2.0 SYNOPSIS

SCHERING-PLOUGH RESEARCH INSTITUTE, A DIVISION OF SCHERING CORPORATION, A SUBSIDIARY OF MERCK & CO., INC. (hereafter referred to as Merck) **SCH 39641** Ragweed AIT, Sublingual Tablet Short Ragweed-Induced Rhinoconjunctivitis	**CLINICAL STUDY REPORT SYNOPSIS**

Title of Study: A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY EVALUATING THE EFFICACY AND LONG-TERM SAFETY OF RAGWEED (*AMBROSIA ARTEMISIIFOLIA*) SUBLINGUAL TABLET (SCH 39641) IN ADULT SUBJECTS WITH A HISTORY OF RAGWEED-INDUCED RHINOCONJUNCTIVITIS WITH OR WITHOUT ASTHMA (PROTOCOL NO. P05233)

Investigator(s)/Study Center(s): Multicenter (80 centers initiated): 67 centers initiated in the United States of America and 13 centers in Canada.

Publication(s): None

Study Period: 21 SEP 2009 To 23 MAY 2011 | **Clinical Phase:** 2/3

Duration of Treatment: Planned 52 weeks; Actual up to 57 weeks

Objective(s):

Primary Objective: To evaluate the efficacy of ragweed sublingual tablet (SCH 39641) versus placebo in the treatment of ragweed-induced rhinoconjunctivitis based on combined (sum of) rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS) averaged over the peak ragweed season (RS).

Key Secondary Objectives:

To assess overall long-term safety and to compare the following between the SCH 39641 and placebo groups:

1. The average combined (sum of) rhinoconjunctivitis DSS and rhinoconjunctivitis DMS for the entire RS
2. The average rhinoconjunctivitis DSS for the peak RS
3. The average rhinoconjunctivitis DSS for the entire RS
4. The average rhinoconjunctivitis DMS for the peak RS

Study Status: Completed.

Study Design: This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study in subjects 18 to 50 years of age, of either sex, and of any race with a history of significant ragweed-induced rhinoconjunctivitis with or without asthma. The subjects were treated once daily with either ragweed sublingual tablet (6 or 12 Amb a 1-U) or placebo, approximately 16 weeks prior to and during the entire RS and following the RS with an overall exposure duration to investigational medicinal product (IMP) of approximately 52 weeks. Prior to treatment initiation, each subject was supplied with self-injectable epinephrine for the treatment of acute severe systemic reactions. Subjects were instructed on how and when to use the medication. Open-label rescue medications for the rhinoconjunctivitis symptoms were supplied prior to the RS and consisted of a stepwise approach of predefined medications (oral antihistamine, antihistamine eye drop, nasal corticosteroid spray, and oral corticosteroid used when subjects had sufficient symptoms and when the RS had started). Subjects visited the study site for at least 11 visits: Screening, Randomization and On-site dosing of IMP (3 visits), Off-season, Preseason, On-season, End-of-season, Post-season (2 visits), and Final Visit, and at Unscheduled Visits as appropriate. The first three doses of IMP were administered at the study site, and the subject was monitored at the site for 30 minutes following dosing. Subsequent administration of IMP was done once daily at home at approximately the same time each day. A follow-up telephone call between the site and the subjects was made daily for the first 4 doses of at-home administration of IMP and also once approximately 1 week after the Final Visit. Additional Off-season Visits were scheduled depending on how early the subjects attended the Randomization Visit, in relation to the anticipated start of the RS.

This study was conducted in conformity with Good Clinical Practice (GCP). However, a total of 5 subjects from Site 63 were excluded from all safety and efficacy analyses due to significant GCP issues.

An external data safety monitoring committee (DSMC) was established prior to the start of the treatment phase. The purpose of the DSMC was to evaluate adverse event (AE) data and to provide recommendations regarding the conduct of the study to ensure the safety of the subjects.

Subject Disposition: A total of 565 subjects were randomized in a 1:1:1 ratio to either 12 or 6 Amb a 1-U ragweed AIT or Placebo. However, a total of 5 subjects from Site 63 were excluded from all safety and efficacy analyses due to significant GCP issues. Only 560 subjects who received double-blind treatment with either 12 Amb a 1-U ragweed AIT (n=186) or 6 Amb a 1-U ragweed AIT (n=188) or placebo (n=186) were analyzed.

Dosage/Formulation Nos.:
Test Product, Dose, Mode of Administration, Batch No: SCH 39641: 6 Amb a 1-U, and 12 Amb a 1-U (*Ambrosia artemisiifolia* extract) administered sublingually once daily, preferably at the same time each day. Batch Numbers for 6 and 12 Amb a 1-U were: W-H02635 (849967) and W-H02637 (849969); W-H02632 (849970) and W-H02634 (849972), respectively.
Reference Therapy, Dose, Mode of Administration, Batch No: Matching placebo (to test product) administered sublingually once daily, preferably at approximately the same time each day.
Batch Number for placebo was W-H02640 (848361).

Duration of Treatment: Approximately 52 weeks. Subjects were treated for approximately 16 weeks prior to start of the Ragweed Season (RS). The start and end of the RS was determined on the basis of the regional ragweed pollen count. The start date of the RS was defined as the first day of 3 consecutive recorded days with a ragweed pollen count of ≥10 grains/m^3, to the last day of the last occurrence of 3 consecutive recorded days with a ragweed pollen count ≥10 grains/m^3, and was determined after the site completed the last subject last visit and prior to database lock for each study period. A period of 15 consecutive recorded days with the highest moving average was defined as the peak RS.

Diagnosis and Criteria for Inclusion: Subjects, of either sex, and of any race, with a clinical history of significant ragweed-induced allergic rhinoconjunctivitis (with or without asthma) were selected for this study. Subjects from 18 to 50 years of age who had received treatment for their disease during the previous RS were recruited.

Key Inclusion Criteria:

1. Subject must have been 18 to 50 years of age, of either sex, and of any race
2. Subject must have had a clinical history of significant ragweed-induced allergic rhinoconjunctivitis of 2 years duration or more with or without asthma (diagnosed by a physician) and have received treatment for the disease during the previous RS
3. Subject must have had a positive skin prick test response to *Ambrosia artemisiifolia* at the Screening Visit
4. Subject must been positive for specific IgE against *Ambrosia artemisiifolia* (≥IgE Class 2) at the Screening Visit.
5. Subject must have had an forced expiratory volume in 1 second (FEV_1) of at least 70% of predicted value at the Screening Visit
6. A subject's safety laboratory tests and vital signs conducted at the Screening Visit must be within normal limits or clinically acceptable to the investigator/sponsor

Key Exclusion Criteria:

1. Subject had a clinical history of symptomatic seasonal allergic rhinitis and/or asthma having received regular medication, due to another allergen during or potentially overlapping the RS
2. Subject had a clinical history of significant symptomatic perennial allergic rhinitis and/or asthma having received regular medication due to another allergens to which the subject is regularly exposed
3. Subject had received an immunosuppressive treatment within 3 months prior to the Screening Visit (except steroids for allergic and asthma symptoms)
4. Subject had a clinical history of severe asthma
5. Subject had asthma requiring medium or high dose inhaled corticosteroids
6. Subject had a history of anaphylaxis with cardiorespiratory symptoms
7. Subject had a history of chronic urticaria and angioedema
8. Subject had a clinical history of chronic sinusitis during the 2 years prior to the Screening Visit
9. Subject had current severe atopic dermatitis
10. Female subject who was breast-feeding, pregnant, or intending to become pregnant
11. Subject had previous immunotherapy treatment with ragweed allergen or any other allergen within the 5 years prior to the Screening Visit
12. Subject had history of allergy, hypersensitivity or intolerance to the ingredients of the investigational medicinal products (except for *Ambrosia artemisiifolia*), rescue medications, or self-injectable epinephrine
13. Subject had a history of self-injectable epinephrine use

Evaluation Criteria:

Primary Efficacy Endpoint: The primary efficacy endpoint was the combined (sum of) rhinoconjunctivitis DSS and DMS averaged over the peak RS.

The combined score for each subject was calculated as the sum of rhinoconjunctivitis DSS and DMS during the peak RS, divided by the duration of the peak RS.

Key Secondary Efficacy Endpoints:

1. The combined (sum of) rhinoconjunctivitis DSS and rhinoconjunctivitis DMS during the entire RS
2. The average rhinoconjunctivitis DSS during the peak RS
3. The average rhinoconjunctivitis DSS during the entire RS
4. The average rhinoconjunctivitis DMS during the peak RS

Safety: Safety and tolerability were assessed by clinical review of all relevant parameters of AEs, vital signs, and safety laboratory assessments (hematology, blood chemistry, and urine analyses).

Statistical Planning and Analysis:

For the Primary Endpoints: The primary efficacy endpoint of combined (sum of) rhinoconjunctivitis DSS and DMS averaged over the peak RS was evaluated using an analysis of variance (ANOVA) model with baseline asthmatic condition (yes/no), pollen region, and treatment group as fixed effects in the model. Based on the ANOVA model, comparison of each active dose versus placebo was conducted using a step-down method, starting from the comparison of the high dose of SCH 39641 versus placebo, followed by the lower dose in a sequential manner. The inference on the lower dose comparison against placebo was carried out only if the previous comparison was statistically significant ($p<0.05$).

For each dose whose comparison against the placebo, a 2-sided 95% confidence interval (CI) of the difference in adjusted means between the two treatment groups was presented. Also, the difference in adjusted means between the two treatment groups relative to the adjusted mean of the placebo group was presented as a percentage with the corresponding CI.

For the primary endpoint, subjects with at least one post-randomization diary record for the symptom score within the defined peak RS were included in the analysis.

The PP population was used to performed supportive analyses for the primary efficacy endpoint (TCS during the peak RS), to corroborate the conclusions drawn from the FAS analyses. In addition to the per-protocol analysis, three sensitivity analyses were performed on the primary efficacy endpoint to assess the robustness of findings from the primary efficacy analysis, which include the mixed model for repeated measurements, last observation carried forward (LOCF), and Worst Case analyses.

For the Key Secondary Efficacy Endpoints: The secondary endpoints were evaluated using analytical methods similar to the primary endpoint. For the key secondary endpoints, the type I error rate was controlled. For each dose whose comparison against the placebo which meets the primary endpoint, testing of the key secondary endpoints was conducted in a stepwise manner as described in [**9.7.3.5**].

The Full Analysis Set (FAS) served as the primary population for the efficacy analyses. FAS population was defined as all randomized subjects who received at least one dose of study medication with at least one post-randomization efficacy measurement.

The PP population was used to performed supportive analyses for the key secondary endpoints (DSS during the peak RS, TCS and DSS during the entire RS, and DMS during the peak RS), to corroborate the conclusions drawn from the FAS analyses.

Safety Analysis: Safety and tolerability were assessed by a statistical and clinical review of all safety parameters, including AEs, laboratory values, and vital signs. Statistical tests were performed and the 95% CIs and p-values were displayed for the Tier 1 AEs (any treatment-emergent AEs [TEAE], any TEAE leading to study discontinuation, pre-specified local application site reactions [oral pruritis, ear pruritis, throat irritation, and oedema mouth] and serious hypersensitivity reaction). For Tier 2 events (that includes any related AE, any serious AE, any serious and related AE, and individual AEs that occurred in at least 4 subjects in one or more treatment groups), 95% CIs of the between treatment groups difference of incidence rates were provided. The p-values and 95% CIs of were derived using Miettinen and Nurminen (1985) method. For all other clinical and laboratory AEs, events were listed and summarized by frequency of occurrence, only the counts and percentages were tabulated by treatment group. Vital signs and selected laboratory tests were also summarized.

The All-Subjects-As-Treated (ASaT) approach was used for the safety analyses. ASaT population includes all randomized subjects who received at least one dose of study medication.

Missing Data: For DMS, the missing data were imputed as zero if the DSS was non-missing on the same day; otherwise, DMS remained as missing. No imputation of missing data were performed for the total combined score (TCS) and DSS endpoints.

Summary: A total of 565 subjects were randomized into the study. However, a total of 5 subjects from Site 63 were excluded from all safety and efficacy analyses due to significant GCP issues. Only 560 subjects who received double-blind treatment with either 12 Amb a 1-U ragweed AIT (n=186) or 6 Amb a 1-U ragweed AIT (n=188) or placebo (n=186) were analyzed. A total of 423 (74.9%) randomized subjects completed the protocol-specified, double-blind treatment period. The median preseasonal duration of treatment was approximately 17 weeks. Demographic and Baseline characteristics were well matched between the treatment groups. Overall, the median age was 37 years, 51% of subjects were female, and approximately 78% were white. Twenty-one percent of subjects had a diagnosis of asthma. Median duration of ragweed allergy at Baseline was approximately 18 years. All subjects tested positive by serum specific IgE measurements to *Ambrosia artemisiifolia* and all subjects tested positive for short ragweed pollen (*Ambrosia artemisiifolia*) by skin prick testing at Screening. In addition, 85.1% of all subjects were multi-sensitized to additional allergens, with notable trends in sensitization to other pollens such as grasses and/or trees. Approximately, one third of subjects were sensitized to perennial allergens including danders and dust mites. More than 20% of the population showed IgE reactivity to *Alternaria* (mold).

Results and Conclusions: All of the pre-specified primary and key secondary objectives covered by the multiplicity control, yielded statistically significant results in favor of ragweed AIT 12 Amb a 1-U as compared to placebo. A summary for the magnitude of treatment effect expressed in least square (LS) means (adjusted means) for the primary and key secondary endpoints are provided in **Table 1**. The endpoints are listed in the order consistent with multiplicity strategy. There was a dose-related response for the primary and all the key efficacy endpoints.

Table 1 Summary of TCS, DSS, and DMS Efficacy Results of P05233

Endpoint	N	Adjusted Mean	Treatment Difference (Ragweed AIT – Placebo) (95% CI)	% Relative to Placebo (95% CI)	P-Value
TCS Peak					
12 Amb a 1-U	159	6.22	-2.24 (-3.41, -1.07)	-26.49 (-38.74, -14.59)	0.0002
6 Amb a 1-U	150	6.70	-1.76 (-2.95, -0.57)	-20.82 (-34.06, -7.08)	0.0039
Placebo	164	8.46	---	---	---
TCS Entire RS					
12 Amb a 1-U	160	5.21	-1.80 (-2.78, -0.82)	-25.66 (-37.55, -13.48)	0.0003
6 Amb a 1-U	152	5.92	-1.09 (-2.08, -0.09)	-15.50 (-29.55, -1.65)	0.0320
Placebo	166	7.01	---	---	---
DSS Peak					
12 Amb a 1-U	159	4.65	-0.94 (-1.70, -0.19)	-16.87 (-28.64, -4.62)	0.0144
6 Amb a 1-U	150	4.81	-0.78 (-1.54, -0.01)	-13.89 (-26.51, - 0.04)	0.0472
Placebo	164	5.59	---	---	---
DSS Entire RS					
12 Amb a 1-U	160	4.05	-0.82 (-1.46, -0.18)	-16.85 (-28.47, -4.54)	0.0125
6 Amb a 1-U	152	4.41	-0.46 (-1.11, 0.19)	-9.39 (-22.67, 4.28)	0.1686
Placebo	166	4.87	---	---	---
DMS Peak					
12 Amb a 1-U	159	1.57	-1.30 (-1.95, -0.64)	-45.26 (-65.39, -26.99)	0.0001
6 Amb a 1-U	150	1.89	-0.98 (-1.65, -0.32)	-34.28 (-54.97, -13.31)	0.0039
Placebo	164	2.87	---	---	---

TCS (total combined score) is the sum of DSS (daily symptom score) and DMS (daily medication score) and ranges from 0-54. RS=ragweed season; CI=confidence interval; Difference is compared to placebo; % Relative to Placebo= (ragweed AIT-placebo)*100.
Due to Site issues, subjects from site 63 are excluded from the efficacy analysis.

The conclusions from the primary and key secondary endpoints are as follows:

- Ragweed AIT (12 and 6 Amb a 1-U ragweed allergy immunotherapy tablet) improved the TCS compared to placebo during the peak ragweed pollen season. Results were statistically significantly lower than placebo in the 12 Amb a 1-U (26.49%; -2.24; p=0.0002) and 6 Amb a 1-U (20.82%; -1.76; p=0.0039) treatment groups
- Statistically significant results for the 12 Amb a 1-U ragweed AIT treatment group compared to placebo were revealed for all key secondary endpoints. The 6 Amb a 1-U group demonstrated statistically significant improvement for all key secondary endpoints with the exception of DSS over the entire RS
- Results for all key efficacy endpoints were consistent in showing a more pronounced treatment effect for the 12 Amb a 1-U dose compared to the 6 Amb a 1-U dose
- Overall results of the key efficacy endpoints analyzed on the FAS were confirmed by the results on the per protocol (PP) subject population

Results from the additional secondary endpoints further supported the effects of ragweed AIT. The conclusions from the additional secondary endpoints are as follows:

- Subjects treated with 12 and 6 Amb a 1-U ragweed AIT demonstrated lower (24.09% and 13.58%, respectively) total rhinoconjunctivitis quality of life questionnaire with standardised activities (RQLQ[S]) score over placebo during the peak RS, indicating improved disease specific QoL. The difference in RQLQ(S) scores demonstrated statistical significance in favor of the 12 Amb a 1-U ragweed AIT group (-0.44; p=0.0025)
- Each of the 12 and 6 Amb a 1-U ragweed AIT treatments decreased the need for rescue medication over placebo during the entire RS. Results were statistically significantly lower than placebo in the 12 Amb a 1-U (45.86%; -0.98; p=0.0004) and 6 Amb a 1-U (29.37%; -0.63; p=0.0245) treatment groups. The treatment difference was seen at the start of the RS and was maintained throughout the season
- A greater number of minimal symptom days during the RS was observed for subjects in each of the 12 and 6 Amb a 1-U ragweed AIT treatment groups (13.76 days and 14.36 days, respectively) as compared to subjects in the placebo group (12.03 days), however, none of the differences between ragweed AIT treatments groups and the placebo were statistically significant (14.43% in the 12 Amb a 1-U group and 19.40% in the 6 Amb a 1-U group)
- The analysis of work productivity and activity impairment-allergy specific questionnaire (WPAI-AS) subscale score indicated that treatment with ragweed AIT did not significantly impact work productivity in ragweed pollen allergic subjects during the ragweed season
- In line with the lower DSS results in the ragweed AIT groups, the visual analogue scale (VAS) also showed lower symptom score during the entire RS and peak RS in the 12 and 6 Amb a 1-U treatment groups over the placebo group, with statistically significant results in the 12 Amb a 1-U (-5.65; p=0.0088 [entire RS] and -6.38; p=0.0086 [peak RS])
- Asthma DSS results for asthmatics during the peak RS displayed numerical trends in favor of the 12 and 6 Amb a 1-U ragweed AIT treatment groups over placebo, with 55.51% and 13.64%, respectively, lower asthma symptoms during the peak RS compared to placebo
- Asthma DSS results for asthmatics during the entire RS displayed numerical trends in favor of the 12 and 6 Amb a 1-U ragweed AIT treatment groups over placebo, with 49.75% and 15.14%, respectively, lower asthma symptoms during the entire RS compared to placebo

The results from the immunological measures demonstrated overall a significant increase in IgE and IgG4 activity:

- Higher induction of *Ambrosia artemisiifolia* specific IgE levels was noted between ragweed AIT and placebo treatment groups
- *Ambrosia artemisiifolia* specific IgG4 showed a substantially larger immunological response in subjects treated with 12 and 6 Amb a 1-U ragweed AIT compared to placebo

The following safety conclusions can be drawn from this study:

- There were no reports of anaphylactic shock and no life threatening AEs related to study drug
- Treatment with ragweed AIT (6 and 12 Amb a 1-U) was well tolerated with most discontinuations due to treatment-emergent adverse events (TEAEs) assessed as mild or moderate in severity
- Statistically significantly higher proportions of subjects discontinued due to TEAEs in the 12 and 6 Amb a 1-U ragweed AIT groups compared to the placebo group (10.2% in the 12 and 8.0% in the 6 Amb a 1-U groups versus 1.6% for placebo; p=0.001)
- Statistically significantly higher proportions of subjects reported any TEAEs, and local AEs such as throat irritation, ear pruritus, and oral pruritus in the 12 and 6 Amb a 1-U ragweed AIT groups compared to the placebo group; the between-treatment differences ranged from 9% to 24% for the 12 Amb a 1-U group versus the placebo ($p \leq 0.001$), and from 6% to 20% for the 6 Amb a 1-U group versus placebo ($p \leq 0.004$)
- The most frequently reported treatment-related TEAEs were expected, local application site reactions of mouth, throat, and ear (primarily oral pruritus, throat irritation, ear pruritus, and paraesthesia oral; the majority were reported by subjects in the ragweed AIT groups, and were considered mild or moderate in severity. These events are the common events that occur early (Day 1) in treatment, as have been seen in previous trials with sublingual AIT
- Nine subjects (3 subjects in the 12 Amb a 1-U group, 2 subjects in the 6 Amb a 1-U group, and 4 subjects in the placebo group) reported serious adverse events (SAEs) (14 events in 9 subjects) during the study. All SAEs were considered to be unlikely related to study drug
- There was no indication of a differential response to treatment with regard to AEs between asthmatic and non-asthmatic subjects, and there were no safety signals that emerged in the asthmatic group
- Two subjects (one each, in the 6 and 12 Amb a 1-U groups) received epinephrine during the study. One was considered probably related to IMP and the other unrelated to IMP
- No deaths occurred during the study
- No clinically relevant changes in vital signs, pulmonary function tests (FEV_1 and forced vital capacity [FVC]), and laboratory values (hematology and blood chemistry) were observed
- There was no obvious difference in the overall safety profile between the 6 Amb a 1-U and 12 Amb a 1-U treatment groups
- No new safety signals as compared to previous studies were detected

The overall safety profile of 12 and 6 Amb a 1-U was similar, and therefore, due to the larger treatment effect, the 12 Amb a 1-U dose is recommended for future ragweed AIT trials.

Date of Report: 25 OCT 2011