2.0 SYNOPSIS

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC. MK-7243 Grass AIT, Sublingual Tablet Grass-Induced Rhinoconjunctivitis	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of Grass (*Phleum pratense*) Sublingual Tablet (MK-7243/SCH 697243) in Subjects Between 5 and 65 Years of Age, with a History of Grass Pollen-Induced Rhinoconjunctivitis, With or Without Asthma (Protocol No. P08067) #P08067

INVESTIGATOR(S)/STUDY CENTER(S): 173 Sites Initiated: 145 in the US and 28 in Canada

PUBLICATION(S): None

PRIMARY THERAPY PERIOD: ***02 Dec 2011 to 03 Aug 2012*** **CLINICAL PHASE:** 3

DURATION OF TREATMENT: Approximately 24 weeks

OBJECTIVE(S):

Primary Objective: (1) To evaluate the efficacy of grass sublingual tablet (MK-7243/SCH 697243) versus placebo in the treatment of grass pollen-induced rhinoconjunctivitis based on the combined (sum of) rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS), also called total combined score (TCS), averaged over the entire grass pollen season (GPS). (2) To evaluate the safety and tolerability of MK-7243 when administered sublingually, once daily, to subjects with a history of grass pollen-inducted rhinoconjunctivitis, with or without asthma.

Key Secondary Trial Objectives: To compare the MK-7243 and placebo treatment groups with regard to: (1) the average rhinoconjunctivitis DSS over the entire grass pollen season; (2) the average rhinoconjunctivitis TCS over the peak grass pollen season; (3) the average Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities (RQLQ(S)12+) overall score over the peak grass pollen season (subjects ≥ 12 years of age only) and (4) the average rhinoconjunctivitis DMS over the entire grass pollen season.

Other Secondary Trial Objectives: To compare MK-7243 and placebo treatment groups with regard to: (1) the average rhinoconjunctivitis DSS over the peak grass pollen season; (2) the average Paediatric Standardised Rhinoconjunctivitis Quality of life Questionnaire (PRQLQ) overall score over the peak grass pollen season (subjects 6 to <12 years of age) and (3) the average rhinoconjunctivitis DMS over the peak grass pollen season.

STUDY STATUS: Completed

STUDY DESIGN: This was a multicenter, double-blind, randomized, placebo-controlled, parallel group study evaluating the efficacy and safety of grass (*Phleum pratense*) sublingual tablet (MK-7243) in subjects 5 to 65 years of age, with a history of grass pollen-induced rhinoconjunctivitis, with or without asthma. Subjects were treated with MK-7243 (2800 Bioequivalent Allergen Units (BAU) of *Phleum pratense* extract [hereafter referred to as MK-7243]), or matching placebo, for at least 12 weeks prior to the anticipated start of the grass pollen season (GPS), and throughout the 2012 GPS season. Subjects randomized to the MK-7243 group were instructed to administer MK-7243 sublingually once daily. Subjects randomized to the placebo group received matching placebo tablets to be administered once daily. Rescue medications were provided by the SPONSOR/designee to the study site to be given to the subjects as pre-defined, open-label medication to be taken in a step-wise fashion depending on the persistence, severity, and type of symptoms for allergic rhinoconjunctivitis and asthma. Subjects visited the study site for at least six visits: Screening (Visit 1), Randomization (Visit 2), Off-Season (Visit 3), Pre-Season (Visit 4), On-season (Visit 5), End-of-season (Visit 6), and at Unscheduled Visits, as necessary. A telephone call between the investigator/designee and the subject/parent/guardian occurred daily for the first 2 days of at-home administration of study drug (after Visit 2) and once approximately 7 days after Visit 6 (Visit 7).

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SUBJECT/PATIENT DISPOSITION: A total of 1501 subjects were randomized in approximately 1:1 ratio to MK-7243 or placebo. 752 subjects were in the MK-7243 group and 749 subjects were in the placebo group. Three subjects were randomized but did not receive treatment.

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

Subjects that were randomized, but never treated were included in the Discontinued Treatment Phase.
Full Analysis Set (FAS) included randomized subjects who took at least one dose of study medication and had at least one post-randomization efficacy measurement.
Per Protocol (PP) population included all FAS subjects without major protocol deviations.
Subjects from site 0003 (4 randomized subjects) were excluded from the FAS and PP population for efficacy analyses due to GCP issues.

The denominator for percentages was based on number of all randomized subjects.

DOSAGE/FORMULATION NOS.:
Test Product, Dose, Mode of Administration, Batch No: MK-7243 2800 BAU (*Phleum pratense* extract) tablet administered sublingually once daily, preferably at the same time each day.
Batch number for MK-7243: 1194744
Reference Therapy, Dose, Mode of Administration, Batch No: Matching placebo tablet (to test product) administered sublingually once daily, preferably at approximately the same time each day.
Batch number for placebo: 1194743

DIAGNOSIS/INCLUSION CRITERIA: Subjects with a history of grass pollen-induced rhinoconjunctivitis with or without asthma who met all inclusion criteria and none of the exclusion criteria were selected to participate in the trial.

Key Inclusion Criteria

1. Subject must be 5 to 65 years of age, of either sex, and of any race.
2. Subject must have a clinical history of significant allergic rhinoconjunctivitis to grass (with or without asthma) diagnosed by a physician and have received treatment for their disease during the previous GPS.
3. Subject must have a positive skin prick test response (average wheal diameter ≥5 mm larger than the saline control after 15 to 20 minutes) to *Phleum pratense* at the Screening Visit.
4. Subject must have positive specific IgE against *Phleum pratense* (≥ 0.70 k_AU/L, Class 2) at the Screening Visit.
5. Subject must have an FEV1 ≥70% of predicted value at the Screening and Randomization Visits.
6. A subject's ECG conducted at the Screening Visit must be within normal limits or clinically acceptable to the investigator. Note: ECG was required only for subjects between 55 and 65 years of age within 3 months of screening regardless of medical history.

Key Exclusion Criteria

1. Subject with a clinical history of symptomatic seasonal allergic rhinitis and/or asthma, having received regular medications due to another allergen during or potentially overlapping the GPS.

2. Subject with a clinical history of significant symptomatic perennial allergic rhinitis and/or asthma having received regular medication due to an allergen to which the subject is regularly exposed.
3. Subject has received an immunosuppressive treatment within 3 months prior to the Screening Visit (except steroids for allergic and asthma symptoms).
4. Subject with a clinical history of severe asthma.
5. Subject with history of anaphylaxis with cardiorespiratory symptoms.
6. Subject with history of self-injectable epinephrine use.
7. Subject with a history of chronic urticaria and angioedema.
8. Subject with clinical history of chronic sinusitis during the 2 years prior to the Screening Visit.
9. Subject with current severe atopic dermatitis.
10. Subject who has had previous treatment by immunotherapy with grass pollen allergen or any other allergen within the 5 years prior to the Screening Visit.
11. Subject with a known history of allergy, hypersensitivity or intolerance to the ingredients of the study drug (except for *Phleum pratense*), rescue medications, or self-injectable epinephrine.

EVALUATION CRITERIA: Primary endpoint: The primary efficacy endpoint is the daily TCS averaged over the entire grass pollen season (GPS). Key secondary endpoints: (1) the average rhinoconjunctivitis DSS over the entire grass pollen season; (2) the average rhinoconjunctivitis TCS over the peak grass pollen season; (3) the average Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities (RQLQ(S)12+) overall score over the peak grass pollen season (subjects ≥ 12 years of age only); (4) the average rhinoconjunctivitis DMS over the entire grass pollen season. Other secondary endpoints: (1) the average rhinoconjunctivitis DSS over the peak grass pollen season; (2) the average Paediatric Standardised Rhinoconjunctivitis Quality of life Questionnaire (PRQLQ) overall score over the peak grass pollen season (subjects 6 to <12 years of age); (3) the average rhinoconjunctivitis DMS over the peak grass pollen season.

SAFETY MEASUREMENTS: Clinical evaluations (physical examinations), adverse experience monitoring, and baseline laboratory safety tests.

STATISTICAL PLANNING AND ANALYSIS:

The efficacy analyses were based on two subject populations. The Full Analysis Set (FAS) population served as the primary population for the analysis of efficacy data. The FAS population consisted of all randomized subjects who received at least one dose of study medication and had at least one post-treatment efficacy measurement. The Per Protocol (PP) population was used to conduct supportive analyses for the primary and key secondary efficacy endpoints. The PP population excluded subjects with clinically important protocol deviations based on a set of pre-specified criteria. All such protocol deviations were identified and documented prior to the unblinding of the dataset.

The safety analyses were based on the All-Subjects-as-Treated (ASaT) population. The ASaT population consisted of all randomized subjects who received at least one dose of study medication.

Efficacy: The primary efficacy endpoint of daily TCS (sum of rhinoconjunctivitis DSS and DMS) averaged over the entire GPS was evaluated using the pre-specified non-parametric approach. The treatment comparison was conducted using the Wilcoxon rank sum test. Median TCS within each group was reported to represent the treatment effect. The absolute and relative (percent, relative to placebo) differences of the medians between MK-7243 and placebo were reported, with the 95% confidence interval for the relative difference of the medians calculated using the bootstrap re-sampling approach. The assumed normality assumption of the pre-specified analysis of variance (ANOVA) model were examined using the Shapiro-Wilks test and inspection of the Q-Q plots. Due to a severe violation of the normality assumption, the prerequisite for parametric ANOVA, the primary analyses were performed using nonparametric models as pre-specified in the protocol. Additionally, the analyses were also performed using the ANOVA approach.

There were four key secondary endpoints:

1. average DSS over the entire GPS,
2. average TCS over the peak GPS,
3. average RQLQ(S)12+ overall score over the peak GPS,
4. average DMS over the entire GPS.

The first three key secondary endpoints were analyzed in a similar non-parametric approach as the primary endpoint. The average DMS over the entire GPS was analyzed using a zero-inflated lognormal model due to excessive 0 values in the DMS data. The model adjusted for treatment, baseline asthma status, age category (<18 or ≥18), and pollen region as covariates.

The primary and key secondary efficacy endpoints were tested in a sequential order to warrant multiplicity control on the overall Type I error rate. The key secondary endpoints were tested in the order listed above only if the primary endpoint was statistically significant at two-sided alpha = 0.05.

Sensitivity analyses were performed for the primary and key secondary efficacy endpoints based on the PP population. Additional sensitivity analyses by imputing the missing daily TCS scores were also performed.

Safety: A tiered approach was used for the safety analysis. For the pre-specified Tier 1 parameters, the 2-sided p-value and the 95% CI for the treatment difference were provided. The Tier 1 parameters in this study included: oral pruritus, ear pruritus, throat irritation, oedema mouth, systemic allergic reactions (including anaphylactic reactions), any treatment emergent AE (TEAE), any TEAE leading to study discontinuation, and event treated with epinephrine. For Tier 2 parameters, the 95% CI for the treatment difference were provided. The p-value and the 95% CI were calculated using the Miettinen-Nurminen method. The Tier 2 parameters in this study included: any AE, any serious AE, any drug-related AE, any serious and drug-related AE, any AE leading to discontinuation, and AEs and system organ classes with at least 4 incidences in either treatment group. For all other safety parameters which were classified as Tier 3, summary statistics were provided. For all Tier 3 clinical and laboratory AEs, events were listed and summarized by frequency of occurrence, and only the counts and percentages were tabulated by treatment group. Vital signs and selected laboratory tests were also summarized.

RESULTS:

A significant treatment effect of MK-7243 was observed for the primary and all key secondary endpoints.

Efficacy:

The study met its primary objective. The results for the pre-specified primary and key secondary endpoints were summarized in the table below.

Endpoint[†]	MK-7243 2800 BAU (N) Median/Mean	Placebo (N) Median/Mean	Treatment Difference (MK-7243 – PBO)			Difference Relative to PBO (%)[‡]	
			Estimate	95% CI	p-value	Estimate	95% CI
TCS – Entire Season	(N=629) 3.24	(N=672) 4.22	-0.98	(-1.2, -0.4)	<0.001	-23%	(-36%, -13%)
DSS –Entire Season	(N=629) 2.49	(N=672) 3.13	-0.64	(-0.7, -0.2)	0.001	-20%	(-32%, -10%)
TCS – Peak Season	(N=620) 3.33	(N=663) 4.67	-1.33	(-1.4, -0.5)	<0.001	-29%	(-39%, -15%)

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RQLQ(S)12+ - Peak Season	(N=476) 0.93	(N=520) 1.06	-0.13	(-0.2, 0.0)	0.027	-12%	(-27%, 1.0%)
DMS – Entire Season	(N=629) 0.88	(N=672) 1.36	-0.48	(-0.7,-0.2)	<0.001	-35%	(-49%, -21%)

TCS = Total combined score (DSS + DMS);
DSS = Daily Symptom Score; DMS = Daily Medication Score; RQLQ(S)12+ = Rhinoconjunctivitis Quality of Life Questionnaire in subjects ≥ 12 years old;
N= Number of subjects included in analyses;
† Non-parametric analysis for TCS, DSS, and RQLQ(S)12+ endpoints: p-values were based on the Wilcoxon rank sum test and the 95% CI for treatment difference was based on Hodges-Lehmann estimate for median of difference. The group medians were reported, and the estimates of treatment difference and difference relative to placebo were based on group medians;
Parametric analysis using zero-inflated log-normal model for DMS: the estimated group means were reported and difference relative to placebo was based on estimated group means.
‡ Percent reduction in the MK-7243 group compared to placebo: (MK-7243-placebo)/placebo X 100. The confidence intervals were based on bootstrap approach.

Summary of results from the primary and key secondary endpoints:

- MK-7243 (grass allergy immunotherapy tablet; 2800 BAU) improved the TCS more than placebo during the entire grass pollen season (absolute treatment difference -0.98; treatment difference relative to placebo -23%, 95% CI: -36% to -13%, p <0.001).
- MK-7243 also improved DSS over the entire grass pollen season, TCS over the peak season, RQLQ(S)12+ over the peak season, and DMS over the entire grass pollen season compared to placebo.
- Overall results of the key efficacy endpoints analyzed on the FAS were confirmed by the results on the PP population.

Results from the additional secondary endpoints further supported the effects of MK-7243. The conclusions from the additional secondary endpoints were as follows:

- MK-7243 improved DSS and DMS during the peak grass pollen season, when symptoms were expected to be at their worse due to the higher pollen exposure.
- It is notable that compared to historical data, the 2012 grass pollen season was characterized by low average pollen counts (23 grains/m3) and few pollen peaks with an average peak season count of 53 grains/m3, resulting in overall low symptom scores and rescue medication usage in placebo treated subjects

Safety:

In this trial, MK-7243 2800 BAU was found to be generally safe and well-tolerated. Overall adverse events, primarily local allergic reactions that were expected, were more frequently associated with MK-7243 than with placebo. During the trial there were 19 treated subjects who reported SAEs. All of the SAEs were assessed as unlikely related to study medication. One death occurred in a [redacted] subject who had been in the MK-7243 treatment group, approximately 1 month following the last dose of study medication. Cause of death is unknown at the time of this report. The event was not considered related to the study medication.

There was no subject who experienced anaphylactic shock. Two subjects on MK-7243 experienced moderate systemic allergic reactions. These events were not treated with epinephrine. Two subjects received epinephrine for local application site reactions considered related to MK-7243 treatment. The overall incidence and severity of AEs was similar between asthmatic and non-asthmatic

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subjects.

No new safety concerns emerged during the trial.

Number (%) of Subjects Reporting Adverse Events by Category. All-Subjects-as-Treated Population

	MK-7243 (N=753)	Placebo (N=745)	Total (N=1498)
Category	**n(%)**	**n(%)**	**n(%)**
At Least One AE	593(78.8)	508(68.2)	1101(73.5)
Treatment Related AE	441(58.6)	178(23.9)	619(41.3)
Serious AE	11(1.5)	8(1.1)	19(1.3)[a]
Treatment Related Serious AE	0	0	0
Discontinued Due to AE	54(7.2)	18(2.4)	72(4.8)
Discontinued Due to Treatment Related AE	46(6.1)	10(1.3)	56(3.7)
Severe AE	69(9.2)	40(5.4)	109(7.3)
Life-Threatening AE	0	1(0.001)	1(0.001)
Death	1(0.1)	0	1(0.1)

Coded using MedDRA Version 15.0.
The denominator for percentages is based on the number of subjects in each treatment group.
Related: Poss ble or Probable.

Subjects are counted once for each AE Category.

a: Includes treated subjects only.

CONCLUSIONS:

In conclusion, this trial indicated that treatment with MK-7243 for approximately 12 weeks prior to and throughout season was more effective than placebo in reducing the total combined symptom and medication score, as well as relieving daily symptoms with less need for rescue medication in subjects with grass pollen-induced rhinoconjunctivitis. The improvement was shown during the entire grass pollen season with a similar treatment effect recorded during the peak pollen exposure. The treatment was well-tolerated for up to 34 weeks of treatment, with no events of anaphylactic shock. No new safety signals emerged from this trial.