2.0 SYNOPSIS

Title of Study: A 28-DAY STUDY EVALUATING THE SAFETY OF RAGWEED (*AMBROSIA ARTEMISIIFOLIA*) SUBLINGUAL TABLET (SCH 39641) IN ADULT SUBJECTS 50 YEARS OF AGE AND OLDER WITH RAGWEED-INDUCED RHINOCONJUNCTIVITIS (PROTOCOL NO. P06081)	
Investigator(s): Multicenter	
Study Center(s): 30 centers initiated (of 36 total planned centers) in the United States	
Publication(s): None	
Studied Period: 10 NOV 2009 to 22 FEB 2010	**Clinical Phase:** 2
Objective(s): **Primary Objective:** To assess the safety of SCH 39641 (short ragweed sublingual tablets) in subjects 50 years of age and older with ragweed-induced rhinoconjunctivitis, with or without asthma. **Secondary Objective:** To assess the frequency of particular adverse events (AEs) expected to occur commonly with the local application of this therapy, namely, oral pruritus, ear pruritus, throat irritation and mouth edema. Additionally, discontinuations due to treatment-emergent AEs were evaluated.	
Methodology: This was a 28-day (outside of short ragweed season), randomized, placebo-controlled parallel-group, multi-site, double-blind trial in subjects 50 years of age and older, of either sex and of any race with a history of ragweed-induced rhinoconjunctivitis with or without asthma. Following completion of the Screening Period, qualified subjects were randomized at Visit 2 to receive either 6 or 12 Amb a 1-U short ragweed tablets or placebo in a 1:1:1 ratio. At the Randomization Visit (Visit 2), subjects were supplied with self-injectable epinephrine together with instructions on how and when to use it. Subjects were to complete at least 6 visits: Screening, Randomization, 2 trial visits for on-site dosing, a final trial visit, and a follow-up telephone visit to have occurred approximately 1 week after the final trial visit. Starting at Visit 2, subjects were administered investigational medicinal product (IMP) at approximately the same time each day. The first three consecutive daily doses of IMP were administered at the trial site, and the subjects were monitored for at least 30 minutes after each administration for observation of any AEs. Subsequent administration of IMP was done once daily at home at approximately the same time each day. A telephone call between the investigator/designee and the subject was to occur once daily for the first 4 days of at-home administration of IMP and at 1-week intervals during the trial. Unscheduled visits were also to have occurred if needed. This trial was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.	
Number of Subjects: A total of 196 subjects (excluding 7 subjects from Site 31) were randomized in a 1:1:1 ratio to either 6 or 12 Amb a 1-U short ragweed tablet, or placebo; 66 subjects were in the 6 Amb a 1-U short ragweed tablet group, 65 subjects were in the 12 Amb a 1-U short ragweed tablet group, and 65 subjects were in the placebo group.	

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Diagnosis and Criteria for Inclusion: Subjects 50 years of age and older, of either sex and of any race/ethnicity, with a clinical 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 be 50 years of age and older, of either sex, and of any race/ethnicity.
2. Subject must have a clinical history of physician-diagnosed ragweed-induced allergic rhinoconjunctivitis of 2 years duration or more, with or without asthma.
3. Subject must have a positive skin prick test response to *Ambrosia artemisiifolia* at the Screening Visit ($\geq$ 5 mm wheal).
4. Subject must have a forced expiratory volume in 1 second (FEV1) of at least 70% of predicted value at the Screening Visit and at Randomization.
5. A subject's clinical laboratory tests, electrocardiogram (ECG) 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 with asthma who requires inhaled corticosteroids for the treatment of their asthma during the study period.
2. Subject requiring anti-allergy medications during the time period from randomization to study completion.
3. Subject who has received an immunosuppressive treatment within 3 months prior to the Screening Visit (except steroids for allergic and asthma symptoms).
4. Subject with a history of anaphylaxis with cardiorespiratory symptoms.
5. Subject with a history of chronic urticaria or angioedema.
6. Subject with current severe atopic dermatitis.
7. Female subject who is breastfeeding, pregnant, or intending to become pregnant.
8. Subject with a history of allergy, hypersensitivity or intolerance to the ingredients of the investigational medicinal products (IMPs) (except for Ambrosia artemisiifolia), or self-injectable epinephrine.
9. Subject with a history of self-injectable epinephrine use.

Test Product, Dose, Mode of Administration, Batch No(s): Short ragweed sublingual tablets (SCH 39641) 6 and 12 Amb a 1-U *(Ambrosia artemisiifolia extract*) administered sublingually once daily, preferably at the same time each day;

Batch Nos. W-H02635 (849967) and W-H02632 (849970), respectively.

Duration of Treatment: Each subject was to participate in the trial for approximately 10 weeks from the time the subject signed the Informed Consent Form (ICF) through the final contact. After a Screening phase of up to 4 weeks, each subject was to receive assigned treatment for approximately 28 days. After the end of treatment, each subject was to be followed for 7 days. A follow-up telephone visit was to occur approximately 7 days after the final visit.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Matching placebo (to test product) administered sublingually once daily; preferably at the same time each day; Batch No. W-H02640 (848361)

Criteria for Evaluation: Since the primary objective of this trial was to evaluate the safety of the 6 and 12 Amb a 1-U short ragweed tablets, traditional efficacy analysis was not performed. However, measures of lung function were collected to monitor subject safety.

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Prespecified Safety Endpoints: The Prespecified Safety Endpoints were related to the Primary Trial Objective and the Key Secondary Trial Objective.

Primary Safety Endpoint:

The Primary Safety Endpoint for this trial was the proportion of subjects reporting treatment-emergent AEs.

Key Secondary Safety Endpoint:

The Key Secondary Safety Endpoint was the proportion of subjects reporting local AEs that may have occurred with application of this type of therapy, including oral pruritus, ear pruritus, throat irritation, and mouth edema, and the frequency of discontinuations due to treatment-emergent AEs.

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

Safety Analysis:
Prespecified Safety Endpoints (Primary and Key Secondary): The prespecified safety endpoints were the proportion of subjects reporting treatment emergent AEs, local AEs (oral pruritus, ear pruritus, throat irritation, and mouth edema), and the frequency of discontinuation due to treatment-emergent AEs. The incidence of treatment-emergent local AEs and discontinuations were tabulated by treatment and stratification factors (age and asthma status). The prespecified endpoints were based on the All Treated data set and were summarized by treatment group and stratification factors (age and asthma status).
Commonly Occurring Safety Endpoints: The commonly occurring safety events were defined as those AEs that occur in more than 10% of subjects in either short ragweed tablet (SCH 39641) treatment group. Point estimates and two-sided 95% confidence intervals for the difference in proportions between each active treatment arm and placebo were provided for events that occurred in more than 10% of subjects in either short ragweed (SCH 39641) treatment group.
Descriptive Safety Endpoints: The descriptive safety endpoints included vital signs, oral examinations, safety laboratory measurements, spirometry, and physical examinations. The descriptive safety endpoint analyses were based on the All Treated data set, and were summarized by treatment group using descriptive statistics (N, mean, median, standard deviation, range).

Note that no data safety monitoring board was used due to the short duration of the trial.

SUMMARY-CONCLUSIONS:

RESULTS: A total of 196 subjects (excluding Site 31) were randomized to double-blind treatment, with 66 subjects receiving 6 Amb a 1-U short ragweed tablets, 65 subjects receiving 12 Amb a 1-U short ragweed tablets, and 65 subjects receiving placebo outside of the ragweed season. A total of 186 (approximately 94.9%) subjects overall completed the protocol-specified, double-blind treatment period. Overall, demographic and baseline characteristics were well-balanced across the treatment groups. Overall, the mean age was 56 years, approximately 61.7% (121/196) were female, and approximately 84.2% (165/196) were white. Subjects reported a mean history of seasonal-induced short ragweed rhinoconjunctivitis of approximately 31 years. All subjects tested positive for short ragweed pollen (*Ambrosia artemisiifolia)* by skin prick testing at Screening. Overall, approximately 11% of subjects had a diagnosis of asthma.

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.

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Safety: Review of the safety data demonstrates that treatment with both 6 and 12 Amb a 1-U short ragweed tablets was well tolerated in subjects 50 years of age and older with no deaths, anaphylactic shock, life-threatening events, or treatment-related serious adverse events.

For the primary safety variable, higher percentages of treatment-emergent AEs were reported by subjects in the 12 Amb a 1-U short ragweed tablet group (61.5%) and in the 6 Amb a 1-U short ragweed tablet group (51.5%), than by subjects in the placebo group (44.6%). In the active treatment groups, the most frequently reported treatment-emergent AEs were:

- oral pruritus (16.7% in the 6 Amb a 1-U short ragweed tablet group; 16.9% in the 12 Amb a 1-U short ragweed tablet group);
- throat irritation (12.1% in the 6 Amb a 1-U short ragweed tablet group; 9.2% in the 12 Amb a 1-U short ragweed tablet group);
- ear pruritus (6.1% in the 6 Amb a 1-U short ragweed tablet group; 7.7% in the 12 Amb a 1-U short ragweed tablet group);
- oral paraesthesia (4.5% in the 6 Amb a 1-U short ragweed tablet group; 6.2% in the 12 Amb a 1-U short ragweed tablet group); and
- eye pruritus (3.0% in the 6 Amb a 1-U short ragweed tablet group; 6.2% in the 12 Amb a 1-U short ragweed tablet group).

These are expected local allergic reactions commonly experienced with the application of sublingual immunotherapy, and the majority of these events were mild or moderate in severity. In general symptoms occur immediately after tablet administration and resolve quickly and within the first week of treatment.

For the key secondary variables, 49 subjects (approximately 25% overall) reported treatment-related local AEs, with an expectedly higher number of subjects reporting these events in the active treatment groups (21 subjects, or 32.3% in the 12 Amb a 1-U short ragweed tablet group; 22 subjects, or 33.3% in the 6 Amb a 1-U short ragweed tablet group; 6 subjects, or 9.2% in the placebo group). The most frequently reported treatment-related local AEs were:

- oral pruritus (16.7% in the 6 Amb a 1-U short ragweed tablet group; 16.9% in the 12 Amb a 1-U short ragweed tablet group);
- throat irritation (12.1% in the 6 Amb a 1-U short ragweed tablet group; 7.7% in the 12 Amb a 1-U short ragweed tablet group);
- ear pruritus (6.1% in the 6 Amb a 1-U short ragweed tablet group; 7.7% in the 12 Amb a 1-U short ragweed tablet group);
- oral paraesthesia (4.5% in the 6 Amb a 1-U short ragweed tablet group; 6.2% in the 12 Amb a 1-U short ragweed tablet group); and
- swollen tongue (4.5% in the 6 Amb a 1-U short ragweed tablet group; 4.6% in the 12 Amb a 1-U short ragweed tablet group).

The treatment-related local AE of mouth edema occurred in only one subject (1.5% in the 6 Amb a 1-U short ragweed tablet group). These local AEs are the common events that occur early in treatment, as similar findings have been seen in previous trials with grass and short ragweed sublingual allergy immunotherapy tablets (AIT). Occurrences of local symptoms of swollen tongue and oral pruritus at tablet administration were not reported after a median of 2 and 5 days after treatment initiation, respectively.

Treatment with both 6 and 12 Amb a 1-U short ragweed tablet was well tolerated with few discontinuations due to adverse events: 2 subjects (3.0%) in the 6 Amb a 1-U short ragweed tablet group, 5 subjects (7.7%) in the 12 Amb a 1-U short ragweed tablet group, and 1 subject (1.5%) in the placebo group.

For the commonly occurring safety variable, only two adverse events occurred in more than 10% of the subjects in either the 6 or 12 Amb a 1-U short ragweed tablet group: oral pruritus and throat irritation. There were no notable differences in the numbers of subjects reporting these events between the 6 and 12 Amb a 1-U short ragweed tablet treatment groups. All of the events of both oral pruritus and throat irritation were mild or moderate in severity.

A total of five local application site AEs (experienced by 2 subjects in the 12 Amb a 1-U short ragweed tablet group) were graded as severe events: four events of swollen tongue and one event of throat tightness. One of these subjects required treatment for the severe events with an antihistamine while the other subject's events

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resolved without treatment. Both subjects discontinued from the trial due to the events.

There were no administrations of epinephrine for treatment-related adverse events. One subject in the 12 Amb a 1-U short ragweed tablet group inappropriately self-administered epinephrine during the study over 24 hours following the last dose of IMP due to gastrointestinal AEs. These events were assessed by the investigator as moderate in severity and unlikely related to study medication. The subject discontinued from the trial.

Although there were few asthmatics included in the trial (n=9 for 6 Amb a 1-U short ragweed tablet; n=6 for 12 Amb a 1-U short ragweed tablet; n=7 placebo), there was no indication of worsening of asthmatic status during the trial.

Additionally, review of vital signs, pulmonary function tests (FEV1 and forced vital capacity [FVC]), and laboratory values (hematology and blood chemistry) revealed no clinically relevant changes. Finally, no new safety signals were detected with either dose of short ragweed tablets.

CONCLUSIONS*:*

- Doses of 6 and 12 Amb a 1-U of the short ragweed tablet were safe and well tolerated in subjects 50 years of age and older for up to 36 days of treatment.

- Primary safety results show that a total of 56.5% of subjects in the active treatment groups (51.5% in the 6 Amb a 1-U short ragweed tablet group; 61.5% in the 12 Amb a 1-U short ragweed tablet group), and 44.6% of subjects in the placebo group reported a treatment-emergent AE during the treatment period.

- The most frequently reported treatment-emergent adverse events (TEAEs) were local events of the mouth, throat, and ear, which are common and expected events that have been seen in previous trials with sublingual AIT (RT-01 and grass AIT trials).

- Key secondary results confirm that local application site reactions are common with short ragweed AIT treatment, with 32.3% of subjects 12 Amb a 1-U short ragweed tablet group, 33.3% in the 12 Amb a 1-U short ragweed tablet group, and 9.2% of subjects in the placebo group reporting these events. The most frequently reported treatment-related local AEs in the active treatment groups were:
    - oral pruritus (16.7% in the 6 Amb a 1-U short ragweed tablet group; 16.9% in the 12 Amb a 1-U short ragweed tablet group);
    - throat irritation (12.1% in the 6 Amb a 1-U short ragweed tablet group; 7.7% in the 12 Amb a 1-U short ragweed tablet group);
    - ear pruritus (6.1% in the 6 Amb a 1-U short ragweed tablet group; 7.7% in the 12 Amb a 1-U short ragweed tablet group);
    - oral paraesthesia (4.5% in the 6 Amb a 1-U short ragweed tablet group; 6.2% in the 12 Amb a 1-U short ragweed tablet group); and
    - swollen tongue (4.5% in the 6 Amb a 1-U short ragweed tablet group; 4.6% in the 12 Amb a 1-U short ragweed tablet group).

  Mouth edema occurred in only one subject (6 Amb a 1-U short ragweed tablet group). The local application site reactions were mild and moderate and resolved spontaneously within the first week.

- Key secondary results also revealed few subjects discontinuing the trial due to treatment-emergent AEs (7 subjects in the active treatment groups and 1 subject in the placebo group). Of the 8 subjects who discontinued from the trial, only 2 actively treated subjects and 1 placebo treated subject discontinued due to treatment-related events.

- Only two commonly occurring AEs were reported by at least 10% of subjects in either short ragweed tablet treatment group: oral pruritus (22 subjects) and throat irritation (14 subjects). All of these events were considered mild or moderate in severity.

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- There was no indication of worsening of asthmatic status during the trial.
- No clinically relevant changes in vital signs, pulmonary function tests (FEV1 and FVC), and laboratory values (hematology and blood chemistry) were observed.
- No new safety concerns emerged during the trial.

Date of the Report: 13 APR 2011