2.0 SYNOPSIS

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC. MK-3641 Ragweed AIT, Sublingual Tablet Short Ragweed-Induced Rhinoconjunctivitis	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A 28-Day Study Evaluating the Safety of Short Ragweed (*Ambrosia artemisiifolia*) Allergy Immunotherapy Tablet (AIT) (SCH 39641/MK-3641) Treatment in Ragweed Allergic Adults (Phase 3, Protocol No. P05751) P05751

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter 72 centers. Out of these 58 centers in the United States and 14 centers initiated in Canada.

PUBLICATION(S): None

PRIMARY THERAPY PERIOD: ***20Dec2012 to 03 April 2012*** **CLINICAL PHASE:** 3

DURATION OF TREATMENT: 28 days

OBJECTIVE(S):

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

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

STUDY STATUS: completed

STUDY DESIGN This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study in subjects 18 years of age or older, of either gender, and of any race with a history of ragweed-induced rhinoconjunctivitis with or without asthma. The subjects were treated once daily with SCH 39641/MK-3641 (hereafter refered to as MK-3641) 12 Amb a 1-U ragweed sublingual tablet or placebo for approximately 28 days. Prior to treatment initiation, each subject was supplied with self-injectable epinephrine for the treatment of acute severe systemic allergic reactions. Subjects were instructed on how and when to use the medication. Subjects completed at least 3 visits: Screening, Randomization, and a final study visit to occur at the end of study treatment (approximately Day 28). The first dose of IMP was administered at the study site, and the subject was monitored for adverse events at the site for 30 minutes following dosing. Subsequent administration of IMP was done once daily at home at approximately the same time each day. A follow-up telephone call between the site and the subjects was made daily for the first 2 doses of at-home administration of IMP and approximately once weekly thereafter. A follow-up telephone contact occurred approximately 7 days after the final study visit

SUBJECT/PATIENT DISPOSITION: A total of 914 subjects were randomized in a 2:1 ratio to 12 Amb a 1-U MK-3641 or placebo. 610 subjects were in the 12 Amb a 1-U group and 304 subjects were in the placebo group. One subject was randomized but did not receive treatment.

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC.

CLINICAL STUDY REPORT SYNOPSIS

	12 Amb a 1-U n (%)	Placebo n (%)	Total n (%)
Randomized	610 (100)	304 (100)	914 (100)
Female (age range)	345 (18-85)	177 (20-76)	522 (18-85)
Male (age range)	265 (18-85)	127 (18-71)	392 (18-85)
Treated	609 (99.8)	304 (100)	913 (99.9)
Completed Study	575 (94.3)	298 (98.0)	873 (95.5)
Discontinued Treatment Phase	35 (5.7)	6 (2.0)	41 (4.5)
-Adverse Event	21 (3.4)	3 (1.0)	24 (2.6)
-Lost To Follow-Up	3 (0.5)	0	3 (0.3)
-Subject Withdrew Consent	4 (0.7)	1 (0.3)	5 (0.5)
-Non-Compliance With Protocol	4 (0.7)	2 (0.7)	6 (0.7)
-Did Not Meet Protocol Eligibility	3 (0.5)	0	3 (0.3)

Percentage is based on number of subjects randomized

DOSAGE/FORMULATION NOS.:
Test Product, Dose, Mode of Administration, Batch No: MK-3641 12 Amb a 1-U (*Ambrosia artemisiifolia* extract) tablet administered sublingually once daily, preferably at the same time each day.
Batch number for 12 Amb a 1-U: W-H04024
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 numbers for placebo: W-H03558

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC.

CLINICAL STUDY REPORT SYNOPSIS

DIAGNOSIS/INCLUSION CRITERIA: Subjects with a history of ragweed-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 have been 18 years of age or older, of either sex, and of any race.
2. Subject must have had a clinical history of physician-diagnosed ragweed-induced allergic rhinoconjunctivitis of 2 years duration or more, with or without asthma.
3. Subject must have had a positive skin prick test response to *Ambrosia artemisiifolia* at the Screening Visit (5 mm wheal).
4. Subject must have had a forced expiratory volume in 1 second (FEV1) of at least 70% of predicted value at the Screening and Randomization Visits.
5. Subject's clinical laboratory tests, electrocardiogram (ECG) in subjects ≥55 years of age, and vital signs conducted at the Screening Visit must have been within normal limits or clinically acceptable to the investigator.

Key Exclusion Criteria

1. A subject with unstable asthma, as judged by the clinical investigator, or a subject who had experienced an occurrence of any clinical deterioration of asthma that resulted in emergency treatment, hospitalization due to asthma, or treatment with systemic corticosteroids (but allowed short-acting beta agonists [SABA]) at any time within the 3 months prior to Screening.
2. Subject received an immunosuppressive treatment within 3 months prior to Randomization (except steroids for allergic symptoms other than asthma).
3. Subject had a history of anaphylaxis with cardiorespiratory symptoms.
4. Subject had a history of chronic urticaria or angioedema.
5. Subject had current severe atopic dermatitis.
6. Female subject who was breast-feeding, pregnant, or intended to become pregnant while the study was ongoing.
7. Subject who had received maintenance doses of immunotherapy with ragweed extract for ≥1 month within the 5 years prior to Randomization.
8. Subject had a history of allergy, hypersensitivity or intolerance to the ingredients of the investigational medicinal product (IMP), (except for *Ambrosia artemisiifolia*), or self-injectable epinephrine.

EVALUATION CRITERIA: The primary objective of this study was to evaluate the safety of the 12 Amb a 1-U short ragweed tablet. Efficacy parameters were not measured.

The Prespecified Safety Endpoints: The Prespecified safety endpoints were related to the primary trial objective and the key secondary trial objective.

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

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

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC.

CLINICAL STUDY REPORT SYNOPSIS

STATISTICAL PLANNING AND ANALYSIS:

Subject Population: All the safety analyses were performed on the all subjects as treated (ASaT) population set, defined as subjects who receive at least one dose of study treatment. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment was required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement was also required.

Efficacy Analysis: No efficacy parameters were measured in this trial, as the objectives were to evaluate the safety of the IMP in subjects with ragweed allergy.

Safety Analysis:

Safety and tolerability were assessed by a statistical and clinical review of all safety parameters, including adverse experiences, laboratory values, vital signs and pulmonary function tests. The analysis of safety results followed a tiered approach.

Tier 1 events (prespecified primary and key secondary safety endpoints include treatment-emergent AEs, prespecified local AEs, and discontinuations due to treatment-emergent AEs) were summarized by treatment group and separately by baseline asthmatic status and age groups (<50 or ≥ 50). The incidence of tier 1 events between the active treatment arm and the placebo were compared using the stratified Miettinen and Nurminen method with the baseline asthmatic status as the factor. Both p-values and 95% confidence intervals were provided for the between-treatment difference in proportions.

Tier 2 events (commonly occurring safety endpoints) included any related AE, any serious AE, any serious and related AE, discontinuations due to treatment-related AEs, and individual AEs that occur in at least 1% of subjects in one or more of the treatment groups. Point estimates and two-sided 95% confidence intervals for the difference in proportions between the active-treatment arm and placebo arm were provided for those events.

All other clinical and laboratory AEs, vital signs, oral examinations, safety laboratory measurements, spirometry, and physical examinations were summarized by treatment group using descriptive statistics (proportions or N, mean, median, standard deviation, range).

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC.

CLINICAL STUDY REPORT SYNOPSIS

RESULTS

Efficacy:

No efficacy parameters were measured in this trial, as the objectives were to evaluate the safety of the IMP in subjects with ragweed allergy.

Safety:

Treatment with MK-3641 12 Amb a 1-U was well-tolerated with a low rate of AEs leading to discontinuation. During the trial, there were no deaths, anaphylactic shocks or life-threatening events in patients treated with the MK-3641. There were 2 subjects who developed systemic allergic reactions – one subject on placebo and one subject treated with MK-3641. The subject on active treatment self-administered epinephrine appropriately and proceeded to the ER. In addition, two subjects treated with MK-3641 were treated with epinephrine due to local reactions on Day 3 and Day 14. The events progressed slowly and allowed subjects to self-administer epinephrine or seek medical attention. There were more subjects who reported any Treatment-Emergent Adverse Events (TEAEs) and who discontinued during the treatment period due to TEAEs in the AIT ragweed 12 Amb a 1-U group compared to that in the placebo group. No new safety concerns emerged during the trial

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

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

Coded using MedDRA Version 15.0.
The denominator for percentages is based on the number of subjects in each treatment group.
Treatment-emergent adverse events (TEAEs) are new or worsening AEs reported on or after treatment start date.
Related :Possible or Probable.
Subjects are counted once for each AE Category.

.

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC.

CLINICAL STUDY REPORT SYNOPSIS

CONCLUSIONS: In a 28 day study evaluating the safety of MK-3641 12 Amb a 1-U short ragweed (*Ambrosia artemisiifolia*) allergy immunotherapy tablet treatment in short ragweed allergic adults it was shown that the safety events rates are similar to what have been observed in previous trials with sublingual ragweed and grass AIT. The safety data showed no new or unexpected safety findings. The most frequently reported treatment-related adverse events were early occurring, transient, self-limited local application site reactions of the mouth, throat, and ear (primarily oral pruritus, throat irritation, and ear pruritus). These events are the common events that have been seen in previous trials with sublingual ragweed and grass AIT. Three subjects treated with MK3641 experienced adverse events, which was treated with epinephrine. Although these events occurred after the first tablet administration they were characterized by clinical symptoms, which progressed slowly and allowed subjects to self-administer epinephrine or seek medical attention in adequate time.