additional cases were identified when reviewing epinephrine usage as a marker of systemic allergic reactions.
- There were no reported local swelling events leading to upper airway obstruction. The local swellings that occurred self-resolved or were managed by pharmacotherapy.
- The safety profile of MK-7243 in subjects with reported asthma was similar to those subjects who did not report a history of asthma. The occurrence of asthma-related events in the asthma subgroups was lower in the MK-7243 group, compared with that in the placebo group. There were no reports of treatment related serious or severe asthma related events.
- Safety findings were similar in subpopulations based on age, race, allergen-sensitization type (sensitized to grass only versus those sensitized to grass plus other non-grass allergens, such as tree, weed, etc.), and subjects with or without reported asthma.

5.4.1 Adverse Event summary

Adverse events regardless of causality were common and occurred more frequently with MK-7243 than placebo in both adult and pediatric populations, (Table 23 and Table 24, respectively). Similarly, treatment related adverse events were observed more commonly in the MK-7243 group. The most frequent adverse events were local allergic reactions, such as oral pruritus and throat irritation.

The number of SAEs was similar between MK-7243 and placebo in both children and adults. No treatment-related SAEs were observed in subjects treated with MK-7243 2800 BAU. One drug related serious adverse event was reported on MK-7243 933 BAU (uvula oedema following first intake of the tablet; the event self-resolved and the subject completed the trial, Sec. 5.4.4).

More subjects treated with MK-7243 compared to placebo discontinued the trials due to an AE in both the adult and pediatric populations. Three deaths were reported (2 on MK-7243; 1 on

placebo [Sec. 5.4.4]), all of which occurred in adult subjects and were assessed as not related to treatment. There were no events of anaphylactic shock.

Table 23: Adverse Events Summary – Adult Phase 2/3 Pooled Clinical Trials (All Randomized 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[a]	97(5.8)	41(2.5)
Discontinued Due to Treatment Related AE[a]	81(4.9)	15(0.9)
Discontinued Due to Serious AE[a]	3(0.2)	6(0.4)
Discontinued Due to Treatment Related Serious AE[a]	0	0
Death	2(0.1)	1(0.1)

[a] Numbers of subject that discontinued due to an Adverse Event are determined from the adverse event data

Table 24: Adverse Events Summary – Pediatric Phase 3 Pooled Clinical Trials (All Randomized 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[a]	29(6.5)	8(1.8)
Discontinued Due to Treatment Related AE[a]	28(6.3)	3(0.7)
Discontinued Due to Serious AE[a]	1(0.2)	0
Discontinued Due to Treatment Related Serious AE[a]	0	0
Death	0	0

[a] Numbers of subject that discontinued due to an Adverse Event are determined from the adverse event data

5.4.2 Common Adverse Events

The most common adverse events for the adult Phase 2/3 and pediatric Phase 3 pooled populations are presented in Table 25 and Table 26, respectively. The percentage of subjects experiencing AEs in MK-7243 was higher than that observed in the placebo group for both the adult and pediatric population. The most common AEs occurring in frequency above placebo in adults treated with MK7243 include local allergic reactions (as defined in Table 20) such as oral pruritus, throat irritations, ear pruritus, mouth edema and oral paraesthesia; and in children include oral pruritus, throat irritation, mouth oedema, and tongue pruritus.

Table 25: Subjects with Specific Adverse Events (Incidence ≥3% in one or more Treatment Groups) – Adult Phase 2/3 Pooled Clinical Trials (All Randomized Subjects)

	MK-7243 2800 BAU n=1669		Placebo n=1645	
	n	%	n	%
SUBJECTS REPORTING ANY ADVERSE EVENT	1383	(82.9)	1118	(68.0)
EAR AND LABYRINTH DISORDERS				
EAR PRURITUS	210	(12.6)	19	(1.2)
EYE DISORDERS				
EYE PRURITUS	67	(4.0)	43	(2.6)
GASTROINTESTINAL DISORDERS				
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)
INFECTIONS AND INFESTATIONS				
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)
NERVOUS SYSTEM DISORDERS				
HEADACHE	170	(10.2)	164	(10.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
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)

Table 26: Subjects with Specific Adverse Events (Incidence ≥3% in one or more Treatment Groups) – Pediatric Phase 3 Pooled Clinical Trials (All Randomized Subjects)

	MK-7243 2800 BAU n=447		Placebo n=434	
	n	%	n	%
SUBJECTS REPORTING ANY ADVERSE EVENT	367	(82.1)	343	(79.0)
EAR AND LABYRINTH DISORDERS				
EAR PRURITUS	33	(7.4)	2	(0.5)
EYE DISORDERS				
EYE PRURITUS	23	(5.1)	16	(3.7)
GASTROINTESTINAL DISORDERS				
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)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
PYREXIA	16	(3.6)	24	(5.5)
INFECTIONS AND INFESTATIONS				
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)
NERVOUS SYSTEM DISORDERS				
HEADACHE	38	(8.5)	39	(9.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
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)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
URTICARIA	17	(3.8)	11	(2.5)

The remainder of the clinical development general safety summary will focus on presentation of treatment related adverse events, as assessed by the investigators. The AEs are related to exposure of allergen; the AEs are known to the investigators; and as a result the AEs are likely to be assessed as related to the treatment by the investigators.

5.4.3 Treatment-Related Adverse Events

Treatment related AEs were more common with MK-7243 than placebo in both the adult and pediatric subjects. The most frequent AEs were allergic reactions occurring in the oral cavity following tablet administration. The treatment-related AEs with the highest incidence in the MK-7243 group for the Adult Phase 2/3 pool compared to placebo were: oral pruritus, throat irritation, ear pruritus and oedema mouth, Table 27. Treatment-related AEs typically occurred early in treatment and were generally assessed as mild or moderate in intensity (Figure 22). The majority of AEs subsided with continued dosing.

The treatment-related AEs with the highest incidence in the MK-7243 treatment group for the Pediatric Phase 3 pool compared to placebo were: oral pruritus, throat irritation, oedema mouth, and tongue pruritus (Table 28).

Table 27: Subjects with Specific Treatment Related Adverse Events (Incidence ≥2% in one or more Treatment Groups) – Adult Phase 2/3 Pooled Clinical Trials (All Randomized Subjects)

	Number (%) of Subjects			
	MK-7243 2800 BAU n=1669		Placebo n=1645	
SUBJECTS REPORTING ANY ADVERSE EVENT	1111	(66.6)	389	(23.6)
EAR AND LABYRINTH DISORDERS				
EAR PRURITUS	208	(12.5)	18	(1.1)
EYE DISORDERS				
EYE PRURITUS	50	(3.0)	29	(1.8)
GASTROINTESTINAL DISORDERS				
DYSPEPSIA	39	(2.3)	1	(0.1)
HYPOAESTHESIA ORAL	38	(2.3)	17	(1.0)
LIP PRURITUS	39	(2.3)	7	(0.4)
LIP SWELLING	67	(4.0)	3	(0.2)
OEDEMA MOUTH	186	(11.1)	13	(0.8)
ORAL PRURITUS	446	(26.7)	57	(3.5)
PARAESTHESIA ORAL	164	(9.8)	33	(2.0)
SWOLLEN TONGUE	46	(2.8)	2	(0.1)
TONGUE PRURITUS	95	(5.7)	8	(0.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
FATIGUE	24	(1.4)	7	(0.4)
NERVOUS SYSTEM DISORDERS				
HEADACHE	35	(2.1)	22	(1.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
DRY THROAT	29	(1.7)	6	(0.4)
DYSPNOEA	19	(1.1)	7	(0.4)
OROPHARYNGEAL PAIN	26	(1.6)	16	(1.0)
PHARYNGEAL OEDEMA	56	(3.4)	2	(0.1)
RHINORRHOEA	34	(2.0)	27	(1.6)
SNEEZING	34	(2.0)	23	(1.4)
THROAT IRRITATION	378	(22.6)	46	(2.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
PRURITUS	40	(2.4)	16	(1.0)

Table 28: Subjects with Specific Treatment-Related Adverse Events (Incidence ≥2% in one or more Treatment Groups) – Pediatric Phase 3 Pooled Clinical Trials (All Randomized Subjects)

	Number (%) of Subjects			
	MK-7243 2800 BAU N=447		Placebo N=434	
	n	%	n	%
SUBJECTS REPORTING ANY ADVERSE EVENT	260	(58.2)	104	(24.0)
EAR AND LABRYINTH DISORDERS				
EAR PRURITUS	32	(7.2)	2	(0.5)
EYE DISORDERS				
EYE PRURITUS	15	(3.4)	9	(2.1)
GASTROINTESTINAL DISORDERS				
DYSPHAGIA	9	(2.0)	0	
LIP PRURITUS	13	(2.9)	1	(0.2)
LIP SWELLING	32	(7.2)	2	(0.5)
OEDEMA MOUTH	44	(9.8)	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)	5	(1.2)
SWOLLEN TONGUE	11	(2.5)	0	
TONGUE PRURITIS	41	(9.2)	4	(0.9)
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS				
CHEST DISCOMFORT	9	(2.0)	2	(0.5)
NERVOUS SYSTEM DISORDERS				
HEADACHE	15	(3.4)	8	(1.8)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS				
COUGH	12	(2.7)	5	(1.2)
DRY THROAT	12	(2.7)	2	(0.5)
DYSPNOEA	9	(2.0)	2	(0.5)
OROPHARYNGEAL PAIN	18	(4.0)	6	(1.4)
PHARYNGEAL ERYTHEMA	16	(3.6)	3	(0.7)
PHARYNGEAL OEDEMA	13	(2.9)	0	
THROAT IRRITATION	95	(21.3)	11	(2.5)

Onset of treatment related adverse events typically occurred within the first 1-2 weeks of treatment with the highest percentage of subjects experiencing a treatment related AE on Day 1 (Table 29 and Table 30).

Table 29: Treatment Related Adverse Events by Time to Onset (Incidence ≥0% in one or more Treatment Groups) – Adult Phase 2/3 Pooled Clinical Trials (All Randomized Subjects)

	With any Treatment related AEs			
	MK-7243 2800 BAU (N=1669)		Placebo (N=1645)	
	n	(%)	n	(%)
Day 1	873	52.3	172	10.5
Day 2	271	16.2	56	3.4
Day 3	114	6.8	26	1.6
Day 1 to Day 7	987	59.1	257	15.6
Day 1 to Day 14	1020	61.1	265	16.1
Day 1 to Day 28	1049	62.9	282	17.1
Day 1 to Day 60	1077	64.5	318	19.3
Day 1 to Day 90	1092	65.4	348	21.2
Overall	1111	66.6	389	23.6

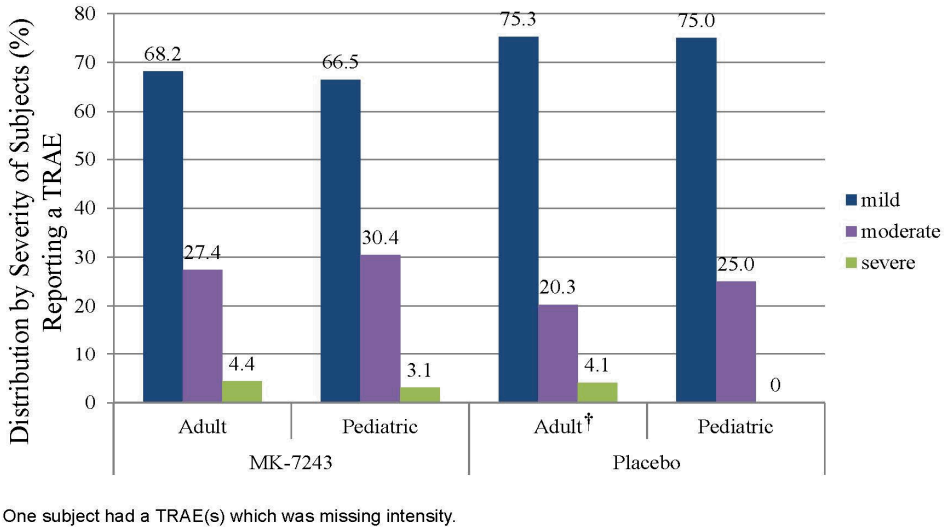
Numbers in the table for Day 1, 2, and 3 are not cumulative. Day 1 to Day 7-14-28-60-90 is cumulative.

Table 30: Treatment Related Adverse Events by Time to Onset (Incidence ≥0% in one or more Treatment Groups) – Pediatric Phase 3 Pooled Clinical Trials (All Randomized Subjects)

	With Any Treatment Related AEs			
	MK-7243 2800 BAU N=447		Placebo N=434	
	n	%	n	%
Day 1	181	40.5	38	8.8
Day 2	89	19.9	18	4.1
Day 3	56	12.5	8	1.8
Day 1 to Day 7	220	49.2	53	12.2
Day 1 to Day 14	231	51.7	60	13.8
Day 1 to Day 28	241	53.9	68	15.7
Day 1 to Day 60	249	55.7	78	18.0
Day 1 to Day 90	252	56.4	85	19.6
Overall	260	58.2	104	24.0

The denominator for percentages is based on the number of subjects in each treatment group.
Treatment related: Assessed by the investigator as possible or probable
Numbers in the table for Day 1, 2, and 3 are not cumulative. Day 1 to Day 7-14-28-60-90 is cumulative.

The majority of treatment related AEs were assessed as mild or moderate in intensity for the adult Phase 2/3 pooled trials in MK-7243 and placebo. Similar results were demonstrated in pediatric subjects on MK-7243 and placebo, Figure 22. A list of the specific treatment related adverse events by intensity is located in Appendix 3.



† One subject had a TRAE(s) which was missing intensity.

Figure 22: Treatment-Related Adverse Events (Incidence ≥2% in one or more Treatment Groups) by Intensity Classification – Adult and Pediatric Phase 2/3 Pooled Clinical Trials (All Randomized Subjects)

TRAE = treatment related adverse event

5.4.4 Deaths, Serious Adverse Events, and Discontinuation Due to an Adverse Event

Deaths

In the 13 MK-7243 clinical trials, there were 3 deaths in adult subjects reported; 2 subjects randomized to MK-7243 and, 1 subject randomized to placebo. None of the deaths were considered related to study treatment with MK-7243. A description of the events is provided below:

- A 28 year-old male subject from P05238 Trial with a history of allergic rhinitis, depression, anxiety and insomnia was randomized to MK-7243 2800 BAU. The subject was found dead due to a multiple drug overdose (including prescription and illegal drugs) that was considered not related to study drug by the investigator. The death occurred (b) (6) days after the last dose of study drug.
- A 43 year old male subject from P08067, with no relevant medication history and no reported use of concomitant medications, was randomized to MK-7243 2800 BAU. The subject completed the trial. The trial site was notified that the subject had passed away (b) (6) days after the last dose of study medication. An autopsy deemed the cause of death to be due to arteriosclerotic cardiovascular disease with combined drug toxicity. The manner of death was an accident due to drug abuse. The investigator considered the SAE unrelated to study medication.

- A 31 year old male subject from GT 08 Trial Year 1 was randomized to placebo. The subject was hospitalized due to vomiting and convulsions on study day 153 and was diagnosed with a subarachnoid hematoma / subarachnoid hemorrhage, confirmed by a computed tomography (CT) scan on Day 154. The last dose of study medication was taken the day prior to diagnosis via CT scan. The subject subsequently died from the event approximately 2 weeks after diagnosis. The investigator considered the event unlikely related to study medication.

Serious Adverse Events (SAE)

The incidence of SAEs was low and similar between MK-7243 and placebo in both the adult and pediatric pools, Table 31 and Table 32. No treatment related SAEs were reported for MK-7243 2800 BAU. There was one drug related serious adverse event reported in the GT-02 trial in the 933 BAU group (uvula oedema after first tablet intake). The event was upgraded by the Sponsor from non-serious to serious after closure of the database as a conservative approach following evaluation by the trial principal investigator. The subject experienced after intake of the first tablet an itching feeling of the tongue and a localized oedema of the uvula developed. The subject was observed at the clinic for two hours and was thereafter released to his home. No treatment was given and the subject continued in the trial and completed the trial according to protocol. There was one treatment related SAE (abdominal pain) which occurred in a subject on placebo (Table 23).

Table 31: Serious Adverse Event Summary (Incidence ≥0% in one or more Treatment Groups) During the Treatment Period – Adult Phase 2/3 Pooled Clinical Trials (All Randomized Subjects)

	MK-7243 2800 BAU N=1669 n(%)	Placebo N=1645 n(%)
SUBJECTS REPORTING ANY ADVERSE EVENT	**20 (1.2)**	**20 (1.2)**
CARDIAC DISORDERS	**1 (0.1)**	**0**
PERICARDITIS	1 (0.1)	0
GASTROINTESTINAL DISORDERS	**0**	**1 (0.1)**
ABDOMINAL PAIN	0	1 (0.1)
COLITIS ULCERATIVE	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**3 (0.2)**	**0**
CHEST PAIN	1 (0.1)	0
DEATH	1 (0.1)	0
DEVICE DISLOCATION	1 (0.1)	0
INFECTIONS AND INFESTATIONS	**3 (0.2)**	**4 (0.2)**
APPENDICITIS	1 (0.1)	1 (0.1)
CHOLECYSTITIS INFECTIVE	0	1 (0.1)
DIVERTICULITIS	1 (0.1)	1 (0.1)
PELVIC ABSCESS	0	1 (0.1)
PNEUMONIA	1 (0.1)	1 (0.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**7 (0.4)**	**3 (0.2)**
CLAVICLE FRACTURE	1 (0.1)	0
EPICONDYLITIS	0	0
FOOT FRACTURE	0	2 (0.1)
FOREARM FRACTURE	1 (0.1)	0
JAW FRACTURE	1 (0.1)	0
JOINT INJURY	1 (0.1)	1 (0.1)

	MK-7243 2800 BAU N=1669 n(%)		**Placebo** N=1645 n(%)	
LACERATION	1	(0.1)	0	
MULTIPLE DRUG OVERDOSE	1	(0.1)	0	
UPPER LIMB FRACTURE	1	(0.1)	0	
METABOLISM AND NUTRITION DISORDERS	**1**	**(0.1)**	**1**	**(0.1)**
DIABETIC KETOACIDOSIS	1	(0.1)	0	
HYPOKALAEMIA	0		1	(0.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**2**	**(0.1)**	**1**	**(0.1)**
INTERVERTEBRAL DISC DEGENERATION	1	(0.1)	0	
INTERVERTEBRAL DISC PROTRUSION	1	(0.1)	0	
OSTEOARTHRITIS	0		1	(0.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**1**	**(0.1)**	**3**	**(0.2)**
COLON CANCER	0		1	(0.1)
LUNG ADENOCARCINOMA	0		1	(0.1)
MALIGNANT MELANOMA	1	(0.1)	0	
UTERINE LEIOMYOMA	0		1	(0.1)
NERVOUS SYSTEM DISORDERS	0		2	(0.1)
SUBARACHNOID HAEMORRHAGE	0		1	(0.1)
SYNCOPE	0		1	(0.1)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	**1**	**(0.1)**	**0**	
ABORTION SPONTANEOUS	1	(0.1)	0	
PSYCHIATRIC DISORDERS	**0**		**2**	**(0.1)**
ALCOHOL ABUSE	0		1	(0.1)
BULIMIA NERVOSA	0		1	(0.1)
DEPRESSION	0		1	(0.1)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**0**		**2**	**(0.1)**
DYSMENORRHOEA	0		1	(0.1)
PELVIC ADHESIONS	0		1	(0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**1**	**(0.1)**	**1**	**(0.1)**
ASTHMA	1	(0.1)	0	
PULMONARY EMBOLISM	0		1	(0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**0**		**1**	**(0.1)**
LEUKOCYTOCLASTIC VASCULITIS	0		1	(0.1)
SURGICAL AND MEDICAL PROCEDURES	**1**	**(0.1)**	**2**	**(0.1)**
CAESAREAN SECTION	0		1	(0.1)
INGUINAL HERNIA REPAIR	0		1	(0.1)
TOE OPERATION	1	(0.1)	0	
VASCULAR DISORDERS	**0**		**2**	**(0.1)**
DEEP VEIN THROMBOSIS	0		1	(0.1)
VENOUS THROMBOSIS	0		1	(0.1)

Table 32: Serious Adverse Event Summary (Incidence ≥0% in one or more Treatment Groups) During the Treatment Period – Pediatric Phase 3 Pooled Clinical Trials (All Randomized Subjects)

	MK-7243 2800 BAU n=447 n(%)	Placebo n=434 n(%)
SUBJECTS REPORTING ANY ADVERSE EVENT	**3 (0.7)**	**4 (0.9)**
GASTROINTESTINAL DISORDERS	**0**	**2 (0.5)**
ABDOMINAL PAIN	0	1 (0.2)
VOMITING	0	1 (0.2)
INFECTIONS AND INFESTATIONS	**0**	**1 (0.2)**
APPENDICITIS	0	1 (0.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**0**	**1 (0.2)**
FEMUR FRACTURE	0	1 (0.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**1 (0.2)**	**0**
SYNOVITIS	1 (0.2)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**2 (0.4)**	**0**
ASTHMA	2 (0.4)	0

Although not assessed as treatment related, there were a total of 4 SAEs of asthma in 3 subjects treated with MK-7243. Summaries are as follows:

- One adult subject had been on MK-7243 treatment for 89 days when hospitalized for an asthma exacerbation. The subject completed the trial without any treatment interruptions.
- One 8 year old subject experienced a severe, life-threatening asthma exacerbation on day 94 of MK-7243 treatment. The exacerbation began 10 minutes after ingestion of an herbal mixture for cough. No information was reported regarding the time to onset in relation to MK-7243. The subject was also birch pollen allergic and the herbal mixture ingested was thought to contain birch pollen. The subject was withdrawn from the trial due to the event.
- One 16 year old subject had 2 SAEs of asthma. The first asthma exacerbation started on day 52 of MK-7243. The event led to a hospitalization. MK-7243 was not interrupted. The event was considered to be due to an airway infection. The same subject experienced a 2nd SAE of asthma on day 199 of treatment. The subject was hospitalized and study medication was discontinued at the time of this second serious adverse event.

Discontinuation Due to Adverse Events

Treatment related adverse events leading to discontinuation in the pooled adult Phase 2 and Phase 3 trials are shown in Table 33. A higher rate of discontinuation in the MK-7243 group, compared to placebo was observed. The most common treatment related AEs leading to discontinuation were non-serious local allergic adverse events.

Table 33: Subjects with Discontinuation due to Treatment Related Adverse Events (Incidence ≥0% in one or more Treatment Groups) – Adult Phase 2/3 Pooled Clinical Trials (All Randomized Subjects)

	MK-7243 2800 BAU n=1669 n(%)	Placebo n=1645 n(%0
SUBJECTS REPORTING ANY ADVERSE EVENT	**81 (4.9)**	**15 (0.9)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**1 (0.1)**	**0**
LYMPHADENOPATHY	1 (0.1)	0
EAR AND LABYRINTH DISORDERS	**3 (0.2)**	**1 (0.1)**
EAR CONGESTION	1 (0.1)	0
EAR PRURITUS	1 (0.1)	0
VERTIGO	1 (0.1)	1 (0.1)
EYE DISORDERS	**3 (0.2)**	**0**
EYE PRURITUS	2 (0.1)	0
EYE SWELLING	1 (0.1)	0
LACRIMATION INCREASED	1 (0.1)	0
GASTROINTESTINAL DISORDERS	**43 (2.6)**	**4 (0.2)**
ABDOMINAL DISCOMFORT	0	1 (0.1)
ABDOMINAL PAIN UPPER	0	1 (0.1)
DIARRHOEA	1 (0.1)	0
DYSPEPSIA	2 (0.1)	0
DYSPHAGIA	2 (0.1)	0
ENLARGED UVULA	1 (0.1)	0
GASTROOESOPHAGEAL REFLUX DISEASE	1 (0.1)	0
GINGIVAL SWELLING	1 (0.1)	0
LIP OEDEMA	1 (0.1)	0
LIP PRURITUS	1 (0.1)	1 (0.1)
LIP SWELLING	4 (0.2)	0
NAUSEA	3 (0.2)	2 (0.1)
ODYNOPHAGIA	1 (0.1)	0
OEDEMA MOUTH	7 (0.4)	0
ORAL DISCOMFORT	1 (0.1)	0
ORAL MUCOSAL BLISTERING	2 (0.1)	0
ORAL PAIN	1 (0.1)	0
ORAL PRURITUS	12 (0.7)	0
PALATAL OEDEMA	1 (0.1)	0
SALIVARY GLAND ENLARGEMENT	3 (0.2)	0
SALIVARY HYPERSECRETION	1 (0.1)	0
STOMATITIS	2 (0.1)	0
SWOLLEN TONGUE	6 (0.4)	0
TONGUE DISORDER	1 (0.1)	1 (0.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**11 (0.7)**	**1 (0.1)**
ADVERSE DRUG REACTION	1 (0.1)	0
CHEST DISCOMFORT	5 (0.3)	0
CHEST PAIN	2 (0.1)	0
FATIGUE	1 (0.1)	0
FEELING JITTERY	0	1 (0.1)
MALAISE	1 (0.1)	0
SENSATION OF FOREIGN BODY	1 (0.1)	0
IMMUNE SYSTEM DISORDERS	**6 (0.4)**	**0**
ANAPHYLACTIC REACTION	1 (0.1)	0
HYPERSENSITIVITY	5 (0.3)	0
INFECTIONS AND INFESTATIONS	**1 (0.1)**	**0**
CELLULITIS	1 (0.1)	0
NERVOUS SYSTEM DISORDERS	**3 (0.2)**	**4 (0.2)**
DYSGEUSIA	1 (0.1)	0
HEADACHE	2 (0.1)	3 (0.2)
POOR QUALITY SLEEP	0	1 (0.1)

	MK-7243 2800 BAU n=1669 n(%)	**Placebo n=1645 n(%0**
PSYCHIATRIC DISORDERS	**2 (0.1)**	**1 (0.1)**
ANXIETY	0	1 (0.1)
DEPRESSION	1 (0.1)	0
INSOMNIA	1 (0.1)	0
SLEEP DISORDER	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**22 (1.3)**	**6 (0.4)**
ASTHMA	2 (0.1)	0
BRONCHOSPASM	1 (0.1)	0
COUGH	4 (0.2)	1 (0.1)
DRY THROAT	1 (0.1)	0
DYSPHONIA	3 (0.2)	0
DYSPNOEA	4 (0.2)	1 (0.1)
NASAL CONGESTION	0	1 (0.1)
NASAL DISCOMFORT	1 (0.1)	0
NASAL OEDEMA	0	1 (0.1)
OROPHARYNGEAL PAIN	1 (0.1)	1 (0.1)
PHARYNGEAL ERYTHEMA	2 (0.1)	0
PHARYNGEAL OEDEMA	11 (0.7)	1 (0.1)
PRODUCTIVE COUGH	0	1 (0.1)
RHINORRHOEA	1 (0.1)	0
THROAT IRRITATION	2 (0.1)	1 (0.1)
THROAT TIGHTNESS	3 (0.2)	0
WHEEZING	0	1 (0.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**11 (0.7)**	**4 (0.2)**
ANGIOEDEMA	3 (0.2)	0
PRURITUS	2 (0.1)	1 (0.1)
RASH	1 (0.1)	0
RASH MACULAR	1 (0.1)	0
RASH PRURITIC	0	1 (0.1)
SKIN LESION	1 (0.1)	0
SWELLING FACE	2 (0.1)	0
URTICARIA	3 (0.2)	2 (0.1)
VASCULAR DISORDERS	**1 (0.1)**	**0**
FLUSHING	1 (0.1)	0

Treatment related adverse events leading to discontinuation in the pooled pediatric Phase 3 trials, are shown in Table 34. A higher rate of discontinuation in the MK-7243 group, compared to placebo was observed. The most common AEs leading to discontinuation overall were non-serious local allergic adverse events.

Table 34: Subjects with Discontinuation due to Treatment-Related Adverse Events (Incidence ≥0% in one or more Treatment Groups) – Pediatric Phase 3 Pooled Clinical Trials (All Randomized Subjects)

	MK-7243 2800 BAU n=447 n(%)	Placebo n=434 n(%)
SUBJECTS REPORTING ANY ADVERSE EVENT	**28 (6.3)**	**3 (0.7)**
CARDIAC DISORDERS	**1 (0.2)**	**0**
PALPITATIONS	1 (0.2)	0
EAR AND LABYRINTH DISORDERS	**1 (0.2)**	**0**
EAR PRURITUS	1 (0.2)	0
GASTROINTESTINAL DISORDERS	**20 (4.5)**	**1 (0.2)**
ABDOMINAL DISCOMFORT	1 (0.2)	0
ABDOMINAL PAIN UPPER	1 (0.2)	1 (0.2)
APHTHOUS STOMATITIS	0	1 (0.2)
DYSPEPSIA	2 (0.4)	0
DYSPHAGIA	3 (0.7)	0
GLOSSODYNIA	1 (0.2)	0
LIP BLISTER	1 (0.2)	0
LIP SWELLING	2 (0.4)	0
NAUSEA	1 (0.2)	0
OEDEMA MOUTH	5 (1.1)	0
ORAL DISCOMFORT	2 (0.4)	0
ORAL PRURITUS	3 (0.7)	0
RETCHING	1 (0.2)	0
SWOLLEN TONGUE	2 (0.4)	0
TONGUE BLISTERING	1 (0.2)	0
TONGUE PRURITUS	1 (0.2)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**6 (1.3)**	**0**
CHEST DISCOMFORT	2 (0.4)	0
CHEST PAIN	1 (0.2)	0
NON-CARDIAC CHEST PAIN	1 (0.2)	0
SENSATION OF FOREIGN BODY	1 (0.2)	0
SWELLING	1 (0.2)	0
IMMUNE SYSTEM DISORDERS	**1 (0.2)**	**1 (0.2)**
ANAPHYLACTIC REACTION	0	1 (0.2)
HYPERSENSITIVITY	1 (0.2)	0
NERVOUS SYSTEM DISORDERS	**1 (0.2)**	**1 (0.2)**
HEADACHE	1 (0.2)	0
MIGRAINE	0	1 (0.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**11 (2.5)**	**1 (0.1)**
COUGH	2 (0.4)	0
DYSPHONIA	1 (0.2)	0
DYSPNOEA	3 (0.7)	0
OROPHARYNGEAL PAIN	0	1 (0.2)
PHARYNGEAL OEDEMA	1 (0.2)	0
RHINORRHOEA	1 (0.2)	1 (0.2)
THROAT IRRITATION	6 (1.3)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**3 (0.7)**	**1 (0.2)**
HYPERHIDROSIS	1 (0.2)	0
PRURITUS	1 (0.2)	0
RASH	1 (0.2)	0
RASH ERYTHEMATOUS	1 (0.2)	0
RASH PAPULAR	1 (0.2)	0
RASH PRURITIC	1 (0.2)	0
VASCULAR DISORDERS	**1 (0.2)**	**0**
FLUSHING	1 (0.2)	0

5.4.5 Vital Signs, Labs, and Pulmonary Function Tests

In the Phase 2/3 development program, vital signs and pulmonary function tests were completed at Screening visits and for most trials they were also conducted towards the end of the trial period. Laboratory assessments were generally collected at screening and at the end of the trials; the most recent North American trial included safety laboratory assessments at screening but at no additional time point since prior trials had not revealed an effect on standard chemistry or hematologic parameters. The changes from baseline in vital signs, laboratory parameters and pulmonary function tests observed in subjects on MK-7243 were similar to those for placebo. Evaluation of the values by treatment group revealed no clinically meaningful changes in the values over the course of the trials in both the adult and pediatric populations. There are no trends that would indicate an adverse effect of MK-7243 on these parameters for both the adult and pediatric populations.

5.5 Adverse Events of MK-7243 Pertinent to Immunotherapy Safety Concerns

The allergic adverse events of main interest when administering sublingual allergen to allergic individuals are 1) systemic allergic reactions including anaphylactic shock, 2) local swellings which may result in upper airway obstruction, and 3) asthma-related events.

Systemic allergic reactions including anaphylactic shock and local swellings which may result in upper airway obstruction are summarized below. Asthma related events are discussed in Sec. 5.10.

5.5.1 Systemic Allergic Reactions Including Anaphylactic Shock

Numbers of subjects with systemic allergic reactions are summarized in Table 35. There were a total of 10 systemic allergic reactions in 9 subjects for both the adult and pediatric populations; 8 subjects (with 9 events) on MK-7243, 1 subject (with 1 event) on placebo. Narratives for these events are located in Appendix 4. All events were assessed as non-serious and none were considered severe in intensity. There were no reports of anaphylactic shock among the subjects treated with MK-7243 for up to three years in the clinical trials.

The incidence rate of systemic allergic reactions observed with MK-7243 in the development program combining the adult and pediatric phase 2/3 safety pools is 0.42% (9 events/2116 pts treated).

Table 35: Systemic Allergic Reactions in Adult and Pediatric Subjects Randomized to MK-7243 in Phase 2/3 Clinical Trials (All Randomized Subjects)

	Phase 2 and 3 Adults 2800 BAU N= 1669 n(%)	Phase 2 and 3 Adults Placebo N= 1645 n(%)	Phase 3 Pediatrics 2800 BAU N=447 n(%)	Phase 3 Pediatrics Placebo N=434 n(%)
Any AE of systemic allergic reaction (all mild or moderate in intensity)[ac]	7[b] (0.5)	0	1 (0.2)	1 (0.2)
Treatment related AE of systemic allergic reaction (all mild or moderate in intensity)[ac]	7[b] (0.5)	0	1 (0.2)	1 (0.2)
Serious AE of systemic allergic reaction[a]	0	0	0	0
AE of anaphylactic shock[a]	0	0	0	0

a. MedDRA PT: Anaphylactic reaction; Hypersensitivity; Type 1 hypersensitivity
b. 8 events occurred in 7 subjects.
c. The subjects included in the "Any AE row" and the "Treatment relates AE" row represents the same rather than unique subjects.

Table 36 provides a summary of the systemic allergic events that are tabulated in Table 35. There were no reported systemic allergic reactions in any other trials in the development program. For subjects randomized to MK-7243, six subjects experienced the events while the subject was under supervision in the investigator's office. The 2 subjects who reported symptoms outside of the medical office did not require medical attention. In these two cases, symptoms self-resolved without pharmacologic treatment.

Table 36: Systemic Allergic Adverse Events Summary – Adult Phase 2/3 and Pediatric Phase 3 Pooled Clinical Trials (All Randomized Subjects)

Treatment group	Trial	Subject ID	AE Term	Symptoms of the Reaction	Serious	Onset Day	Duration (Days)	Relationship to Study Medication	Intensity	Treatments for systemic AE	Discontinued Trial
Adults Subjects											
MK-7243 2800	GT-14	4005	Anaphylactic reaction	Swelling of lips, itchy mouth, itchy tongue, itchy throat and dysphagia	No	1	1	Probable	Moderate	Epinephrine, antihistamine	Yes
MK-7243 2800	GT-14	10001	Anaphylactic reaction	Light- headed-ness, headache, sleepiness and itching of ears	No	1	1	Probable	Mild	None	No
MK-7243 2800	GT-14	10003	Anaphylactic reaction	Light-headed-ness, itching of mouth	No	1	1	Probable	Mild	None	No
MK-7243 2800	GT-14	10004	Anaphylactic reaction	Itching under the tongue, itchy throat, itchy ears, itchy nose, sneezing, rhinorrhea, throat irritation	No	1	1	Probable	Mild	Epinephrine, antihistamine	No
			Anaphylactic reaction	Burning sensation under tongue and left ear, rhinorrhea, throat irritation	No	2	1	Probable	Mild	None	No
MK-7243 2800	P08067	103134	Hypersensitivity	Chest tightness and shortness of breath	No	42	2	Probable	Moderate	None	Yes
MK-7243 2800	P08067	101062	Hypersensitivity	Edema on lower lips, redness on corners of the mouth and chin, epigastric discomfort. dizziness.	No	2	1	Possible	Moderate	None	Yes

Treatment group	Trial	Subject ID	AE Term	Symptoms of the Reaction	Serious	Onset Day	Duration (Days)	Relationship to Study Medication	Intensity	Treatments for systemic AE	Discontinued Trial
MK-7243 2800	P05238	11387	Drug hypersensitivity	Chest discomfort, dysphagia, dysphonia, oropharyngeal pain, palatal edema, pharyngeal edema, pruritus, macular rash, throat irritation	No	1	2	Probable	Mild	Epinephrine, antihistamine, prednisone	Yes
Pediatric Subjects											
Placebo	P08067	100056	Anaphylactic reaction	Wheezing, cough and increased nasal congestion	No	1	1	Possible	Moderate	Beta 2 agonist, antihistamine	Yes
MK-7243 2800	P05239	2482	Hypersensitivity	Lip angio-edema, dysphagia due to the sensation of a lump in the throat, and intermittent cough	No	1	1	Probable	Moderate	Epinephrine	Yes

Identification of subjects with potential systemic allergic reactions, including anaphylaxis, according to the diagnostic criteria proposed by NIAID/FAAN was conducted. [66] The review of the database of all AEs to determine if a subject had more than one AE affecting more than one organ system on the same day did not reveal additional subjects with events consistent with anaphylactic shock or systemic allergic reactions.

5.5.2 Local Swellings Which May Result in Upper Airway Obstruction

The number of subjects with oropharyngeal/laryngeal swellings that could have the potential to occlude the upper airway are events of interest and are summarized in Table 37. None of the events of local swelling were considered serious and resulted in upper airway obstruction or respiratory compromise for subjects on MK-7243 2800 BAU.

Fifteen subjects in the adult Phase 2/3 pool and one subject in the Pediatric Phase 3 pool treated with 2800 BAU developed treatment related severe swellings in the mouth or throat and are described in Table 38. In general, the events occurred early in treatment. Approximately half of these subjects ultimately continued in the trials. The subjects who discontinued did not experience an upper airway obstruction, and the events resolved with the termination of treatment.

There was one drug related local swelling that was reported as a serious adverse event on MK-7243 933 BAU (uvula oedema following first intake of the tablet; events self-resolved and the subject completed the trial, Sec. 5.4.4).

Table 37: Local Swellings in Adult and Pediatric Subjects Randomized to MK-7243 in Phase 2/3 Clinical Trials (All Randomized Subjects)

	Phase 2 and 3 Adults 2800 BAU N= 1669 n(%)	**Phase 2 and 3 Adults Placebo N= 1645 n(%)**	**Phase 3 Pediatrics 2800 BAU N=447 n(%)**	**Phase 3 Pediatrics Placebo N=434 n(%)**
Treatment related AE of local swelling[a] (any intensity)	348 (20.9)	29 (1.8)	74 (16.6)	1 (0.2)
Treatment related **severe** local swellings[a]	15 (0.9)	0	1 (0.2)	0
Serious AE of swellings[bc]	0	0	0	0

a. MedDRA preferred terms: Oedema mouth, Oropharyngeal swelling, Palatal oedema, Pharyngeal oedema, Tongue oedema, Swollen tongue, Throat tightness, Laryngeal edema
b. MedDRA preferred terms: Oedema mouth, Oropharyngeal swelling, Palatal oedema, Pharyngeal oedema, Tongue oedema, Swollen tongue, Throat tightness, Laryngeal edema
c. In GT-02, one drug related serious adverse event of uvula oedema in the 933 BAU group was reported. The event was upgraded from non-serious to serious after closure of the database.

Table 38: Severe Intensity Treatment Related Local Swellings during the Phase 2/3 Clinical Development Program (All Randomized Subjects)

Treatment Group	Trial	Subject ID	AE Term	Serious	Onset Day	Duration (Days)	Relationship to Study Medication[a]	Intensity	Other Treatments	Discontinued Trial
Adult Subjects										
MK-7243 2800 BAU	GT-02	26031	pharyngeal oedema	N	1	36	related	severe	none	no
MK-7243 2800 BAU	GT-02	27012	mouth oedema	N	1	20	related	severe	none	yes
MK-7243 2800 BAU	GT-08	332	mouth oedema	N	2	13	related	severe	anti-histamine	no
MK-7243 2800 BAU	GT-08	340	swollen tongue	N	1	31	related	severe	anti-histamine	no
MK-7243 2800 BAU	GT-02	33001	mouth oedema	N	23	31	related	severe	none	no
MK-7243 2800 BAU	P08067	100816	throat tightness	N	10	1	related	severe	none	yes
MK-7243 2800 BAU	GT-08	519	pharyngeal oedema	N	18	1	related	severe	anti-histamine and glucocorticosteroid	yes
MK-7243 2800 BAU	GT-08	605	mouth oedema	N	8	4	related	severe	none	no
MK-7243 2800 BAU	GT-02	72015	swollen tongue	N	74	1	related	severe	epinephrine[a], anti-histamine and glucocorticosteroid	yes
MK-7243 2800 BAU	P08067	102625	mouth oedema	N	20	9	related	severe	none	no
MK-7243 2800 BAU	P08067	102921	mouth oedema	N	17	26	related	severe	none	no
MK-7243 2800 BAU	P08067	103163	pharyngeal oedema	N	2	1	related	severe	none	yes
MK-7243 2800 BAU	P08067	103166	mouth oedema	N	1	56	related	severe	none	no
MK-7243 2800 BAU	P08067	103055	pharyngeal oedema	N	1	8	related	severe	anti-histamine	no
MK-7243 2800 BAU	P08067	108072	pharyngeal oedema	N	9	1	related	severe	none	yes
Pediatric Subject										
MK-7243 2800 BAU	P08067	100039	mouth oedema	N	17	2	related	severe	anti-histamine	yes

a Case narrative is found in Appendix 5.

5.5.3 Evaluation of Epinephrine Administration

Epinephrine was supplied to all subjects as an emergency medication in 3 of the 4 North American trials P05238, P05239, and P08067. In the first US trial (GT-14), epinephrine was not supplied, nor was it supplied to subjects enrolled in the European trials. As an additional measure to identify potential systemic allergic reactions or significant local allergic reactions, all epinephrine administrations were evaluated in all trials (regardless of whether epinephrine was supplied by the Sponsor).

Cases of epinephrine administration were reviewed to determine if systemic allergic reactions were represented in events not reported or encoded as anaphylactic reaction, hypersensitivity reaction, anaphylaxis; anaphylactic shock, systemic allergic reaction; allergic reaction.

The numbers of subjects with reports of epinephrine administration are summarized in Table 39. Epinephrine was utilized a total of 13 times (10 with MK-7243, 3 with placebo) during the clinical development program. Twelve administrations of epinephrine occurred in North American subjects, while one administration was given to a European subject. Five (5) administrations were for AEs considered unrelated to MK-7243 by the investigator, and 8 administrations were for treatment related AEs. Narratives for the reports of epinephrine administration are located in Appendix 5.

Table 39: Epinephrine Administration in Adult and Pediatric Subjects Randomized to MK-7243 in Phase 2/3 Clinical Trials (All Randomized Subjects)

	Phase 2 and 3 Adults 2800 BAU N=1669 n(%)	Phase 2 and 3 Adults Placebo N=1645 n(%)	Phase 3 Pediatrics 2800 BAU N=447 n(%)	Phase 3 Pediatrics Placebo N=434 n(%)
Epinephrine administration	7 (0.4)	2 (0.1)	3 (0.7)	1 (0.2)
Treatment related epinephrine administration	6 (0.4)	0	2 (0.5)	0
Systemic allergic reaction	3 (0.2)	0	1 (0.2)	0
Local swellings[a]	3 (0.2)	0	1 (0.2)	0

[a] In addition to one subject (72015) already included in the local swellings category (Sec. 5.5.2) there are 3 additional subjects who received treatment with epinephrine for local allergic events that were local reactions. Two adult subjects (8010 and 100963) had local allergic reactions that were assessed as moderate in intensity. One pediatric subject (17 years old, 101670) had a severe local allergic reaction which had not been identified in the local swelling of severe intensity category but was identified through the review of epinephrine administrations.

Table 40 summarizes the epinephrine administrations in the clinical program. Of the 13 administrations, 4 subjects were included in the systemic reaction category and already described in Table 35 and Table 36, and 1 subject was already included in the local allergic c swelling category and described in Table 38. There are 3 additional subjects who received treatment with epinephrine for allergic events that were local reactions (2 local allergic reactions of moderate intensity and 1 severe local allergic reaction), all of which are described in Table 40. There were an additional 5 administrations for AEs considered unrelated to MK-7243 by the investigator.

One of the 8 administrations due to a treatment related adverse event occurred outside of a medical facility. One subject self-administered epinephrine at home for a local allergic event. The event was unreported until the subject presented to the site several weeks after the incident for a discontinuation visit. Overall, 3 subjects self-administered epinephrine; 2 of the 3 administrations were for events unrelated to MK-7243 (idiopathic urticaria rash later attributed as due to bed bugs; anxiety).

None of the events which prompted the administration of epinephrine was assessed by the investigators as serious.

Table 40: Epinephrine Administrations during the Phase 2/3 Clinical Development Program (All Randomized Subjects)

Trial	Subject	Dose	Subject Age/Sex	Preferred Term	Symptoms	Day of Onset	Intensity	Serious	Relationship to Study Medication	Outcome
Not Previously Discussed										
GT-14	8010	2800 BAU	46 F	Adverse Drug Reaction	Itchy throat, itchy mouth, dry cough, urticaira on lower lip, red uvula and post nasal drip	1	Moderate	No	Probably	Discontinued trial
P08067	100963	2800 BAU	65 M	Hypersensitivity	Oral symptoms, hoarseness	14	Moderate	No	Probably	Discontinued trial drug/discon
P08067	101670	2800 BAU	18 M	Swelling Throat Irritation	Worsening of swollen feeling; worsening of itchy throat	3	Severe	No	Possibly	Discontinued trial drug/discon
Already discussed in Tables 36 and 38										
GT-02	72015	2800 BAU	30 M	Swollen Tongue	Swollen tongue	74	Severe	No	Probably	Discontinued trial
GT-14	4005	2800 BAU	25 F	Anaphylactic Reaction	Swelling of lips, itchy mouth, itchy tongue, itchy throat and dysphagia	1	Moderate	No	Probably	Discontinued trial
GT-14	10004	2800 BAU	26 F	Anaphylactic Reaction	Itching under the tongue; itching of the throat, ears, and nose; sneezing; rhinorrhea; and throat irritation	1	Mild	No	Probably	Completed
P05238	011387	2800 BAU	50 M	Drug Hypersensitivity	Dysphagia, uvular edema, pharyngeal edema, and flush/macular rash on the chest and back with associated pruritus and chest discomfort	1	Mild	No	Probably	Discontinued trial
P05239	002482	2800 BAU	13 M	Hypersensitivity	Lip angioedema, dysphagia due to the sensation of a lump in the throat, and intermittent cough	1	Moderate	No	Probably	Discontinued trial

Trial	Subject	Dose	Subject Age/Sex	Preferred Term	Symptoms	Day of Onset	Intensity	Serious	Relationship to Study Medication	Outcome
Unrelated to MK-7243 Adverse Events										
P05238	012285	2800 BAU	58 M	Anxiety	Anxiety	4	Moderate	No	Not Related	Discontinued
P05239	002180	2800 BAU	16 M	Viral Infection	Pharyngitis	23	Severe	No	Not Related	Completed
P05239	002873	Placebo	6 M	Wheezing	Wheezing, cough, and suprasternal notch chest retractions	137	Moderate	No	Not Related	Discontinued trial
P08067	102634	2800 BAU	37 M	Idiopathic Urticaria	Idiopathic urticarial due to bed bugs	2	Severe	No	Not Related	Discontinued trial
P08067	103108	Placebo	52 M	Leukocytoclastic Vasculitis	Urticarial vasculitis	50	Severe	Yes	Not Related	Discontinued trial

5.6 Safety of Treatment Interruptions

MK-7243 was designed to be administered beginning with the maintenance dose. If the first administration is tolerated, reintroduction of MK-7243 in subjects who initially tolerated the first dose following a treatment interruption is expected also to be well-tolerated. This was demonstrated initially in GT-01, where there was a planned interruption of approximately 6 weeks prior to re-introducing MK-7243. No systemic and no severe local allergic AEs following re-introduction of MK-7243 were observed.

Within the MK-7243 Phase 2/3 program, there were circumstances in which treatment interruptions for up to 7 days were allowed, such as in the case of oral surgery, viral infections in asthmatic children, or any reason deemed necessary by the investigator. Following a treatment interruption, subjects restarted therapy without medical supervision. A review of subjects who experienced treatment interruptions from the controlled clinical trials does not reveal a risk to interrupting and restarting treatment with MK-7243. Overall, 5.6% of subjects randomized to 2800 BAU (n=93) had study treatment interrupted due to AEs (related and unrelated) in the adult pool and 5.4% in the pediatric pool (n=24). Subjects with new onset allergic AEs have not been identified following interruptions in treatment.

The data from the clinical trial program reveal that restarting therapy after an interruption is well-tolerated. There is no indication that subjects are more likely to have treatment related allergic AEs following a treatment interruption. It is acknowledged that the number of subjects with treatment interruptions is limited in the clinical program.

5.7 Safety of In-Season Treatment Initiation

Studies with subcutaneous immunotherapy indicate that down-titration may be required to decrease risk of allergic reactions during the season and initiation during the season may increase the risk of AEs. [17; 92] As pre-seasonal treatment induction is important for the efficacy of MK-7243, all efficacy trials were designed with a pre-seasonal treatment period. One post-EU-registration market-support study, GT-18 a placebo-controlled study, evaluated the tolerability of starting MK-7243 in season. Approximately 40% of the subjects included in the study reported history of asthma by baseline. Subjects tolerated treatment without the need for dose adjustment and no changes to the adverse event profile were identified. [93] Table 41 reveals an overall AE summary compared to the Adult Phase 2/3 pool. There were no treatment related serious AEs and no treatment related systemic allergic reactions or local swellings of severe intensity in MK-7243 2800 BAU.

In GT-18, subjects were treated for an average of approximately 9 weeks; whereas, subjects in the Phase 2/3 efficacy pool were treated for approximately 24 weeks. Although the treatment periods differed between GT-18 and the Phase 2/3 pooled efficacy trials, most treatment related AEs in the Phase 2/3 trials occurred during the first 4 weeks of treatment. Since treatment related AEs typically occur around the time of MK-7243 initiation, an indirect comparison of AE incidences between the AE summary of GT-18 and the Phase 2/3 pool can be conducted (Table 41).

Table 41: Overall AE Summary for In-Season Dose Initiation (GT-18 Trial) Compared with Adult Phase 2/3 Clinical Trials (All Randomized Subjects)

	GT-18 2800 BAU N=219 n (%)	Phase 2 and 3 2800 BAU N=1669 n (%)
Overall AE	127 (58.0)	1383 (82.9)
Treatment Related AE	97 (44.3)	1111(66.6)
SAE	4 (1.8)	20 (1.2)
Treatment Related SAE	0	0[a]
Discontinued due to AE	6 (2.7)	97 (5.8)
Discontinued due to Treatment Related AE	4 (1.8)	81 (4.9)

a. In GT-02, one drug related serious adverse event of uvula oedema after first table intake in the 933 BAU group was reported. The event was upgraded from non-serious to serious after closure of the database.

5.8 Duration of Observation Period Following First Dose in a Health Care Setting

In the Phase 2/3 trials, subjects remained under investigator supervision for approximately 30 minutes following tablet intake to monitor for the occurrence of adverse events. Subjects not experiencing significant reactions were allowed to leave the study site approximately 30 minutes after the first dose of study drug had been given. The 30 minute observation period was initially proposed based on the current recommendations for observation periods following the administration of subcutaneous immunotherapy. This recommendation is based on historical subcutaneous immunotherapy data indicating that life-threatening anaphylactic reactions after 30 minutes are rare. [17] The time course of systemic allergic reactions in the MK-7243 clinical development program support the 30 minute duration of observation in that all systemic allergic reactions occurred within 30 minutes following tablet administration and no delayed systemic allergic reactions occurring more than 30 minutes following tablet intake were reported.

5.9 Safety of Self-Administration Following Initial Dose in a Health Care Setting

The safety profile of MK-7243 supports self-administration once the first dose has been safely administered under medical supervision in a health care setting (as was done in the majority of the trials with MK-7243 and as is current practice in Europe). Two North American trials (P05238 and P05239) evaluated initial dosing of the tablet for 3 days in the office.

The additional days of dosing in the office beyond the first administration did not identify subjects who had systemic allergic reactions or severe local swellings requiring treatment or emergency intervention, Table 36 and Table 38.

In line with the prescribing recommendations in Europe and supported by the safety database, FDA had agreed that the most recent North American trial P08067 would require that subject should be kept under observation for 30 minutes following the first dose of study medication. Based on the subject's response to the first dose, the administration of subsequent doses under medical supervision could have been conducted at the discretion of the investigator. The safety

data from P08067 identified no changes to the adverse event profile compared to the trials with 3 days of initial in office dosing.

5.10 Safety Subgroup Analyses

The safety of MK-7243 was evaluated in sub-populations based on asthma status, age, race, and allergen-sensitization pattern, for the pooled Phase 2/3 adult population and the pooled Phase 3 pediatric population. The data indicate that the most frequent individual AEs were similar in the subgroups to that of the overall population. Overall, there appeared to be no differences in the AE profile based on these subgroup analyses. These results should be interpreted with caution given the smaller sizes of these subgroup populations.

Use in Subjects with Asthma

There is significant co-morbidity between allergic rhinitis/rhinoconjunctivitis and asthma, and studies with subcutaneous immunotherapy indicate that subjects with asthma may be at higher risk for treatment-related AEs. [94; 95] Safety of subjects with reported asthma was therefore evaluated in the MK-7243 development program.

Subjects with a self-reported history of controlled asthma and an FEV_1 ≥70% of predicted value at the Screening and Randomization Visits were allowed to enroll in the trials. This asthma population could be described clinically as intermittent or mild-to-moderate. Subjects requiring continuous inhaled corticosteroids for asthma outside of grass pollen season were not eligible for enrollment.

As expected, the adverse event rate was higher in MK-7243 treated subjects with reported asthma compared to placebo, similar to trends in the population as a whole (Table 42).

Table 42: Number (%) of Subjects with Adverse Events, by Asthma Status – Adult Phase 2/ 3 Pooled Clinical Trials (All Randomized Subjects)

	MK-7243 2800 BAU Asthma N=415		Placebo Asthma N=383		MK-7243 2800 BAU No Asthma N=1254		Placebo No Asthmas N=1262	
	n	%	n	%	n	%	n	%
Subjects reporting any adverse event	358	86.3	275	71.8	1025	81.7	843	66.8

The percent of pediatric asthma subjects who had AEs was similar to pediatric subjects without asthma in both the MK-7243 and the placebo groups (Table 43). As expected, the adverse event rate was higher in MK-7243 treated subjects with reported asthma compared to placebo, similar to trends in the population as a whole.

Table 43: Number (%) of Subjects with Adverse Events by Asthma Status – Pediatric Phase 3 Pooled Clinical Trials (All Randomized Subjects)

	MK-7243 2800 BAU Asthma N=140		Placebo Asthma N=136		MK-7243 2800 BAU No Asthma N=307		Placebo No Asthma N=298	
	n	%	n	%	n	%	n	%
Subjects reporting any adverse event	115	82.1	106	77.9	252	82.1	237	79.5

For a better understanding of asthma-related events in subjects with reported asthma, two sets of data were compiled: (1) asthma symptoms recorded in the e-diaries by the subject and (2) the physician reported adverse events associated with asthma. The definitions are provided below:

- e-diary asthma symptoms included the following: wheezing, cough, chest tightness/discomfort, or exercise-induced symptoms
- Asthma AEs included the following: dyspnea, wheezing, cough, chest tightness/discomfort, or exercise-induced symptoms

Events recorded through the e-diary and as AEs were compiled (no double-counting) and are presented below for adults and children. The occurrence of asthma-related events in the asthma subgroups was numerically lower in the MK-7243 group, compared with that in the placebo group (Table 44 and Table 45, adults and pediatrics respectively).

Table 44: Summary of Asthma Related Symptoms during the Treatment Period Adult Phase 2/3 Pooled Clinical Trials (All Randomized Subjects with Asthma)

Number and % of Subjects	MK-7243 2800 BAU N=415		Placebo N=383	
	n	%	n	%
e-diary or Adverse Events	323	(77.8)	336	(87.7)
Asthma	19	(4.6)	13	(3.4)
Chest Tightness/Discomfort	259	(62.4)	296	(77.3)
Cough	290	(69.9)	306	(79.9)
Dyspnoea	10	(2.4)	4	(1.0)
Exercise Induced symptoms	251	(60.5)	274	(71.5)
Wheezing	259	(62.4)	285	(74.4)

Table 45: Summary of Asthma Related Symptoms during the Treatment Period Pediatric Phase 3 Pooled Clinical Trials (All Randomized Subjects with Asthma)

Number and % of Subjects	MK-7243 2800 BAU N=140		Placebo N=136	
	n	%	n	%
e-diary or Adverse Events	125	(89.3)	130	(95.6)
Asthma	9	(6.4)	16	(11.8)
Chest Tightness/Discomfort	93	(66.4)	95	(69.9)
Cough	118	(84.3)	125	(91.9)
Dyspnoea	6	(4.3)	3	(2.2)
Exercise Induced symptoms	100	(71.4)	104	(76.5)
Wheezing	89	(63.6)	104	(76.5)

In summary, there has been no indication that treatment with MK-7243 results in worsening of asthma in the study population from the controlled clinical trials. [67; 96] Additionally, a trial in mild to moderate allergic asthma subjects (GT-07 Trial) supported that there is a similar adverse event profile for mild to moderate, controlled asthmatics, as seen in the subgroup of subjects without asthma.

Additional controlled trials in subjects with moderate/severe persistent or uncontrolled asthma have not been conducted with MK-7243.

Age

Adverse events were evaluated in the subgroup of randomized subjects defined by age (5 to <12 years vs. 12 to <18 years in pediatric subjects and 18 to <50 years vs. 50 to <65 years in adult subjects). The population based overall adverse event rate of MK-7243 2800 BAU administered to children and adolescents was similar to that when administered in adults. The overall adverse event rate of MK-7243 2800 BAU was similar between adults 18 to <50 years (83.4%) and 50 to <65 years (78.6%). Children and adults have similar rates of overall AEs (82% compared to 83%, respectively). Children experienced a slightly lower rate of treatment-related AEs compared to adult (58.2% compared to 66.6% respectively).

Additionally, there have been no reported cases of tablet aspiration, a risk which is reduced by the rapid disintegration (within a few seconds) of the tablet at mucosal contact.

Race

A pre-specified adverse event assessment in the subgroup of randomized subjects defined by race (Caucasian/Non-Caucasian) was not performed a priori. A post-hoc analysis on the adult Phase 2/3 and pediatric Phase 3 populations for the treatment-related adverse event profile for Caucasian/Non-Caucasian are shown, Table 46 and Table 47, respectively.

In the adult Phase 2/3 and pediatric Phase 3 populations, Caucasians who received MK-7243 had a numerically higher percent of treatment related AEs than Non-Caucasians who received MK-7243. The percent of adverse events were similar for Caucasian/Non-Caucasian who received placebo.

Table 46: Summary of Treatment-Related Adverse Events (≥0% Incidence) during the Treatment Period by Race Subgroup– Adult Phase 2/3 Pooled Clinical Trials (All Randomized Subjects)

	MK-7243 2800 BAU Caucasian N=1465		Placebo Caucasian N=1449		MK-7243 2800 BAU Non-Caucasian N=204		Placebo Non-Caucasian N=196	
	n	%	n	%	n	%	n	%
Subjects reporting any adverse event	1007	68.7	346	23.9	104	51.0	43	21.9

Table 47: Summary of Treatment-Related Adverse Events (0% Incidence) during the Treatment Period by Race Subgroup – Pediatric Phase 3 Pooled Clinical Trials (All Randomized Subjects)

	MK-7243 2800 BAU Caucasian N=385		Placebo Caucasian N=393		MK-7243 2800 BAU Non-Caucasian N=62		Placebo Non-Caucasian N=41	
	n	%	n	%	n	%	n	%
Subjects reporting any adverse event	235	61.0	96	24.4	25	40.3	8	19.5

Allergen-Sensitization Patterns

A pre-specified adverse event assessment in the subgroup of randomized subjects defined by mono- (Timothy and cross-reactive grasses only) and polysensitization (e.g. sensitized to grasses and other allergens such as, trees, house dust mite, etc.) was not performed a priori. A post-hoc analysis on the adult Phase 2/3 and pediatric Phase 3 populations showed the treatment-related adverse event profile for those who were monosensitized compared to those subjects who were polysensitized were similar for both the adult and pediatric populations, Table 48 and Table 49, respectively.

Table 48: Summary of Treatment-Related Adverse Events (≥0% Incidence) during the Treatment Period by Allergen Sensitization Type Subgroup– Adult Phase 2/3 Pooled Clinical Trials (All Randomized Subjects)

	MK-7243 2800 BAU mono-sensitized N=332		Placebo mono-sensitized N=321		MK-7243 2800 BAU poly-sensitized N=1337		Placebo poly-sensitized N=1323	
	n	%	n	%	n	%	n	%
Subjects reporting any adverse event	225	67.8	85	26.5	886	66.3	303	22.9

Sensitization type was not available for 1 placebo subject.

Table 49: Summary of Treatment-Related Adverse Events (≥0% Incidence) during the Treatment Period by Allergen Sensitization Type Subgroup – Pediatric Phase 3 Pooled Clinical Trials (All Randomized Subjects)

	MK-7243 2800 BAU mono-sensitized N=61		Placebo mono-sensitized N=50		MK-7243 2800 BAU poly-sensitized N=385		Placebo poly-sensitized N=383	
	n	%	n	%	n	%	n	%
Subjects reporting any adverse event	37	60.7	12	24.0	222	57.7	92	24.0

Sensitization type was not available for 1 MK-7243 and 1 placebo subject.

5.11 Long-Term Safety, Withdrawal and Rebound Effects

In the GT-08 Trial, a total of 634 subjects (316 active, 318 placebo) were enrolled and received at least one dose of study medication during the first year of the trial. The AE data over the entire 5-year duration of this trial show that the percentages of subjects reporting new AEs while on MK-7243 decreased over time and rates of AEs in the MK-7243 group became similar to those treated with placebo. The long-term GT-08 trial demonstrated that there were no new safety concerns that emerged during 3 years of continuous treatment or during a 2- year follow-up period.

Withdrawal and rebound effects were not formally studied. However, in the 4th and 5th years of GT-08 Trial, subjects were evaluated for 2 years following cessation of therapy and no unusual AEs were noted during this period, including those potentially related to withdrawal. Among the AEs that occurred during the 4th and 5th year of treatment, only nasopharyngitis was reported more frequently in the subjects in the MK-7243 group than in the placebo group for both years.

5.12 Conclusions Regarding the Safety of MK-7243 from the Clinical Development Program

1. MK-7243 has an acceptable safety and tolerability profile, which has been well-characterized in a clinical program with ~2570 subjects treated for up to three years. This profile is further supported by 6 post-EU-submission market-support clinical trials in 1666 subjects (discussed in Sec. 5.13).

2. There were no reports of anaphylactic shock or of treatment-related death during the clinical development program.
3. The incidence of systemic allergic events including anaphylactic reactions in the clinical development program was low, with no serious, severe, and/or life-threatening events (MK-7243: 9/2116 = 0.4%; placebo 1/2079 = 0.04%).
4. There were no reports of local swellings leading to upper airway obstruction. The local swellings that occurred self-resolved or were managed by standard pharmacotherapy.
5. Overall, the most common allergic adverse events reported in excess of placebo were mild to moderate local allergic reactions such as oral pruritus, throat irritation, mouth edema and ear pruritus.
6. There were no serious treatment related asthma events in the clinical program, which excluded subjects with severe or unstable asthma.
7. The safety profile of MK-7243 was consistent across the clinical development program regardless of age, race, gender, allergen sensitization pattern or asthma status.

5.13 Post EU-Registration Market Support Trials

Six post EU registration market-support studies conducted during the post-approval phase in Europe provide additional safety information. Table 50 provides a description of the six post-EU registration trials. These trials were performed by ALK as life cycle management trials and not as post-approval commitment trials. These trials provided exposure data to treatment with MK-7243 2800 BAU for up to 48 weeks for 1666 subjects and thus provide additional safety data. The primary objective of these trials was to confirm the safety profile of MK-7243 obtained during the controlled clinical development program as well as further characterize the safety and tolerability within a real-life setting. Subjects in these trials were prescribed MK-7243 according to normal clinical practice and in accordance with the approved product label (first dose provided under medical supervision in a health care setting with approximately a 30 minute observation period following dosing). Evaluation of safety and tolerability was based on assessment of AEs (start, stop, severity, seriousness, causality, treatment, and outcome). Data collection occurred during treatment visits that were part of the normal course of care. In this regard, AEs were recorded after the first intake of MK-7243 and at all follow up visits during the trial period. In general, a total of 3 subject visits with approximately 3 months in between visits were planned, and accordingly, subjects were generally followed for a period of 6 months.

Table 50: European Post-approval Trials: Adult Supportive Safety Trials in the Grass Allergy Immunotherapy Tablet

Trial No. N	Trial Title	Design	Subject Population	Relevant Treatment
GT-10 460	A Randomized, Parallel Group, Open, Controlled **Phase 3b** Trial Assessing the Treatment Compliance with GRAZAX® in Subjects with Seasonal Grass Pollen Induced Rhinoconjunctivitis	Subjects received treatment for approximately 6-12 weeks prior to and during the 2006 GPS. Subjects were randomized (1 :1) to either the compliance device or not. All subjects received GRAZAX® (2800 BAU) once daily.	Subjects with grass pollen induced allergic rhinoconjunctivitis, with or without asthma.	460 active
GT-10 Extension 264	Extension of: A Randomized, Parallel Group, Open, Controlled **Phase 3b** Trial Assessing the Treatment Compliance with GRAZAX® in Subjects with Seasonal Grass Pollen Induced Rhinoconjunctivitis	All subjects who completed GT-10 were offered the use of the compliance device until GRAZAX® was commercially available in each respective country, approximately 1 year.	Subjects with grass pollen induced allergic rhinoconjunctivitis who completed GT-10.	264 active
GT-15 628	Observational National Clinical Trial of Safety and Tolerance in Patients Suffering of an Allergic Grass Pollen Rhinitis and Treated by GRAZAX® in Real Life Settings	Multicenter, Observational Trial conducted in France according to the local SPC from Nov 2007 to Dec 2008. All subjects received 2800 BAU once daily.	Adult subjects over 18 who presented with grass pollen allergic rhinitis previously diagnosed (previously performed skin prick test and/or specific IgE assay available) and for which treatment with tablet based specific immunotherapy was initiated.	628 active (avg exposure 9 mo.)
GT-16 78	A Randomized, Double-Blind, Placebo-Controlled **Phase 3b** Trial Investigating Changes in Immunological Parameters and Cutaneous reactivity Induced by Short Course Immunotherapy with ALK Grass Tablets	Subjects received treatment for approximately 2 to 4 months prior to and during the 2007 GPS. Subjects were randomized (2 :1) to GRAZAX® (2800 BAU) or placebo once daily.	Subjects age 18-68 with at least 1 year history of rhinitis (with or without concurrent asthma) to grass pollen. Positive skin prick test (wheal diameter $\geq$3mm) documented positive IgE against grass pollen $\geq$ class 2	52 active, 26 pbo
GT-17 261	A Randomized, Parallel-Group**, Phase 4** Open Trial Evaluating Compliance to the Treatment with GRAZAX® tablets in Patients with Seasonal Grass Pollen Rhinoconjunctivitis	Subjects were randomized (1 :1) to either receive a compliance device or not. All subjects received GRAZAX® (2800 BAU). Treatment occurred for 48 weeks plus a 1 week post-treatment visit	Subject with a history of grass pollen induced allergic rhinoconjunctivitis (with or without asthma); received treatment during the previous grass pollen season. Positive skin prick test (wheal diameter >3mm) documented positive IgE against grass pollen > class 2	261 active

Trial No. N	Trial Title	Design	Subject Population	Relevant Treatment
GT-18 276	A **Phase 3b** Trial Assessing the Pharmacodynamic Effect and the Tolerability of GRAZAX® Treatment Initiated in the Grass Pollen Season in Subjects with Seasonal Grass Pollen Induced Rhinoconjunctivits	Treatment was at least 8 weeks during the 2008 GPS. Subjects were randomized (4 :1) to GRAZAX® (2800 BAU) or placebo once daily.	Subjects with a history of moderate to severe rhinoconjunctivitis for at least 2 years with skin prick test wheal ≥ 3 mm and positive specific IgE to *Phleum pratense* ≥ class 2 (≥0.7 kU/L); FEV1 > 70%.	219 active, 57 pbo
GT-19 46	A **Phase 3b** trial Evaluating the Tolerability of GRAZAX® treatment in combination with Antihistamine in Subjects with Seasonal Grass Pollen Induced Rhinoconjunctivitis	Subjects reporting treatment related allergic AEs at screening after intake of GRAZAX® were randomized (1:1) to 1 of 2 treatment procedures. Subjects received concomitant antihistamine, matching pbo and GRAZAX® (2800 BAU) for 1 day separated by approximately 2 week washout in a crossover design.	Adult subjects with at least 2-yr history of grass pollen induced allergic rhinoconjunctivitis Treatment-related local application site reaction in mouth and throat after intake of MK-7243 at screening.	46 active
			Total Active Total Placebo	1666 83

5.13.1 Summary of Adverse Advents of Interest for MK-7243 from Post-Approval Trials

Systemic Allergic Reactions:

There was one treatment-related, serious event of an anaphylactic reaction assessed as life-threatening from GT-10 Trial on Day 1 of MK-7243. The subject had a history of asthma and developed local allergic symptoms as well as asthma symptoms within 1 minute of tablet administration. The subject responded to treatment (epinephrine, beta-2 agonist and prednisolone per os [p.o.]) at the clinical site. There were no other reported events of systemic allergic reaction(s), including Anaphylactic or Hypersensitivity reactions. Based on this result the incidence of systemic allergic reactions is 0.06% (1/1666) in the post-approval trials.

Serious Local Allergic Swellings:

There were no serious local swellings.

Serious Asthma Related Events:

Two treatment related SAEs of asthma were identified out of a total of 1666 subjects on active treatment. Both subjects discontinued study medication and both subjects' AEs resolved. A brief description of the events is provided below:

- GT-10, Subject 126, a 42-year old female with a history of active asthma and treated with bricanyl (terbutaline), seretide (fluticasone propionate + salmeterol), singulair

(montelukast sodium), and unixan (theophylline). This subject experienced recurrence of oral pruritus of moderate severity for approximately 2 months. No concomitant treatment was given for this event. Approximately 5 weeks following treatment start, the subject developed an asthma exacerbation. Ten days following the start of the asthma exacerbation, the subject was treated with prednisone. The event was judged serious and severe with a probable causal relationship to study medication. The subject withdrew due to the event on Day 10 of prednisone and approximately 2 months after starting MK-7243.

- GT-15, Subject 151-002, a 28-year old male with a history of asthma induced by house dust mites and treated with salbutamol, experienced an asthma attack with malaise and dyspnea 10 minutes after the 1st intake of MK-7243. The subject was treated with ebastin and salbutamol. During the following hours in the physician's office, the asthma attack resolved. Study medication was discontinued on the same day.

6 OVERVIEW OF SAFETY POST-MARKETING EXPERIENCE

The safety profile of MK-7243 is supported by over 7 years of experience from marketed use in Europe and 24 observational studies of real world use. The estimated patient exposure inclusive of the post-approval surveillance studies in the EU and the marketed use is 134,000 patient-treatment years since launch in Europe in 2006.

ALK-Abelló A/S is the sponsor in Europe and they provide the ongoing monitoring of post-marketing use safety. The post-marketing experience has further characterized the safety profile of MK-7243; however, no new risks beyond allergic reactions have been identified. The adverse event profile is consistent with the known allergic reactions associated with allergen immunotherapy, which include systemic allergic reactions of varying intensity. Local adverse events of allergic nature are generally reported as non-serious. Serious adverse events of interest are uncommon and generally similar to what has been observed in clinical trials. Rarely, clinically important adverse events such as systemic allergic reactions, including some with anaphylactic shock/hemodynamic changes, are reported but have been manageable with standard pharmacotherapies. The post-marketing experience with MK-7243 supports the safety results seen in the clinical development program and demonstrates favorable benefit risk in real world use.

6.1 Post-Marketing Data

The post-marketing data are composed of 1) reports from 24 Observational/Non-Interventional Surveillance studies and 2) pharmacovigilance data from use of MK-7243 in the European market. Post-marketing reports, since they are provided voluntarily from treating physicians and other health care providers, have limitations as compared to data from clinical trials. Reports are limited with regards to completeness of information regarding any aspect of the adverse event, including but not limited to incomplete or missing information on past medical history, comorbidities, drug therapies, or even crucial information about the adverse events themselves that are being reported. Physician assessment of severity is subjective, not uniformly ascertained and such assessment is often not provided.

Regulatory criteria for "serious" is employed to classify post-marketing safety reports as serious or non-serious similar to what has been described for clinical trials. Events reported in spontaneous cases are captured as MedDRA PTs that match the verbatim clinical event described by the reporter. The sponsor used a consistent selection of MedDRA PTs to identify potential post-marketing reports of Events of Interest for MK-7243. Systemic Allergic Reactions included anaphylactic reactions, anaphylactic shock and hypersensitivity cases (LLT of systemic allergic reaction was used if signs and symptoms involved 3 different system organ classes [SOCs]); Local Allergic Events included specified PTs as reported in the case[3]; Asthma selected PTs as reported in the case[4] were used.

6.2 Post-Marketing Surveillance Studies

As noted above, 24 non-interventional, observational, multicenter post-marketing surveillance studies were initiated as of the cut-off date. Of the 24 studies, 20 studies have been completed. An overview of these studies is in Appendix 6.

Results of these studies, involving approximately 8,500 patients, provide an opportunity to assess frequency of occurrence of the clinical events of interest in a real world use setting. The key limitations of such data is that the level of clinical details obtained to assess severity of events is often missing since data are often obtained retrospectively and are observational in nature.

In these studies a review of the serious adverse events reported demonstrated that:

- Treatment with MK-7243 was generally well tolerated
- The type and frequency of reported AEs were consistent with the safety profile observed in the randomized controlled clinical trials.
- Serious adverse events of interest were uncommon (Table 51).

[3]Local Allergic Reaction with Potential for Airway Compromise: Choking sensation, dysphagia, dysphonia, laryngeal oedema, larynx irritation, oropharyngeal swelling, pharyngeal oedema, stridor, throat tightness, and upper airway obstruction

[4]Asthma: Asthma, asthma exercise induced, bronchial hyperreactivity, bronchial obstruction, bronchospasm, cough, dysphonia, dyspnoea, forced expiratory volume decreased, hyperventilation, obstructive airways disorder, peak expiratory flow rate decreased, prolonged expiration, wheezing, asthma late onset, asthmatic crisis, reactive airways dysfunction syndrome, and status asthmaticus

Table 51: MK-7243 Adverse Events of Interest in Post-Marketing Surveillance Studies

	N=~8,500
Total Number of SAEs	37 (~0.43%)
Serious Allergic Reactions	26 (~0.31%)
Serious Systemic Allergic Reactions[b]	6 (~0.07%)
Anaphylactic shock	0 (~0.00%)
Serious Events Treated with Epinephrine[a]	5 (~0.06%)
Serious Local Events[b]	9 (~0.11%)
Serious Asthma Events[b]	20 (0.23%)

[a] The patients treated with epinephrine are the same patients who had the serious systemic allergic reactions or local events. They are not unique patients.
[b] Events of interest reported in the serious allergic reaction reports, individual patients may have had more than one event (e.g. systemic allergic reactions, local events and asthma events).

A total of 37 patients on MK-7243 participating in the surveillance studies were reported to have serious adverse events as noted in the table above. These SAEs of clinical interest are further discussed below:

Systemic Allergic Reactions

- Six (0.07%) patients had serious systemic allergic reactions reported as anaphylactic reactions or hypersensitivity reactions. None were reported by the treating physician as anaphylactic shock or were associated with clinically important hypotension, defined as systolic blood pressure (BP) of less than 90 mm Hg (for adults; for children the BP is age specific) or greater than 30% decrease from that person's baseline.
  - Three of these 6 patients had the systemic events at the first dose with the other patients experiencing the events beyond day 14.
  - 1 case was considered by the reporter to be potentially life-threatening but treatment included outpatient oral antihistamines and inhaled steroids.
  - Epinephrine was used to treat 3 of the systemic events.

Local Allergic Reactions

- Nine patients (0.11%) had serious local allergic reactions that resulted in swelling in and around the mouth with no respiratory compromise. Three of these events occurred in conjunction with systemic reactions described above.
  - The remaining 6 cases of serious local reactions showed time-to-onset after initiation of MK-7243 on Day 1 in 3 cases and, in the remaining 3, events occurred day 7 or beyond.
  - These 6 events were typically treated with an anti-histamine and/or corticosteroid. One patient received inhaled epinephrine and one received subcutaneous epinephrine.

Asthma Events

- Twenty patients (0.23%) had asthma symptoms, including 5 of the 6 previously described systemic allergic reactions. None of the asthma events were associated with respiratory compromise and all patients with asthma events responded to standard pharmacotherapy.
  - The time-to-onset after first exposure to MK-7243 in the remaining 15 cases with asthma in the absence of systemic reactions ranged from Day 1 (3 reports) to Day 51 of treatment. The majority (11/15 reports) occurred during the first month of therapy, while 4 occurred during the 2nd month of treatment.
  - 10/15 reports noted that patients had pre-existing asthma, most of which were characterized as allergic or seasonal.
  - One case of asthma without systemic signs or symptoms was considered by the reporter to be potentially life-threatening, but the patient had exposure to another allergy trigger and the only treatment was self-administered inhaled beta$_2$-agonist and cromolyn. The patient continued therapy.

Deaths

- No treatment related death was reported in these studies. One report of a fatal outcome that was likely due to primary ischemic cardiac event was received. The patient had prior 6.5 months of treatment without an event. At the time of his cardiac arrest, no allergic reactions, signs or symptoms were noted. In light of antecedent exercise induced pre-cordial pain, ischemic heart disease is likely and no association with drug treatment is evident.

In conclusion, the surveillance study data, representative of real world use, are qualitatively consistent with the overall safety profile of MK-7243 2800 BAU seen in the clinical development program. Importantly, in these studies, occurrences of serious adverse events were uncommon and those of systemic (0.07%) or local allergic reactions (0.11%) even less common. Additionally, there were no systemic reactions that had clinically important hemodynamic changes. These events were all managed with standard pharmacotherapies and all patients recovered from their allergic reactions.

6.3 Post-Marketing Experience Spontaneous Reports

A search of the ALK global safety database was conducted for all serious spontaneous adverse event reports received regarding the use of MK-7243, cumulative through 30Apr2013. As previously noted, pharmacovigilance data that is reported spontaneously have a number of limitations related to case information. Additionally, spontaneous safety data is not the appropriate data to estimate frequency of event occurrence due to the combination of incomplete capture of adverse experiences in a voluntary environment and the lack of ability to reliably determine true exposure to the product. Therefore, spontaneous data do not allow for estimations of incidence rates.

As of the 30Apr2013 database lock for this submission, a total of 1,467 spontaneous AE reports have been received since marketing approval in 2006. Of these, 139 were serious reports and none had fatal outcomes. Of the 139 serious reports, 109 described allergic-type

events; the most frequent of which were asthma-like symptoms, such as dyspnea, or local allergic reactions of the mouth and/or pharynx. This was true of reports for both adult and pediatric patients. To further evaluate the cases that may represent more serious allergic type reactions, those reports of systemic allergic reactions as defined previously are presented first, followed by cases describing other allergic reactions and lastly, all cases in which epinephrine was administered.

Systemic Allergic Reaction including Anaphylactic Shock

Thirty-seven serious spontaneous reports of a systemic allergic reaction (See Sec.6.2, Post-marketing Surveillance Studies for criteria) have been received in the post-marketing period. Of the 37 reports, the number of days between first exposure to MK-7243 and the reaction could be determined in 33 reports.

Among these 33 reports, the systemic allergic reaction occurred on the first day of exposure to MK-7243 (Day 1) in 70% of the patients (23/33). Of the 10 reports experiencing the systemic allergic reaction after Day 1, two events were on Day 2, 6 beyond 7 days but within the first 30 days of treatment, and 2 beyond 30 days. In all reports of events occurring after Day 1, symptoms appeared to be noticed quickly and appropriate medical treatment was readily obtained.

There has been one spontaneous post-marketing case reported by the treating physician as an event of anaphylactic shock among the 37 reports of systemic allergic reaction received for MK-7243. The event occurred on the first day of treatment within 2 minutes of first exposure to MK-7243 while under observation in the physician's office. The symptoms responded within 10 minutes to treatment with epinephrine and corticosteroids with full recovery and release from the clinic after 2 hours of observation.

In the 37 cases of serious systemic allergic reactions received, excluding the case reported as shock above, there were 15 cases reporting hypotensive events . These cases were reviewed to further understand the potential clinical significance of these events.

- Of these 15 cases of hypotensive events in the setting of a systemic allergic reaction,
  - 4 cases BP values were not provided
  - 3 cases with BP decreased, but systolic BP remained above 90 mmHg and did not change more than 30 % from baseline.
  - 8 cases of hypotension with systolic BP ≤ 90 mmHg; however, in three cases, as described below, additional information was provided.
    - 2 cases, the treating physician reported that these events were not consistent with shock.
    - 1 case, the BP change was reported by the treating physician as due to treatment for the allergic reaction.
- Nine of these cases occurred on Day 1 within minutes of exposure to MK-7243.
- Six patients received hospital care.
- Seven patients received epinephrine and the route of administration reported in 5 as intramuscular/subcutaneous (IM/SC, 3) and Inhalation (2).

In all cases, the patients responded to standard pharmacotherapy (e.g. steroids and antihistamines with or without epinephrine) and fully recovered.

Of the 21 remaining reports of systemic allergic reactions, 3 reports had an assessment by a reporter as potentially life threatening; one of which involved a primarily local reaction accompanied by dyspnea. In this case, the treating physician in the ER determined that the event was not life threatening. The other 2 reports described systemic reactions with asthmatic symptoms as the event of primary concern. One was treated with nebulized $beta_2$- agonist, oral anti-histamines and steroids and recovered in 5 minutes; while in the other case, treatment was not reported but the patient was observed for 12 hours. These potentially more significant systemic allergic reactions all occurred while the patients were under medical observation. None of the patients required assisted ventilation or intubation and all recovered.

Serious Reports of Other Allergic-Type Reactions

Of the 72 serious reports received cumulatively of allergic reactions that were not characterized as systemic allergic reactions, asthma or asthma-like symptoms were the most frequent adverse experience described; whether reported in isolation or combined with local allergic reactions. One of these cases was reported as life-threatening and described a patient dysphonia and tongue edema experienced on Day 1 of treatment that was treated with steroids and antihistamines. A second case of angioedema and bronchospasm, although not clinically reported as life threatening since only oral therapy was required, was assessed by a regulatory agency as life-threatening. These reactions, which have a variety of clinical presentations, have been manageable with readily available therapies and all patients had a full recovery.

Epinephrine Use in Spontaneous Reports

To further capture potential cases of medical importance, the ALK database was searched for all cases in which use of epinephrine to manage an adverse reaction have been received cumulatively for MK-7243. Twenty-five of the reports were received as serious and are included in the above mentioned cases; while the remaining 12 were received as non-serious reports.

25 Serious Reports involving Epinephrine Administration

Within the 25 serious reports of events requiring epinephrine use, distribution by event-type grouping and route of epinephrine administration are as follows:

- Systemic allergic reaction (17): 1 intravenous (IV); 7 IM/SC; 5 Inhaled; 4 Unknown Route
- Other Allergic Reactions (8): 5 IM/SC; 3 Inhaled

12 Non-serious Reports of Epinephrine Administration

The distribution by event-type grouping and route of epinephrine administration are as follows:

- Systemic allergic reaction (2): 1 SC; 1 Unknown Route
- Other Allergic Reactions (10): 1 IV; 5 IM/SC; 1 Inhaled; 3 Unknown Route

In all instances except one, MK-7243 was clearly noted to have been delivered in a health care setting. The exception is one case of a serious systemic allergic reaction in a patient with "severe" allergic rhinitis who had an epinephrine pen on hand that had been prescribed because of an anaphylactic reaction with subcutaneous immunotherapy for grass pollen SCIT that occurred before initiating MK-7243. No further information was provided and it is not clear if the epinephrine was self-injected, administered by a family member, or by a health care professional.

Non-Allergy Related Serious Reports

Of the 139 serious adverse event reports received cumulatively for MK-7243, 30 did not include a description of an allergic event. Most were isolated reports of various events involving different organ systems; none indicated a new safety concern for MK-7243.

In summary, the majority of the spontaneous reports of allergic reactions described onset of symptoms early in therapy, with a majority occurring on the first day of medication use. Regardless of the timing of the onset of these allergic events, they were managed by pharmacologic treatment whether the events occurred within or outside of a medical setting and there were no reports of assisted ventilation or intubations. In general, the events observed in the spontaneous reports were similar to those observed in the clinical program. However, there were cases of systemic allergic reactions with clinically important hypotension, including one case reported as anaphylactic shock following first tablet intake, indicating that MK-7243 may induce anaphylaxis/anaphylactic shock, which is a known class effect of allergen immunotherapy.

Conclusions from Post Marketing Experience

Serious systemic allergic reactions are uncommon in real world use as demonstrated by only 6 reports in approximately 8,500 patients in observational studies, for an incidence rate of 0.07%. Systemic allergic reactions with clinically important hemodynamic changes observed in post-marketing are rare as none have been observed in the observational studies of approximately 8,500 patients. These events have generally occurred on the first day of exposure to MK-7243 during the 30 minutes of observation in a health care setting. The few events that occurred later than the first day were readily detected and managed by standard care. Other allergic type reactions were also uncommon, readily detected and readily managed.

6.4 Overview of Safety of MK-7243 Compared to Subcutaneous Allergy Immunotherapy

There are no reported head-to-head comparison trials of grass SCIT to SLIT. In the absence of such data, summarized below for reference is information from datasets that describe what has been published regarding the safety profile of SCIT for both grass and other inhalant allergens.

Clinical Trial Data with Subcutaneous Timothy Grass Immunotherapy

The largest SCIT trial, i.e. the UK-22 trial (N=410), included a Timothy grass allergic population comparable to the MK-7243 trials and administered a similar grass extract subcutaneously. [31] The rate of systemic allergic reactions was evaluated. Sixty-six of the 203 subjects (32.5% as compared to 16.5% on placebo) treated with 3,700 BAU developed systemic allergic reactions within the first 60 minutes of the injection. No subjects experienced anaphylactic shock.

Pharmacovigilance Data with Timothy Grass Immunotherapy

Pharmacovigilance data from 01Jan2006 to 30Apr2013 and originating from the ALK global safety data base of Grass Alutard® which is a similar *Phleum pratense* grass extract licensed for subcutaneous immunotherapy, found a total of 21 events reported as anaphylactic shock with Grass Alutard® 225 (*Phleum Pratense*) (approximately 47,000 patient treatment-years). As noted above, 1 event reported as anaphylactic shock with MK-7243 (approximately 134,000 patient treatment-years) was received.

However, the data must be interpreted with caution as it reflects only events as described by the reporting health care provider. The assessment does not account for potential under-reporting of events for either product and the patient treatment years need to be interpreted appropriately as SCIT is expected to have a lower number of doses per patient since the product is administered approximately every 8 weeks compared to MK-7243 exposure estimate which assumes daily continuous use.

SCIT vs. SLIT Safety Data with Other Allergens

Direct evidence of SLIT being a safer treatment than SCIT is also based on one small (N=71) head-to-head study comparing birch SLIT vs. SCIT. In this study, SCIT resulted in five cases

of systemic reaction grade 3 (i.e. non-life-threatening systemic reactions (urticaria, angio-oedema or severe asthma with a reduction of 20% or more in peak expiratory flow(PEF)), responding well to treatment), and one grade 4 reaction (i.e. anaphylactic shock (rapidly evoked reaction that included itching, flushing, erythema, bronchial obstruction, requiring intensive treatment)). Two cases were treated with epinephrine. No grade 3 or 4 reactions and no reactions requiring epinephrine administrations occurred in the SLIT group. [89]

In the 2009 WAO Position paper on SLIT it is stated that sublingual immunotherapy is generally considered to be better tolerated than SCIT. [18] This assessment was based on a comprehensive review of 66 SLIT studies that provided some information on safety and tolerance, representing 4,378 patients who received approximately 1,181,000 SLIT doses. In the studies that specified the type of reaction, 169 of 314,959 (0.056% of doses administered) were classified as systemic allergic reactions. [97] To provide some perspective based on indirect comparisons SCIT is associated with a risk of systemic allergic reactions and the rate with non-accelerated schedules (single dose increase per visit) has been reported to range between 0.05 to 7% of injections and 0.8 to 46.7% of patients (mean, 12.92%). [25] Based on more recent reviews injection-related systemic reactions reportedly occur in 2% to 7% of patients receiving conventional build-up and maintenance injections of inhalant allergen immunotherapy in North America. [30]

Based on indirect evidence from the most recent 2013 updated meta-analysis including seventeen new placebo-controlled randomized controlled trials (RCTs) evaluating predominantly grass allergens for SCIT and 11 for SLIT by Dretzke et al., systemic reactions were less common for SLIT, and most were graded as mild or moderate in intensity. [32] Furthermore, 19% of systemic reactions after SCIT treatment were considered to be severe compared with only 2% of systemic reactions after SLIT (based on studies that reported this information). [32] No fatalities were reported with either therapy. Discontinuations due to adverse events (approximately 3%) were similar between the interventions. [32]

Fatal reactions have occurred with subcutaneous immunotherapy. One estimate has been that fatal reactions with subcutaneous immunotherapy occur at a rate of 1 death per 2 million injections. [98; 99] It is notable that fatality reports associated with subcutaneous immunotherapy have declined over the past 12 years with 6 fatalities related to subcutaneous immunotherapy reactions between 2001 and 2007 and no fatal reactions indirectly or directly identified between 2008 and 2013. [92] To date, no drug related fatalities have been reported for SLIT. [32]

In summary, there are no trials that directly compare grass SLIT to SCIT and therefore definitive conclusions of the comparative safety of grass SLIT to SCIT cannot be drawn. However, there is indirect evidence that suggests that generally SLIT may have a lower risk of systemic allergic reactions than SCIT with the caveats that all immunotherapy has a potential risk of serious systemic allergic reactions including anaphylactic shock and that the overall market experience with SLIT tablets are limited.

6.5 Conclusions Regarding the Clinical Safety of MK-7243

1. MK-7243 2800 BAU has an acceptable safety and tolerability profile that has been well-characterized in a clinical program with ~2570 subjects treated for up to three years. This profile is further supported by 6 post-EU-submission market-support clinical studies in 1666 subjects and an estimated 134000 patient treatment years which included 24 post-approval studies in approximately 8500 subjects and 6+ years of post-marketing experience. The safety profile of MK-7243 was consistent across the clinical development program regardless of age, race, allergen sensitization pattern or asthma status.
2. The risk of systemic allergic events including anaphylactic reactions is low. Systemic allergic reactions generally occurred within 30 minutes after the first dose. In the clinical development program there were no treatment-related serious, severe, and/or life-threatening systemic allergic events with 2800 BAU MK-7243.
3. The most common treatment-related allergic adverse events are mild to moderate local allergic reactions such as oral pruritus, throat irritation, mouth edema and ear pruritus. While local swelling has the potential to result in airway obstruction, no cases of upper airway obstruction occurred in the clinical development program
4. Adverse events of allergic reactions that have been reported in the 7 years of European marketed use are what can be expected for an allergen immunotherapy. Most of these allergic events were characterized by asthma symptoms, such as dyspnea, cough and shortness of breath, and local allergic reactions of the mouth and throat. Systemic allergic reactions are uncommon and systemic allergic reactions with clinically important hemodynamic changes observed in post-marketing are rare. All serious systemic allergic reactions including events with hypotension and one event reported as anaphylactic shock, resolved with pharmacologic therapies. Regardless of whether the onset was medically observed or not, all reported events were readily detected and appropriate medical care was obtained.

7 RISK MANAGEMENT STRATEGY

A code of practice for the administration of specific immunotherapy has generally been adopted by practioners to ensure the minimization of any untoward effects during administration. [17]

MK-7243 is intended for self-administration at home following an initial supervised dose. Through product labeling and marketing to physicians experienced in the diagnosis and treatment of allergic diseases, the Sponsor plans to provide information to both the health care practitioners and patients about the potential for rare, but possibly severe systemic reactions, including anaphylaxis and anaphylactic shock. The following precautions when prescribing MK-7243 are recommended:

- The first dose should be given by a physician with experience in the diagnosis and treatment of allergic diseases and should only be administered in a healthcare setting under the supervision of a physician prepared to manage a severe systemic or a severe local allergic reaction;
- 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;

- Patients with unstable/uncontrolled asthma should not be treated with MK-7243;
- For patients with difficulty breathing or whose asthma becomes difficult to control, treatment with MK-7243 should be interrupted and a health care provider consulted immediately to evaluate the continuation of treatment;
- In patients with oral wounds or following oral surgery, treatment with MK-7243 should be interrupted;
- Co-administration with other immunotherapy has not been studied; and
- Treatment of systemic allergic reactions may require the administration of medications, including epinephrine, antihistamines, inhaled bronchodilators, and/or corticosteroids.

8 BENEFITS AND RISKS CONCLUSIONS

Allergic rhinitis is a common, chronic disorder of young and old, and although a number of drug therapies have been approved for its treatment, a significant medical need remains unmet. Current pharmacotherapies for allergic rhinitis and conjunctivitis are relatively safe and modestly effective at controlling symptoms temporarily, but do not change the chronic course of disease or have a long-lasting effect. Many patients reported inadequate response to available pharmacotherapies or dissatisfaction with the overall benefit of pharmacotherapy.

Subcutaneous, allergen immunotherapy is a well-established, effective, and generally safe treatment option for allergic rhinitis and conjunctivitis when administered in the physician office. In contrast to pharmacotherapy, immunotherapy modulates the immune system, offering long-term effectiveness and disease modification. Presently in the US, when a physician begins a patient on subcutaneous immunotherapy, it is typically administered in a healthcare setting weekly for 3-6 months during the build-up phase followed by monthly in-office injections for at least 3 years. Since this regimen is not accepted as a practical choice by many patients or their families, many patients with allergic rhinitis who could benefit from immunotherapy choose to go untreated.

MK-7243 is a novel formulation of allergen immunotherapy to be self-administered (following first dose in office) sublingually daily for the treatment of grass pollen induced allergic rhinitis with or without conjunctivitis, and represents a new class of medication for regulatory approval in the United States. Availability of MK-7243 would increase patient access to immunotherapy treatment for their grass pollen induced allergic rhinitis. Unlike SCIT dosing, MK-7243 begins with the maintenance dose and does not require up titration. This formulation represents a well-characterized, alternative approach to the subcutaneous administration of allergen immunotherapy. Such an approach offers disease modifying treatment, and may be an appealing option particularly for those patients (1) who do not benefit from or do not tolerate current pharmacotherapy, (2) who do not have the ability to commit to a rigorous physician visit schedule or (3) who prefer not to receive recurrent injections (e.g. children).

Benefit Risk Profile of MK-7243

The primary benefits of MK-7243 are reduction of Timothy and related grass -induced AR/ARC symptoms and symptomatic medication use after a short induction period prior to the first grass season. Additionally, sustained and clinically meaningful efficacy is maintained during 3 years of daily treatment with a durable disease-modifying effect for at least 2 years

after treatment. The sublingual administration of MK-7243 after the first dose under medical supervision is a convenient and simple form of self-administered immunotherapy. MK-7243 is a first in class allergen immunotherapy drug that has undergone extensive pharmaceutical development and regulatory review.

The efficacy of MK-7243 was studied in six large Phase 3 placebo-controlled trials in adults and children with Timothy grass-induced allergic rhinitis/rhinoconjunctivitis. The treatment effect, which varied dependent on the severity of the grass pollen season, was clinically meaningful both in children and adults and across subgroups as assessed by gender, race, asthma- and mono- vs. poly-sensitization (sensitization to both grass and non-grass allergens, e.g. trees and weeds) status. The efficacy was evident across geographic regions (EU vs. North America) and multiple seasons with highly variable pollen counts. Consistent and meaningful effects were also demonstrated across all secondary endpoints including the individual symptom, medication, and RQLQ scores. The clinical findings were supported by significant changes in immunological parameters including IgG4 blocking antibodies.

Professional society guidelines state subcutaneous immunotherapy is clinically effective. [18; 17; 50] Guidance on the minimum difference in TCS that is noteworthy is yet to be defined. However a minimal magnitude of efficacy of 20% has been proposed to be clinically relevant. [58; 21] A key finding in the development program was the significant and consistent improvement in TCS with MK-7243 relative to placebo (observed in 5 out of 6 trials), ranging from 21% to 34%, which is consistent with the recommendation for a clinically meaningful difference for SLIT by WAO. Although, there are no studies, which directly compare the efficacy of MK-7243 to grass SCIT, data are available supporting that sublingual immunotherapy is similarly efficacious as SCIT.

There is indirect evidence from a study evaluating a similar Timothy grass pollen extract administered as subcutaneous injection therapy. [31]This trial compared two doses of subcutaneous Timothy grass extract 3700 BAU (the maximum recommended maintenance SCIT dose) and 370 BAU to placebo. 3700 BAU administered by the subcutaneous route demonstrated a reduction in daily symptom scores of 29% compared to placebo. The patient population and pollen season in this trial were comparable to that in the first year of the GT-08 trial evaluating 2800 BAU of MK-7243. [31] The reduction in daily symptom scores with MK-7243 was 31% as compared to placebo, suggesting similar efficacy of these comparable Timothy grass pollen extracts regardless of the route of administration.

Furthermore, a recent updated systematic review by Dretzke et al. using Cochrane methodology of double blind randomized clinical trials of SCIT and SLIT was completed. This review showed that both SCIT and SLIT are statistically significantly more effective than placebo based on the combined symptom-medication scores. However, superiority of one mode of administration over the other could not be consistently demonstrated through indirect comparison. [32]

The treatment effect of MK-7243 is also at least as effective as other recommended allergic rhinitis/rhinoconjunctivitis treatments. Current rhinitis guidelines and most clinicians would agree that approved oral antihistamines and intranasal corticosteroids are clinically effective for treatment of allergic rhinitis. [58; 18; 17; 21] However, the magnitude of improvement of MK-

7243 relative to placebo (in trials allowing rescue pharmacotherapy) was similar () to or higher than that seen with traditional pharmacotherapy. Two recent systematic reviews and meta-analysis were published on the effectiveness of leukotriene receptor antagonists (LTRA)s, antihistamines and nasal corticosteroids in subjects with AR. The treatment effect relative to placebo (with no permitted use of rescue medications) of anti-histamines/LTRAs and nasal steroids ranged from 5%-9% and 17-26%, respectively. [15; 14]

This efficacy profile was demonstrated in the context of a generally well tolerated drug, as judged by adverse event reports from a large clinical development program. MK-7243 adverse events generally occurred early in treatment and were, as expected, allergic in nature. The side effects typically were localized to the site of tablet placement, in and around the mouth. Systemic allergic events were few, of mild to moderate intensity, and manageable. Treatment-related AEs occurred in approximately two thirds of subjects and events with the highest incidence were local allergic reactions. The rate of discontinuations for any reason, including treatment related adverse events, in MK-7243-treated subjects was low. Most discontinuations due to treatment related AEs occurred within the first weeks of treatment in subjects with recurrent local allergic adverse events. The incidence of SAEs was low and similar between MK-7243 and placebo in both adults and children.

The safety profile obtained indicates that the initial dose, given when allergic subjects are naïve to the treatment and at greatest risk of an allergic reaction, is also well tolerated. These data demonstrate that MK-7243 can be safely initiated at the maintenance dose without the need for titration. The administration of the first dose of MK-7243 in a health care setting serves as a prudent mitigation of potential events that may occur upon initiation.

There was no evidence of increased risk in subgroups characterized by age, race, gender, poly-sensitization, asthma status or during long-term treatment.

Safety through assessment of the known or potential risks of immunotherapy were carried out by evaluating ECIs. The key ECIs for MK-7243 include systemic allergic reactions (with or without anaphylactic shock), local allergic swellings with the potential to compromise the upper airway, and acute asthma related events. Within the MK-7243 2800 BAU clinical program, there were no serious treatment related systemic allergic reactions or anaphylactic shock, no serious treatment related local allergic swellings or no serious treatment related asthma related events. There were 9 systemic allergic reactions in 8 patients treated with MK-7243. These events were non-serious and were assessed as mild or moderate in intensity by the investigators. The events were characterized by predominantly local symptoms and dyspnea. Events were managed in the office as most occurred at the first administration or resolved without treatment in the two later occurring instances. The reassuring ECI assessments related to patient risk factors known to be of potential concern when administering immunotherapy (e.g. asthma status) supports the favorable safety profile of MK-7243.

For appropriate context it is important, where available, to evaluate data regarding the safety of sublingual and subcutaneous administration of allergen immunotherapy. The 2009 WAO sublingual immunotherapy position paper states that one of the purported advantages of SLIT over SCIT is greater safety, which may allow for administration of this treatment outside of the medical setting. [18] The subcutaneous grass immunotherapy trial by Frew et al. [31]which is

indirectly comparable to the GT-08 trial reported that 4.4% subjects receiving 3700 BAU had early occurring non–life-threatening systemic reactions including urticaria or asthma. No such events occurred in GT-08 trial comprising a similar sample size and patient population. The most recent 2013 systematic review using Cochrane methodology comparing SCIT and SLIT reported there were no fatalities with either mode of administration in a clinical trial setting. [32] However, systemic reactions with SLIT were less common, and most were graded as mild in severity. Furthermore, 19% of systemic reactions after SCIT treatment were considered to be severe compared with only 2% of systemic reactions after SLIT (based on studies that reported this information). Although not observed in the clinical trials with MK-7243, serious allergic reactions, including anaphylactic shock, are considered a risk with all types of allergen immunotherapy. MK-7243 (GRAZAX®) is marketed in 20 European countries and has been used since 2006 with an estimated 49 million tablets dispensed. European post marketing observational study data and spontaneous post marketing reports has revealed that serious systemic allergic reactions are uncommon and rare reports of events with anaphylactic shock/clinically important hypotension can occur. To date, no reports were received of patients requiring more than standard pharmaceutical care to manage these allergic reactions.

The indirect evidence suggests that MK-7243 may have a lower risk of systemic allergic reactions than SCIT. MK-7243 offers the potential for disease modification, unlike pharmacotherapy for allergic rhinitis. Overall, these assessments suggest that MK-7243 tablet therapy offer an alternative to SCIT and compliments pharmacotherapy with a favorable benefit risk.

Overall Benefits and Risks Conclusion

Given the increasing prevalence of allergic diseases in the United States [100; 8], MK-7243 addresses an unmet clinical need by providing an efficient and convenient immunotherapy treatment option to a broader group of patients who experience a medically important burden from their allergic rhinitis symptoms and for whom immunotherapy is appropriate. Subcutaneous immunotherapy is associated with a risk of serious systemic allergic reactions. MK-7243 tablet therapy offers an alternative to SCIT with favorable benefit risk. The adverse event profile of MK-7243 shows that systemic allergic events of significant medical concern are rare and generally occur at the first dose. The risk for later occurring events due to MK-7243 is rare and manageable based on clinical trial data and extensive European post-approval experience. The rare and manageable nature of the significant adverse experiences supports self-administration of MK-7243 outside the office setting as long as the first dose is administered in the office and was shown to be tolerable.

The additional potential benefit of a disease-modifying therapy over pharmacotherapy further augments the benefit/risk consideration and outweighs the potential risks, which are mitigated when appropriate patients are selected for treatment and the recommended precautions are implemented.

In summary, MK-7243, by virtue of its novel formulation and its potential to treat the underlying cause of allergic disease by promoting immunomodulation, unlike currently approved drugs for allergic rhinitis and conjunctivitis, provides a first in class immunotherapy

alternative that expands the therapeutic options available to patients with allergic rhinitis and physicians who treat these patients.

The proposed product labeling communicates the identified risks for MK-7243 and measures to help manage these risks. Patients, who ultimately do not tolerate MK-7243 therapy and should discontinue treatment, are likely to be identified at the first dose or early in the course of treatment. The European post-marketing data suggests that patients are aware or can identify the onset of allergic reactions and, with or without self-treatment, are able to obtain medical care to successfully manage the events. Based on these assessments MK-7243 has an overall favorable safety profile.

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Appendix 1 Analysis Results for the Peak Grass Pollen Season TCS, DSS, DMS across the MK 7243 Phase 3 Individual Trials

Table 1: Analysis results for the Peak Grass Pollen Season TCS, DSS, and DMS across the MK 7243 Phase 3 Individual Trials(Full Analysis Set)

Trial/ Endpoint	MK-7243 Mean (N)	Placebo Mean (N)	Treatment Difference (MK-7243 – Placebo)			Difference Relative to Placebo (%)[a]	
			Estimate	95% CI	p-value	Estimate	95% CI
Trial GT-08 Year 1							
TCS	(N=278) 5.91	(N=281) 8.71	-2.80	(-3.61, -2.00)	< 0.001	-32.0	(-39.6, -24.2)
DSS	(N=278) 3.81	(N=281) 5.27	-1.46	(-1.95, -0.98)	< 0.001	-28.0	(-35.2, -19.7)
DMS	(N=278) 2.12	(N=281) 3.46	-1.34	(-1.84, -0.84)	< 0.001	-39.0	(-49.5, -26.5)
Trial GT-14							
TCS	(N=137) 7.13	(N=143) 8.05	-0.91	(-2.09, 0.27)	0.129	-11.3	(-24.0, 4.7)
DSS	(N=137) 5.99	(N=143) 6.49	-0.50	(-1.38, 0.38)	0.265	-7.7	(-19.5, 7.2)
DMS	(N=137) 1.17	(N=143) 1.57	-0.40	(-0.90, 0.11)	0.123	-25.4	(-49.5, 7.5)
Trial P05238							
TCS	(N=183) 5.76	(N=201) 7.31	-1.55	(-2.74, -0.35)	0.011	-21.0	(-35.6, -3.9)
DSS	(N=183) 4.16	(N=201) 5.24	-1.08	(-1.81, -0.36)	0.003	-21.0	(-32.4, -6.6)
DMS	(N=183) 1.61	(N=201) 2.07	-0.46	(-1.17, 0.26)	0.211	-22.0	(-49.8, 16.1)
Trial GT-12							
TCS[b]	(N=117) 4.78	(N=121) 6.96	-2.19	(-3.56, -0.81)	0.002	-31.4	(-47.9, -13.7)
DSS[b]	(N=117) 2.84	(N=121) 3.91	-1.07	(-1.81, -0.32)	0.006	-27.3	(-43.5, -10.0)
DMS[c]	(N=117) 0.87	(N=121) 2.40	-1.53	(-1.53, -0.13)	0.001	-63.9	(-87.8, -10.4)
Trial P05239							
TCS	(N=147) 4.73	(N=153) 6.85	-2.12	(-3.30, -0.95)	< 0.001	-31.0	(-45.1, -13.7)
DSS	(N=147) 3.81	(N=153) 5.30	-1.49	(-2.30, -0.67)	< 0.001	-28.0	(-40.3, -12.9)
DMS	(N=147) 0.92	(N=153) 1.55	-0.63	(-1.26, -0.00)	0.049	-41.0	(-71.6, 1.3)

Trial/ Endpoint	MK-7243 Mean (N)	Placebo Mean (N)	Treatment Difference (MK-7243 – Placebo)			Difference Relative to Placebo (%)[a]	
			Estimate	95% CI	p-value	Estimate	95% CI
Trial P08067							
TCS[c]	(N=620) 3.33	(N=663) 4.67	-1.33	(-1.4, -0.5)	<0.001	-29.0	(-39.0, -15.0)
DSS[c]	(N=620) 2.71	(N=663) 3.40	-0.69	(-0.9, -0.2)	<0.001	-20.0	(-32.0,-8.3)
DMS[d]	(N=620) 1.01	(N=663) 1.63	-0.62	(-0.94,-0.31)	0.0001	-38.0	(-52.3,-24.1)

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

Note: All trials compared MK-7243 2800 BAU with placebo; all scores presented are for the peak pollen season.

a: Percent reduction in the MK-7243 2800 BAU group compared to placebo: (MK-7243-placebo)/placebo X 100%. Confidence intervals were obtained using the bootstrap method.

b: Parametric analysis (square-root-transformed data), treatment difference and that relative to placebo of back-transformed adjusted means.

c: Non-parametric analysis: Wilcoxon rank sum test with associated Hodges-Lehmann estimate for median difference, the group medians are reported, treatment difference and that relative to placebo of group medians.

d: Parametric analysis (zero-inflated lognormal), treatment difference and that relative to placebo of estimated means.

Appendix 2 GT-08 Extension

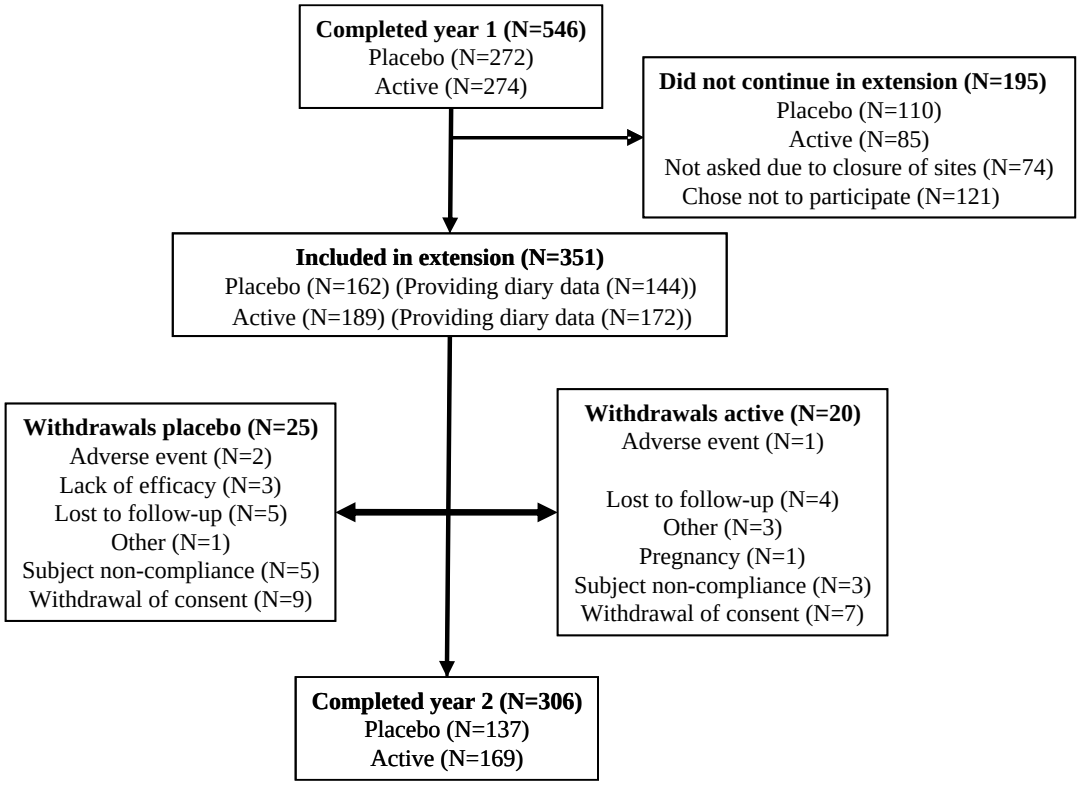

Figure 1: Subject Disposition, GT-08 Extension

Table 1: Demographics for Subjects in the Extension and for Subjects not Continuing in the Extension for GT-08 Trial

	Participating in the extension		NOT participating in the extension	
Treatment Group	**Placebo n(%)**	**MK-7243 n(%)**	**Placebo n(%)**	**MK-7243 n(%)**
Number of Subjects, N (%)	162 (100)	189 (100)	156 (100)	127 (100)
Sex				
Men, N (%)	97 (60)	118 (62)	96 (62)	61 (48)
Women, N (%)	65 (40)	71 (38)	60 (38)	66 (52)
Age (Years)				
Mean (SD)	35.9 (9.61)	35.4 (9.77)	33.0 (10.2)	31.6 (8.90)
Median	35.0	35.0	31.5	30.0
[Q5%; Q95%]	[22.0; 55.0]	[22.0; 56.0]	[20.0 - 53.0]	[21.0 - 49.0]
Ethnic Origin				
White, N (%)	155 (96)	180 (95)	153 (98)	119 (94)
Other, N (%)	7 (4)	9 (5)	3 (2)	8 (6)
Severity of Grass Pollen Allergy				
Moderate, N (%)	71 (44)	72 (38)	73 (47)	65 (51)
Severe, N (%)	91 (56)	117 (62)	83 (53)	62 (49)
Grass Pollen Allergy (Years):				
N	160	187	156	126
Mean (SD)	17.4 (10.4)	18.1 (10.4)	14.7 (10.6)	13.6 (9.18)
Median	17.0	17.0	13.5	11.5
[Q5%; Q95%]	[3.00; 37.5]	[3.00; 36.0]	[2.00 - 34.0]	[2.00 - 30.0]

N: number of subjects; %: percent of group; SD: standard deviation

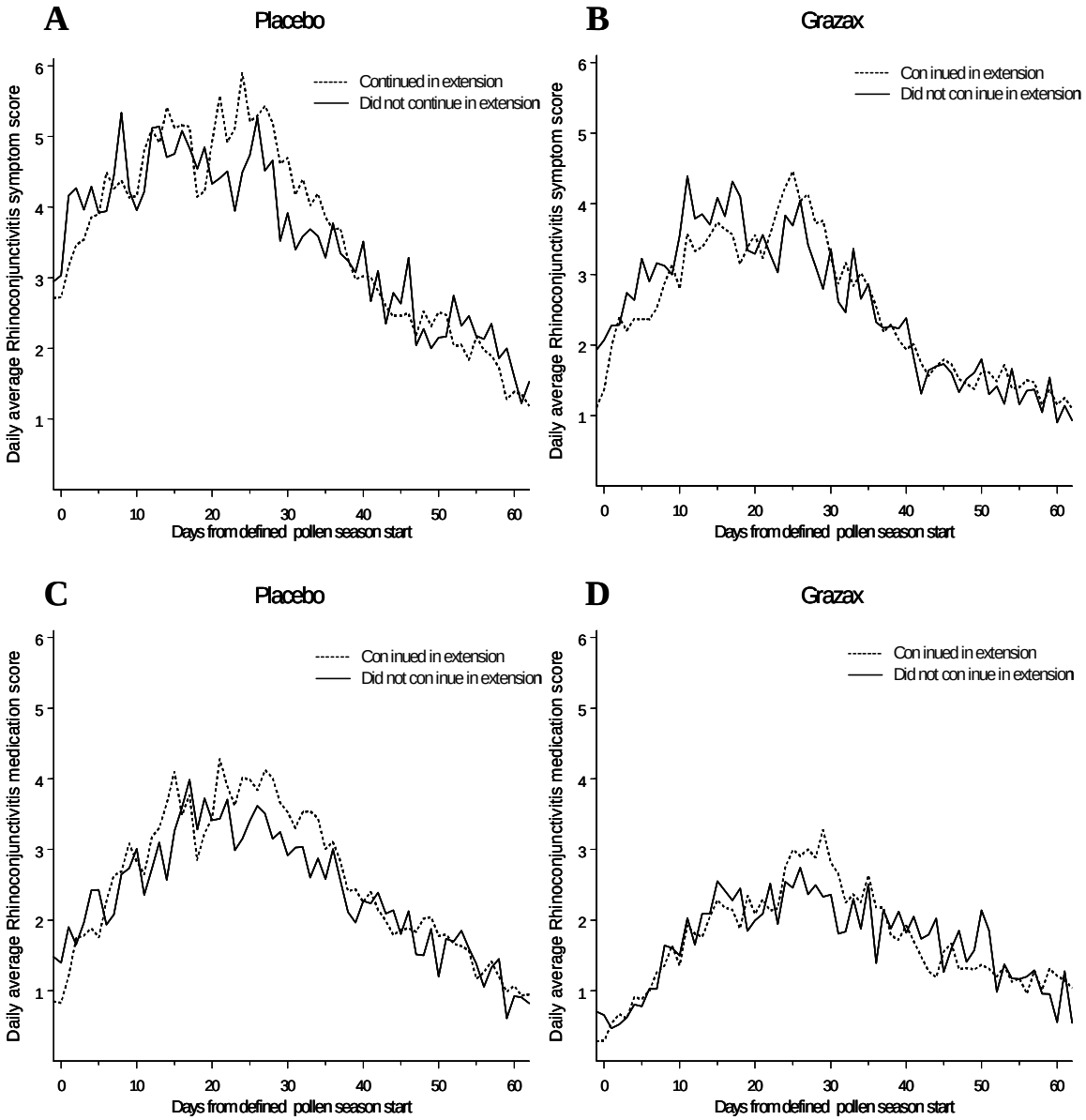

Figure 2: Comparisons of the Rhinoconjunctivitis Symptom and Medication Scores during the Grass Pollen Season 2005 between Subjects Continuing in the Extension and Subjects Not Continuing

Appendix 3 Tables of Treatment Related Adverse Event By Intensity

Table 1: Subjects with Specific Treatment Related Adverse Event By Intensity (Incidence ≥2% in one or more Treatment Groups) for Adults Phase 2/3 Pooled Clinical Trials – MK-7243 2800 BAU (All Randomized Subjects, N=1669)

	N	Mild n (%)	Moderate n (%)	Severe n (%)
SUBJECTS REPORTING ANY ADVERSE EVENT	**1111**	**758 (68.2)**	**304 (27.4)**	**49 (4.4)**
EAR AND LABYRINTH DISORDERS	**216**	**183 (84.7)**	**32 (14.8)**	**1 (0.5)**
EAR PRURITUS	208	177 (85.1)	31 (14.9)	0
EYE DISORDERS	**99**	**59 (59.6)**	**37 (37.4)**	**3 (3.0)**
EYE PRURITUS	50	27 (54.0)	20 (40.0)	3 (6.0)
GASTROINTESTINAL DISORDERS	**889**	**667 (75.0)**	**194 (21.8)**	**28 (3.1)**
DYSPEPSIA	39	21 (53.8)	16 (41.0)	2 (5.1)
HYPOAESTHESIA ORAL	38	32 (84.2)	6 (15.8)	0
LIP PRURITUS	39	30 (76.9)	7 (17.9)	2 (5.1)
LIP SWELLING	67	47 (70.1)	18 (26.9)	2 (3.0)
OEDEMA MOUTH	186	123 (66.1)	56 (30.1)	7 (3.8)
ORAL PRURITUS	446	374 (83.9)	62 (13.9)	10 (2.2)
PARAESTHESIA ORAL	164	148 (90.2)	15 (9.1)	1 (0.6)
SWOLLEN TONGUE	46	29 (63.0)	15 (32.6)	2 (4.3)
TONGUE PRURITUS	95	83 (87.4)	12 (12.6)	0
NERVOUS SYSTEM DISORDERS	**76**	**47 (61.8)**	**25 (32.9)**	**4 (5.3)**
HEADACHE	35	21 (60.0)	11 (31.4)	3 (8.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**525**	**386 (73.5)**	**121 (23.0)**	**18 (3.4)**
PHARYNGEAL OEDEMA	56	35 (62.5)	16 (28.6)	5 (8.9)
RHINORRHOEA	34	26 (76.5)	6 (17.6)	2 (5.9)
SNEEZING	34	26 (76.5)	6 (17.6)	2 (5.9)
THROAT IRRITATION	378	309 (81.7)	62 (16.4)	7 (1.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**98**	**69 (70.4)**	**24 (24.5)**	**5 (5.1)**
PRURITUS	40	33 (82.5)	7 (17.5)	0

Table 2: Subjects with Specific Treatment Related Adverse Event By Intensity (Incidence ≥2% in one or more Treatment Groups) for Adults Phase 2/3 Pooled Clinical Trials – Placebo (All Randomized Subjects, N=1645)

	N	Mild n (%)	Moderate n (%)	Severe n (%)
SUBJECTS REPORTING ANY ADVERSE EVENT†	**389**	**293 (75.3)**	**79 (20.3)**	**16 (4.1)**
EAR AND LABYRINTH DISORDERS	**21**	**17 (81.0)**	**4 (19.0)**	**0**
EAR PRURITUS	18	15 (83.3)	3 (16.7)	0
EYE DISORDERS	**46**	**36 (78.3)**	**10 (21.7)**	**0**
EYE PRURITUS	29	20 (69.0)	9 (31.0)	0
GASTROINTESTINAL DISORDERS	**197**	**170 (86.3)**	**25 (12.7)**	**2 (1.0)**
DYSPEPSIA	1	0	1 (100)	0
HYPOAESTHESIA ORAL	17	17 (100)	0	0
LIP PRURITUS	7	6 (85.7)	1 (14.3)	0
LIP SWELLING	3	3 (100)	0	0
OEDEMA MOUTH	13	12 (92.3)	1 (7.7)	0
ORAL PRURITUS	57	55 (96.5)	2 (3.5)	0
PARAESTHESIA ORAL	33	33 (100)	0	0
SWOLLEN TONGUE	2	1 (50.0)	1 (50.0)	0
TONGUE PRURITUS	8	8 (100)	0	0
NERVOUS SYSTEM DISORDERS	**44**	**32 (72.7)**	**8 (18.2)**	**4 (9.1)**
HEADACHE	22	14 (63.6)	5 (22.7)	3 (13.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**149**	**119 (79.9)**	**25 (16.8)**	**5 (3.4)**
PHARYNGEAL OEDEMA	2	1 (50.0)	1 (50.0)	0
RHINORRHOEA	27	20 (74.1)	6 (22.2)	1 (3.7)
SNEEZING	23	20 (87.0)	2 (8.7)	1 (4.3)
THROAT IRRITATION	46	42 (91.3)	4 (8.7)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**47**	**34 (72.3)**	**13 (27.7)**	**0**
PRURITUS	16	15 (93.8)	1 (6.3)	0

† Missing intensity for 1 subject (0.3%)

Table 3: Subjects with Specific Treatment Related Adverse Event By Intensity (Incidence ≥2% in one or more Treatment Groups) for Pediatric Phase 3 Pooled Clinical Trials - MK-7243 2800 BAU (All Randomized Subjects, N=447)

	N	Mild n (%)	Moderate n (%)	Severe n (%)
SUBJECTS REPORTING ANY ADVERSE EVENT	**260**	**173 (66.5)**	**79 (30.4)**	**8 (3.1)**
EAR AND LABYRINTH DISORDERS	**34**	**28 (82.4)**	**5 (14.7)**	**1 (2.9)**
EAR PRURITUS	32	27 (84.4)	4 (12.5)	1 (3.1)
EYE DISORDERS	**26**	**22 (84.6)**	**4 (15.4)**	**0**
EYE PRURITUS	15	14 (93.3)	1 (6.7)	0
GASTROINTESTINAL DISORDERS	**208**	**159 (76.4)**	**45 (21.6)**	**4 (1.9)**
DYSPHAGIA	9	8 (88.9)	1 (11.1)	0
LIP PRURITUS	13	12 (92.3)	1 (7.7)	0
LIP SWELLING	32	21 (65.6)	10 (31.3)	1 (3.1)
OEDEMA MOUTH	44	32 (72.7)	11 (25.0)	1 (2.3)
ORAL MUCOSAL ERYTHEMA	22	17 (77.3)	5 (22.7)	0
ORAL PRURITUS	109	90 (82.6)	18 (16.5)	1 (0.9)
PARAESTHESIA ORAL	24	24 (100)	0	0
SWOLLEN TONGUE	11	8 (72.7)	3 (27.3)	0
TONGUE PRURITUS	41	38 (92.7)	2 (4.9)	1 (2.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**18**	**7 (38.9)**	**10 (55.6)**	**1 (5.6)**
CHEST DISCOMFORT	9	5 (55.6)	4 (44.4)	0
NERVOUS SYSTEM DISORDERS	**21**	**16 (76.2)**	**5 (23.8)**	**0**
HEADACHE	15	10 (66.7)	5 (33.3)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**138**	**99 (71.7)**	**37 (26.8)**	**2 (1.4)**
COUGH	12	7 (58.3)	5 (41.7)	0
DRY THROAT	12	11 (91.7)	1 (8.3)	0
DYSPNOEA	9	5 (55.6)	3 (33.3)	1 (11.1)
OROPHARYNGEAL PAIN	18	13 (72.2)	5 (27.8)	0
PHARYNGEAL ERYTHEMA	16	15 (93.8)	1 (6.3)	0
PHARYNGEAL OEDEMA	13	11 (84.6)	2 (15.4)	0
THROAT IRRITATION	95	74 (77.9)	20 (21.1)	1 (1.1)

Table 4: Subjects with Specific Treatment Related Adverse Event By Intensity (Incidence ≥2% in one or more Treatment Groups) for Pediatric Phase 3 Pooled Clinical Trials – Placebo (All Randomized Subjects, N= 434)

	N	Mild n (%)	Moderate n (%)	Severe n (%)
SUBJECTS REPORTING ANY ADVERSE EVENT	**104**	**78 (75.0)**	**26 (25.0)**	**0**
EAR AND LABYRINTH DISORDERS	**2**	**2 (100)**	**0**	**0**
EAR PRURITUS	2	2 (100)	0	0
EYE DISORDERS	**16**	**13 (81.3)**	**3 (18.8)**	**0**
EYE PRURITUS	9	9 (100)	0	0
GASTROINTESTINAL DISORDERS	**39**	**35 (89.7)**	**4 (10.3)**	**0**
DYSPHAGIA	0	0	0	0
LIP PRURITUS	1	1 (100)	0	0
LIP SWELLING	2	2 (100)	0	0
OEDEMA MOUTH	1	1 (100)	0	0
ORAL MUCOSAL ERYTHEMA	4	4 (100)	0	0
ORAL PRURITUS	9	8 (88.9)	1 (11.1)	0
PARAESTHESIA ORAL	5	5 (100)	0	0
SWOLLEN TONGUE	0	0	0	0
TONGUE PRURITUS	4	4 (100)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**6**	**6 (100)**	**0**	**0**
CHEST DISCOMFORT	2	2 (100)	0	0
NERVOUS SYSTEM DISORDERS	**13**	**7 (53.8)**	**6 (46.2)**	**0**
HEADACHE	8	4 (50.0)	4 (50.0)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**39**	**30 (76.9)**	**9 (23.1)**	**0**
COUGH	5	4 (80.0)	1 (20.0)	0
DRY THROAT	2	2 (100)	0	0
DYSPNOEA	2	1 (50.0)	1 (50.0)	0
OROPHARYNGEAL PAIN	6	5 (83.3)	1 (16.7)	0
PHARYNGEAL ERYTHEMA	3	3 (100)	0	0
PHARYNGEAL OEDEMA	0	0	0	0
THROAT IRRITATION	11	11 (100)	0	0

Appendix 4 Systemic Allergic Reaction Narratives

Table 1: Narratives for Systemic Allergic Reactions from the Phase 2/3 Clinical Development Program (All Randomized Subjects)

Trial	Allocation Number	Treatment Group	Narrative
Adult			
GT-14	4005	MK-7243 2800 BAU	A 25 year old female experienced moderate anaphylaxis about 5 min. after first trial drug administration. Symptoms included swelling of lips, itchy mouth, tongue and throat and dysphagia. An oral exam was done with no abnormalities noted. The subject indicated that she was having difficulties swallowing but was able to swallow. Ten minutes after first symptom onset the subject was treated with Epinephrine 0.2 ml. subcutaneous as per site SOP and Cetirizine 10 mg. Blood pressure was normal. The subject was withdrawn from the study due to adverse event.
GT-14	10001	MK-7243 2800 BAU	A 46 year old female experienced a systemic reaction with symptoms of light headedness, headache, sleepiness and itching of ears after first intake of MK-7243. The onset of symptoms in relation to tablet intake is unknown. No reported signs of hypotension. No treatment was initiated due to the event. The subject was reported recovered from the event on the same day. The subject continued through the remainder of the trial.
GT-14	10003	MK-7243 2800 BAU	A 37 year old female experienced a systemic reaction with symptoms of light headedness and itching in mouth after first intake of MK-7243. The onset of symptoms in relation to tablet intake is unknown. No reported signs of hypotension. No treatment was initiated due to the event. The subject was reported recovered from the event on the same day.
GT-14	10004	MK-7243 2800 BAU	A 32 year old female subject 6 minutes post dosing, experienced a mild anaphylactic reaction following first tablet intake. Symptoms included itching under the tongue, throat, ears and nose, sneezing, rhinorrhea, throat irritation. No signs of hypotension. The subject was treated with Epinephrine 0.3 mg subcutaneous and Loratadine 20 mg. oral. The subject was considered as recovered from the event on the same. The following day the subject experienced another episode of anaphylactic reaction. Symptoms included mild burning sensation under tongue and left ear, rhinorrhea and slight irritation in back of the throat. No treatment was initiated due to the event and the subject was considered recovered on the same day. This subject continued through the remainder of the trial.
P08067	103134	MK-7243 2800 BAU	A 23 year old subject tolerated the first 2 weeks of study medication without AEs. Starting on Day 15, the subject developed throat tightness lasting ~ 5 minutes after dosing. The subject's AEs worsened over the next several weeks, and the subject began experiencing tongue edema following dosing. On day 42, the subject developed chest tightness and shortness of breath after taking study medication. The symptoms resolved over 30 minutes. The subject did not require treatment. The event was assessed by the PI as a moderate systemic allergic reaction; the subject discontinued the trial.
P08067	101062	MK-7243 2800 BAU	A 45 year old female tolerated the first dose of study medication with mild local adverse events. Following 2nd dosing of MK-7243, she experienced edema of lower lips, redness on corners of the mouth and chin, epigastric discomfort and dizziness. The onset of symptoms in relation to tablet intake is unknown. Symptoms resolved after 1 hour without treatment. The subject did not seek medical intervention. The event was assessed by the PI as a moderate systemic allergic reaction; the subject discontinued the trial.

Trial	Allocation Number	Treatment Group	Narrative
P05238	11387	MK-7243 2800 BAU	A 50 year old male developed the symptoms of dysphagia, uvular edema, pharyngeal edema, and flush/macular rash on the chest and back with associated pruritus and chest discomfort within minutes following the first dose of study drug. The subjects had no reported signs of hypotension. The subject was treated with epinephrine, loratadine and prednisone. The subject was reported recovered from the event on the same day and discontinued from the study.
Pediatric			
P08067	100056	Placebo	A 13 year old male with a history of asthma was treated with placebo and experienced an anaphylactic reaction on Day 1 of study drug dosing. The subject developed symptoms of wheezing, cough and increased nasal congestion within10 minutes of 1st dose of study medication. Vital signs were normal. The subject was treated with β-agonist and antihistamine and recovered. Study drug was discontinued and the subject discontinued from the trial. The investigator determined causality as possibly related to study drug.
P05239	2482	MK-7243 2800 BAU	A 13-year-old subject developed lip angioedema, slight dysphagia due to the sensation of a lump in the throat, and intermittent cough within minutes following the first dose of study medication administration. The subject did not experience wheezing, respiratory distress, urticaria, vomiting/diarrhea or hypotension. Epinephrine was administered to the subject and the symptoms resolved within minutes. The investigator graded this event as moderate in severity. The subject recovered from the event without requiring transfer to an emergency department or hospital.

Appendix 5 Epinephrine Administration Narratives

Table 1: Narratives of Epinephrine Administration during the Phase 2/3 Clinical Development Program (All Randomized Subjects)

Trial	Allocation Number	Treatment Group	Narrative
Not Discussed in Systemic Allergic Reactions or Local Swellings			
GT-14	8010	MK-7243 2800 BAU	A 46-year old female subject was treated with MK-7243 2800 BAU from 19 JAN 2007 to 19 JAN 2007 for seasonal grass pollen induced rhinoconjunctivitis. The subject had a medical history of hives when severely allergic to an item. On 19 JAN 2007, at 09:55 hrs., immediately after initial study drug intake, the subject experienced itchy throat, itchy mouth, dry cough, and one hive on left side of lower lip. Furthermore, the uvula was reported as being red and post nasal drip was noted. The lungs were reported as "being clear". At 10:00 hrs., 20 mg of loratadine was administered. At 10:08 hrs., blood pressure was measured (125/78 mmHg). At 10:08 hrs., epinephrine 0.3 mg intramuscular was given in the right arm. Following the administration of epinephrine, the itching improved and the hive flattened; however the subject still presented with dry cough. The blood pressure was measured at 10:12 hrs. (130/70 mmHg) and again at 10:17 hrs. (110/70 mmHg). At 10:23 hrs., the subject was given prednisone 20 mg orally. Another blood pressure measured at 10:25 hrs. was 112/70 mmHg, and the last blood pressure measured at 10:30 hrs. was 115/70 mmHg. The subject was considered recovered on 19 JAN 2007 at 11:15 hrs. The relationship between the AE and the investigational medicinal product was judged as probable by the investigator. There were no signs of hypotension at any time. The subject was discontinued from the trial.
P08067	100936	MK-7243 2800 BAU	A 65 year old female subject had a worsening of oral symptoms over the first week of dosing. On Day 14, within 15 minutes of study drug dosing, the subject developed mouth edema, uvular edema, tongue edema, pharyngeal edema, difficulty swallowing, rhinorrhea and hoarse voice. She went to the clinic and the investigator's exam revealed that the lungs were clear and vital signs were normal. Due to the local symptoms and hoarseness, the subject was administered epinephrine and loratadine. Epinephrine was administered about 1 hour after tablet intake. The investigator's assessment was that the subject experienced a moderate local allergic reaction probably related to study drug. Study drug was permanently discontinued.
P08067	101670	MK-7243 2800 BAU	A 17 year old male subject developed itchy throat and a "swollen feeling" in the throat approximately 3 hours and 20 minutes following 3rd dosing of study drug dosing. No difficulty breathing or swallowing. Immediate local events were also experienced following the 1st and 2nd dose of study drug. On Day 3, the subject self-administered epinephrine but did not tell his parent or seek medical attention. The subject's parent reported at the Day 3 phone call that the subject wished to discontinue study drug. Approximately 1 month after the event, the subject presented to the site for the early termination visit and reported the AE and use of epinephrine. The investigator assessed the events as a mild local allergic reaction.
Previously Discussed in Systemic Allergic Reactions and Local Swellings			
GT-02	72015	MK-7243 2800 BAU	A 30-year old male subject was treated with MK-7243 2800 BAU. On Day 74 of treatment, the subject experienced an AE with increasing swelling of the tongue and difficulty swallowing. There had been no intake of food before the tablet was taken. The subject felt dizzy but there was no dyspnea. The onset of symptoms in relation to tablet intake is unknown. The subject contacted the ER. In the ER, the subject had no signs of respiratory of cardiovascular compromise. His exam was notable for a swollen tongue and possibly mild laryngeal edema. The subject was treated with an antihistamine, corticosteroid and epinephrine. The subject was monitored for two hours and then discharged. The subject stopped taking the study drug and contacted the clinic after the weekend; 2 days later. At that time, the subject was withdrawn from the trial.

Trial	Allocation Number	Treatment Group	Narrative
			The subject had experienced itchy mouth on the first day of treatment and tiredness at Day 6 of treatment. Both events resolved within 1 and 3 days, respectively, and were considered by the investigator as being probably and possibly related, respectively, to study drug. At a telephone contact for further information, the subject stated that he at times experiences itchy mouth when eating various vegetables. On two previous occasions, the subject has experienced mild edema of the lips and tongue after intake of caviar. During the trial, the subject had experienced daily itchy mouth from the first day of treatment. Furthermore, occasionally localized swelling of the tongue and lips had occurred. The events were reported during the GPS.
GT-14	4005	MK-7243 2800 BAU	A 25 year old female experienced moderate anaphylaxis about 5 min. after first trial drug administration. Symptoms included swelling of lips, itchy mouth, tongue and throat and dysphagia. An oral exam was done with no abnormalities noted. The subject indicated that she was having difficulties swallowing but was able to swallow. Ten minutes after first symptom onset the subject was treated with Epinephrine 0.2 ml. subcutaneous as per site SOP and Cetirizine 10 mg. Blood pressure was normal. The subject was withdrawn from the study due to adverse event.
GT-14	10004	MK-7243 2800 BAU	A 32 year old female subject 6 minutes post dosing, experienced a mild anaphylactic reaction following first tablet intake. Symptoms included itching under the tongue, throat, ears and nose, sneezing, rhinorrhea, throat irritation. No signs of hypotension. The subject was treated with Epinephrine 0.3 mg subcutaneous and Loratadine 20 mg. oral. The subject was considered as recovered from the event on the same. The following day the subject experienced another episode of anaphylactic reaction. Symptoms included mild burning sensation under tongue and left ear, rhinorrhea and slight irritation in back of the throat. No treatment was initiated due to the event and the subject was considered recovered on the same day. This subject continued through the remainder of the trial.
P05238	11387	MK-7243 2800 BAU	A 50 year old male developed the symptoms of dysphagia, uvular edema, pharyngeal edema, and flush/macular rash on the chest and back with associated pruritus and chest discomfort within minutes following the first dose of study drug. The subjects had no reported signs of hypotension. The subject was treated with epinephrine, loratadine and prednisone. The subject was reported recovered from the event on the same day and discontinued from the trial.
P05239	2482	MK-7243 2800 BAU	A 13-year-old subject developed lip angioedema, slight dysphagia due to the sensation of a lump in the throat, and intermittent cough within minutes following the first dose of IMP administration. The subject did not experience wheezing, respiratory distress, urticaria, vomiting/diarrhea or hypotension. Epinephrine was administered to the subject and the symptoms resolved within minutes. The investigator graded this event as moderate in severity. The subject recovered from the event without requiring transfer to an emergency department or hospital.
Unrelated Events			
P05238	12285	MK-7243 2800 BAU	A 58-year old subject received the first 3 doses of IMP under supervision without AEs. On the day following the 4th dose of study medication, the subject developed anxiety while at a shopping mall several hours following tablet intake. Other symptoms included a feeling of faintness, dry mouth, and weakness. The subject self-administered self-injectable epinephrine and was taken to the ER for observation. In the ER, she had no signs or symptoms of an allergic reaction, and she received lorazepam. The investigator assessed the event as unrelated to study medication and compatible with anxiety. The use of an EpiPen® in response to an anxiety attack is not an approved indication nor medically appropriate. The subject completed the trial.

Trial	Allocation Number	Treatment Group	Narrative
P05239	2180	MK-7243 2800 BAU	A 16-year old male subject developed a sore throat. He was seen by his private medical doctor who diagnosed a viral pharyngitis. The onset of symptoms in relation to tablet intake is unknown. Several days later the sore throat persisted and the subject went to the emergency department with his parent (Day 23). In the ER, the subject's only complaint was sore throat. His last dose of study drug was the day before his visit to the ER. Oral examination revealed large tonsils and the ER physician indicated that the large tonsils could be a sign of an allergic reaction. Epinephrine was administered. As the epinephrine did not alter the throat exam, the subject was discharged from the ER with the diagnosis of viral pharyngitis. The subject remained on study drug.
P05239	2873	Placebo	A 6-year old subject experienced inspiratory and expiratory wheezing, cough, and suprasternal notch chest retractions on Day 137 of IMP intake. The symptoms occurred approximately 12 hours following daily IMP intake. Symptoms were temporally related to exposure to a grassy field. One day following the onset of symptoms, the subject presented to the investigational site. Respiratory symptoms were present on exam; however, the subject did not experience urticaria or local application site AEs. Lung function tests were attempted, but the subject was unable to perform due to lack of coordination. Levalbuterol nebulizer (1.25 mg), loratadine (10 mg), epinephrine (0.15 mg), and prednisone (20 mg oral) were administered. Symptoms markedly improved within about 10 minutes and the subject was monitored in the office for approximately 1.5 to 2 hours before discharge to home. On the day following epinephrine administration, the subject was administered prednisone for asthma during an office visit. The subject was instructed to continue to take 15 mg of prednisone in the morning for 3 more days, 2 sprays Proventil® as needed, 10 mg loratadine, Nasonex® 1 spray per nostril daily, and Pataday™ 1 drop per eye as needed. This was the first known asthmatic event for the subject. The case indicates that importance of environmental triggers and asthma exacerbations. The investigator graded the event as moderate in severity and unrelated to the study drug. The subject was discontinued from the trial.
P08067	102634	MK-7243 2800 BAU	A 37 year old male subject tolerated the first dose with mild oral tingling. On Day 2, the subject experienced mild sublingual swelling following the dose. Twelve hours after study drug dosing on Day 2, subject developed a rash, shortness of breath, throat tightness and "heaviness" of the tongue. He self-administered epinephrine and an antihistamine. The next day, he took the 3rd dose of study medication without events (no supervision). On Day 4, the subject was seen in the PIs office where he received the study medication under supervision and he experienced mild oral tingling. The subject realized that he had been exposed to bed bugs and discussed this with the investigator. The investigator's final diagnosis was Idiopathic Urticaria/bug bites; respiratory symptoms due to anxiety. The subject had no further events and continued in the trial.
P08067	103108	Placebo	A 52 year old male subject experienced urticarial vasculitis after ingesting jelly beans over several different occasions. Symptoms included urticaria, fatigue, cold hands, rhinorrhea, itchy feet and lip swelling. Treatment with pseudophedrine and AH alleviated most of the symptoms, but the lip swelling and urticaria persisted. On Day 50 the subject experienced syncope, and his spouse administered epinephrine and took the subject to the hospital. Treatment with epinephrine continued, along with steroids, H2 receptors and antihistamines. The onset of symptoms in relation to tablet intake is unknown. A skin biopsy was taken a few days later and was consistent with urticarial vasculitis. The subject discontinued the study due to syncope. The investigator felt the event was unlikely related to study drug. This event met the criteria for a SAE.

Appendix 6 Completed and Ongoing MK-7243 Observational, Non-Interventional Postmarketing Studies

Table 1: Overview of Completed and Ongoing MK-7243 Observational, Non-Interventional Postmarketing Studies (cut-off date: 30Apr2013)

Studies	Title	Country	Centers	Subjects[a] N
Completed Studies				
SHX0801	GRAZAX® START	Germany	434	1109
SHX0802	GRAZAX® LQ- Study	Germany	154	364
SHX0804	GRAZAX® Patient Satisfaction Study (PSS)	Germany	117	271
PMS-GT-AT-01	An observational trial Assessing the Tolerability of GRAZAX®	Austria	73	577
PMS-GT-NL-01	GRAZAX® in Patients with Rhinoconjunctivitis induced by Grass Pollen: evaluation of Safety, Tolerability and Patient Satisfaction	Netherlands	49	247
PMS-GT-SE-01	An Observational Trial Assessing the Tolerability of GRAZAX®	Sweden	48	269
PMS-GT-SE-02	An Observational Trial Assessing the Tolerability of GRAZAX®	Sweden	16	74
PMS-GT-FI-01	An Observational Trial Assessing the Tolerability of GRAZAX®	Finland	29	47
PMS-GT-01	Immunotherapy with GRAZAX in Adult Patients with Specific IgE Mediated Grass Pollen Allergy	Switzerland	35	247
PMS-GT-02[b]	GRAZAX® Kinder START Observational Study with GRAZAX® in children, adolescents, and adults (Post Marketing)	Germany	358	1718
PMS-GT-03[b]	An Observational Trial Assessing the Safety and Tolerability of GRAZAX® in Children and Adolescents from 5-14 years	Austria	13	43
PMS-GT-04	Monitoring Safety and Tolerability of GRAZAX® in Children aged 5-17 years	Netherlands	40	245
PMS-GT-05	Pharmacovigilance Study to Assess the Tolerability of GRAZAX® in Patients With Rhinitis by Grass Sensation	Spain	10	115
PMS-GT-06	An Observational trial Assessing the Tolerability of GRAZAX® in Children aged 5-17 Years	Finland	35	156
PMS-GT-07	GRAZAX® in Adults and Children Adherence Study (GUIDANCE)	Netherlands	19	55
PMS-NI-GT-08	GRAZAX® Non-Interventional, observational Study of the Intra-seasonal Start of Treatment with the Grass Allergy Immunotherapy Tablet (Post Marketing)	Germany	290	672
OBS-SIT-01	Collection of Causitics for Specific Immunotherapy with GRAZAX®, AVANZ, Alutard®	Germany	N/A	655
IMMUNIS	No Protocol: this was a Patient Assistance Therapy Programme to Increase Compliance and Adherence with GRAZAX® therapy.	Germany	N/A	61
NI-GT-09	Non-interventional Patient Satisfaction Study with GRAZAX® in Austria	Austria	50	364
NI-GT-12	Retrospective observational Study on the Expectations, Clinical management and Satisfaction of Patients with Moderate/Severe Allergic Rhinoconjunctivitis Treated with Specific Immunotherapy as Oral Lyophilisate Under Routine Clinical Practice Conditions	Spain	20	129
NI-GT-15	A Non-interventional observational Study Assessing the Safety and Tolerability of GRAZAX®	N/A	cancelled	Not Applicable

Studies	Title	Country	Centers	Subjects[a] N
Ongoing				
NI-GT-10[c]	Non-interventional Observational Study Assessing the safety and tolerability of GRAZAX® in Daily Routine Use in Children and Adolescents (5-17 years)	Switzerland	17	47
NI-GT-13[e]	Non-interventional Observational Study Assessing the Adherence of Quality of Life During Three years of GRAZAX® Treatment in Adults and Children >=5 years	Finland	50	399
NI-GT-14[de]	A Pharmacoepidemiological Observational Study: Description of the Reached Population, Administration, safety of GRAZAX®: EPIGRAM Study	France	86	494
NI-GT-16[d]	A non-interventional, observational Study in Adults and Children from 5 years of Age Assessing the Safety and Tolerability of GRAZAX® in Case of Concomitant Specific Immunotherapy (SCIT or SLIT)	Germany	37	164
			Total number of subjects	8552

a. Subjects exposed to GRAZAX®
b. Data from PMS-GT-02 and PMS-GT-03 have been analysed together and described in a single study report. 797 subjects were <17 years of age
c. Pediatric study.
d. Study contains both pediatric and adult subjects ≥5 years of age.
e. Study is completed. Study report is not yet available.