

## Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults

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**Background:** In North America and Europe, millions of patients experience symptoms of allergic rhinitis with or without conjunctivitis (AR/C) on exposure to ragweed pollen. The disease burden can be significant, with most patients relying on symptomatic medications without disease-modifying potential. However, novel sublingual immunomodulatory treatment options may potentially play an important role if efficacy and side effect profiles allow the convenience of self-administration. **Objectives:** This study evaluated an allergy immunotherapy tablet (AIT; SCH 39641/MK-3641) for treatment of ragweed-induced AR/C in the first large randomized, double-blind multinational trial of this therapeutic modality for ragweed allergy.

**Methods:** Adults (n = 784) with short ragweed-induced AR/C were randomly assigned to approximately 52 weeks of daily self-administered ragweed AIT of 1.5, 6, or 12 units of *Ambrosia artemisiifolia* major allergen 1 (Amb a 1-U) or placebo. Subjects

could use as-needed allergy rescue medication. Symptoms and medications were recorded daily. The primary efficacy end point was total combined daily symptom/medication score (TCS) during peak ragweed season. Safety was monitored through adverse event diaries maintained through study duration.

**Results:** During peak ragweed season, ragweed AIT of 1.5, 6, and 12 Amb a 1-U reduced TCS by 9% (−0.76; *P* = .22), 19% (−1.58; *P* = .01), and 24% (−2.04; *P* = .002) compared with placebo. During the entire season, ragweed AIT of 1.5, 6, and 12 Amb a 1-U reduced TCS by 12% (−0.88; *P* = .09), 18% (−1.28; *P* = .01), and 27% (−1.92; *P* < .001) compared with placebo. Treatment was well tolerated; no systemic allergic reactions occurred.

**Conclusions:** In this trial, ragweed AIT of 12 Amb a 1-U was effective and tolerable with a safety profile that permitted daily self-administration of ragweed allergen immunotherapy. (J Allergy Clin Immunol 2013;131:1342-9.)

**Key words:** Allergy immunotherapy tablet, allergic conjunctivitis, allergic rhinitis, allergic rhinoconjunctivitis, specific immunotherapy, ragweed pollen, sublingual immunotherapy

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The pollen of short ragweed (*Ambrosia artemisiifolia*; common ragweed) is an important seasonal aeroallergen, native to North America, that cross-reacts with other ragweed species and is often cross-reactive with its European relative mugwort.<sup>1-4</sup> Ragweed sensitization is one of the most common allergies, thought to exist in approximately 26% of the US population.<sup>5</sup> A warming climate may be contributing to a longer ragweed pollen season.<sup>6</sup> In addition, ragweed is expanding in range, and, whereas it was predominantly a North American problem until recently, high rates of prevalence and sensitization are now seen in many European countries.<sup>7</sup>

Currently available treatments consist of symptomatic pharmacotherapy and subcutaneous immunotherapy injections, which have shown the advantage of disease-modifying potential.<sup>8-11</sup> However, patients have cited the need for regular physician visits to receive injections over a full course of immunotherapy as a key reason to discontinue or not to initiate therapy.<sup>12</sup> Immunotherapy carries risks of systemic allergic reactions of various severities. In recent results from a surveillance program that included 630 allergist practices, systemic reactions were observed at a rate of 9.7 per 10,000 injection visits, with 17% of practices reporting at least 1 severe anaphylactic reaction over a year.<sup>13</sup> Fatal reactions, although previously estimated to be as rare as 1 in every 2.45

#### Abbreviations used

|            |                                                          |
|------------|----------------------------------------------------------|
| AE:        | Adverse event                                            |
| AIT:       | Allergy immunotherapy tablet                             |
| Amb a 1-U: | Units of <i>Ambrosia artemisiifolia</i> major allergen 1 |
| AR/C:      | Allergic rhinitis with or without conjunctivitis         |
| DMS:       | Daily medication score                                   |
| DSS:       | Daily symptom score                                      |
| RS:        | Ragweed pollen season                                    |
| TCS:       | Total combined score                                     |
| VAS:       | Visual analog scale                                      |

million injections and appearing to be declining in frequency, remain a cause for caution.<sup>13,14</sup>

Immunotherapy administered via sublingual allergen tablets or drops, although not approved in the United States, is an established mode of therapy in Europe.<sup>15-17</sup> Allergy immunotherapy tablet (AIT) treatments are under investigation in North America as alternatives to subcutaneous immunotherapy for patients with allergic rhinitis with or without conjunctivitis (AR/C). In North American trials, AIT treatment for AR/C induced by timothy and related grasses has been found effective and well tolerated.<sup>18,19</sup> Evidence from clinical trials suggests that sublingual tablets may be associated with a more benign adverse event (AE) profile than injections. Limited research has investigated sublingual drops or tablets in subjects with ragweed allergy<sup>20-24</sup>; efficacy and safety of ragweed AIT have remained to be confirmed in large-scale randomized double-blind trials.

This study was conducted to investigate the efficacy and tolerability of daily administration of a novel ragweed AIT (SCH 39641/MK-3641) formulation, which may permit self-administered sublingual immunotherapy treatment in adult subjects with ragweed pollen-induced AR/C with or without asthma in North America, Europe, and Russia.

## METHODS

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-ranging study (<http://clinicaltrials.gov/show/NCT00770315>); 72 centers were initiated in the United States, 12 in Canada, 20 in Hungary, 8 in Ukraine, and 2 in Russia. The study was conducted in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines. Institutional review boards for each center approved the protocol, and all subjects gave written informed consent before any study activity.

Subjects were aged 18 to 50 years, of either sex, with a physician-diagnosed history of ragweed-induced AR/C of  $\geq 2$  years' duration with or without asthma and had received treatment for their AR/C during the previous ragweed pollen season (RS). At screening, subjects were required to meet these inclusion criteria: positive response of skin prick test to *Ambrosia artemisiifolia* (wheal  $\geq 5$  mm larger than saline control) with the use of ragweed extract standardized by the Food and Drug Administration and Duotip prick device provided by ALK-Abelló, Inc; positive for specific IgE against *Ambrosia artemisiifolia* ( $\geq$ IgE class 2;  $\geq 0.7$  kU/L); and an FEV<sub>1</sub>  $\geq 70\%$  of predicted value. Reasons for exclusion included symptomatic (as per clinical history) seasonal or perennial AR/C and/or asthma (requiring regular medication) because of another allergen during or potentially overlapping RS; immunosuppressive treatment within the past 3 months (except low-dose inhaled corticosteroids for allergic/asthma symptoms); previous immunotherapy with ragweed or other allergen within the past 5 years; severe asthma or asthma that required medium/high-dose inhaled corticosteroids; severe atopic dermatitis; and history of anaphylaxis with cardiorespiratory symptoms, chronic urticaria and

angioedema, chronic sinusitis within the past 2 years, or self-injectable epinephrine use. Additional inclusion/exclusion criteria were included (see this article's **Methods** section in the Online Repository at [www.jacionline.org](http://www.jacionline.org)).

Subjects were randomly assigned in appropriately sized blocks according to a computer-generated randomization schedule in a 1:1:1:1 ratio to once-daily treatment with standardized short ragweed AIT tablets (1.5, 6, or 12 units of *Ambrosia artemisiifolia* major allergen 1 [Amb a 1-U]) or placebo, initiated approximately 16 weeks before and continuing throughout the RS and thereafter (total, 52 weeks). Fig E1 (in the Online Repository at [www.jacionline.org](http://www.jacionline.org)) shows the study design. Doses were selected on the basis of the results of a safety trial of ragweed AIT (RT-01; [www.clinicaltrials.gov](http://www.clinicaltrials.gov) registration NCT00330083).<sup>24</sup> Additional study design details are available (see this article's **Methods** section in the Online Repository).

The first 3 doses of investigational medication were administered at the study site, with subjects monitored for 30 minutes after dosing for AEs; subsequent doses were self-administered at home. As a precaution, each subject was supplied with self-injectable epinephrine for use in the event of an acute severe systemic allergic reaction. Subjects in all treatment groups had access to predefined, open-label allergy rescue medications to use in a stepwise manner during RS if a prespecified AR/C symptom threshold was met.

The primary end point of the study was the total combined score (TCS), which is the sum of the AR/C daily symptom score (DSS) and daily medication score (DMS), averaged over the peak RS. Key secondary end points were the average AR/C TCS over the entire RS, the average AR/C DSS over peak RS, the average AR/C DSS over the entire RS, and the average AR/C DMS over peak RS. The AR/C DMS over the entire RS and symptoms measured via a visual analog scale (VAS) were additional secondary end points. Subjects who received at least 1 dose of study medication and provided at least 1 posttreatment diary data entry were included in primary efficacy analyses (full analysis set, following the intent-to-treat principle). At trial conception, the primary end point was TCS over the entire RS; before results were known, this was changed to TCS over the peak RS. This decision was informed by the experience with grass AIT sublingual therapy. From a clinical perspective, measuring TCS while subjects have the most significant burden of AR/C symptoms due to the highest pollen exposure was considered the best means of evaluating the efficacy of this therapy and appropriately assessing the robustness of the treatment effect. The DSS and DMS evaluations included as key secondary end points were also changed to reflect peak-season scores; entire-season TCS and DSS also became key secondary end points.

The RS was defined as beginning on the first of 3 consecutive recorded days with pollen count  $\geq 10$  grains/m<sup>3</sup> and ending on the last day of the last occurrence of 3 consecutive days with pollen count  $\geq 10$  grains/m<sup>3</sup>. Peak season was defined as the 15 consecutive recorded days within the RS with the highest 15-day moving average pollen count for each site. Pollen regions were defined according to pollen stations and included sites within an acceptable distance from pollen counters (counters were within approximately 50 miles from the subject's home). Seven pollen regions were in Canada, 36 in the United States, and 21 in Ukraine/Russia/Hungary.

Six AR/C (runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes) and 3 asthma (cough, wheeze, and chest tightness/shortness of breath) symptom scores were recorded once daily in an electronic diary, reflecting the past 24 hours, from randomization through end of RS. The AR/C DSS was calculated as the sum of scores for the 6 AR/C symptoms each measured as follows: 0, no symptoms; 1, mild symptoms; 2, moderate symptoms; or 3, severe symptoms. Stepwise rescue medication use was scored as follows to calculate the DMS: loratadine 10-mg tablet (Merck Sharp & Dohme Corp, Whitehouse Station, NJ), 6 points/tablet, maximum 6 points/day; olopatadine HCl 0.1% ophthalmic solution (Alcon, Hünenberg, Switzerland), 1.5 points/drop, maximum 6 points/day; mometasone furoate nasal spray 50  $\mu$ g (Merck Sharp & Dohme Corp), 2 points/spray, maximum 8 points/day; prednisone 5-mg tablet (West-Ward Pharmaceuticals, Lionville, Pa), 1.6 points/tablet, maximum 16 points/day. Scoring was based on clinical benefit seen in

TABLE I. Baseline characteristics (n = 784)

|                                                              | PBO (n = 198) | 1.5 Amb a 1-U (n = 197) | 6 Amb a 1-U (n = 195) | 12 Amb a 1-U (n = 194) |
|--------------------------------------------------------------|---------------|-------------------------|-----------------------|------------------------|
| Age, (y) mean $\pm$ SD                                       | 37 $\pm$ 9    | 36 $\pm$ 9              | 37 $\pm$ 9            | 36 $\pm$ 9             |
| Female, %                                                    | 49            | 56                      | 53                    | 47                     |
| Race, %                                                      |               |                         |                       |                        |
| White                                                        | 85            | 89                      | 87                    | 89                     |
| Black or African American                                    | 11            | 7                       | 11                    | 7                      |
| Other                                                        | 4             | 4                       | 3                     | 4                      |
| Asthmatic, %                                                 | 16            | 17                      | 16                    | 19                     |
| Ragweed skin sensitivity, wheal diameter (mm), mean $\pm$ SD | 12 $\pm$ 4    | 12 $\pm$ 4              | 13 $\pm$ 5            | 12 $\pm$ 4             |
| Ragweed IgE level (kU/L), mean $\pm$ SD                      | 18 $\pm$ 23   | 14 $\pm$ 17             | 17 $\pm$ 24           | 16 $\pm$ 21            |
| Multisensitized, %*                                          | 76            | 79                      | 78                    | 79                     |
| Tree†                                                        | 56            | 58                      | 60                    | 54                     |
| Timothy grass                                                | 47            | 49                      | 58                    | 54                     |
| Mold‡                                                        | 19            | 22                      | 22                    | 25                     |
| Cat                                                          | 37            | 39                      | 34                    | 35                     |
| Dog                                                          | 28            | 31                      | 30                    | 29                     |
| Dust mite§                                                   | 36            | 34                      | 25                    | 32                     |
| Preseason duration, %                                        |               |                         |                       |                        |
| <12 wk                                                       | 10            | 10                      | 9                     | 15                     |
| $\geq$ 12 to <16 wk                                          | 17            | 13                      | 18                    | 16                     |
| $\geq$ 16 wk                                                 | 73            | 76                      | 73                    | 69                     |
| Region, %                                                    |               |                         |                       |                        |
| Ukraine/Russia/Hungary                                       | 30            | 28                      | 31                    | 28                     |
| Canada                                                       | 16            | 18                      | 16                    | 18                     |
| United States                                                | 54            | 54                      | 53                    | 54                     |

PBO, Placebo.

\*Indicated by elevated serum-specific IgE values to 1 or more allergens (ie, house dust mite, grass, tree, cat/dog, and mold) in addition to short ragweed.

†Tree mix 1 (oak, elm, birch, walnut, maple).

‡*Alternaria tenuis*.§*Dermatophagoides pteronyssinus*.

previous clinical trials of these medications (see the study protocol, available in the Online Repository). Overall AR/C symptom severity was also recorded by subjects daily in the evening with the use of the VAS, indicating a point on a line between no symptoms (0) and severe symptoms (100).

Blood samples were drawn to investigate changes in specific IgE and IgG<sub>4</sub> levels against *Ambrosia artemisiifolia* during the study (see this article's Methods section in the Online Repository).

Safety variables included AEs (recorded in a paper diary and inquired about via general questioning at visits), vital signs, physical examinations, and safety laboratory assessments, summarized by treatment groups (see this article's Methods section in the Online Repository).

## Statistical analysis

Subjects (n = 800) were to be randomized in a 1:1:1:1 ratio to ragweed AIT of 1.5, 6, and 12 Amb a 1-U or placebo. The power to detect difference between active and placebo groups (5% level of significance, 2-sided test) was 90% to detect  $-1.80$  (25%) in TCS over the peak RS (primary end point). The assumptions in these power calculations were derived from the results of 2 pivotal evaluations of timothy grass AIT in persons with AR/C in North America.<sup>18,19</sup>

Statistical significance of the efficacy measurements was evaluated with an analysis of variance model with asthmatic condition (yes/no) and pollen region as covariates and treatment group as a fixed effect. All reported *P* values and CIs were 2-sided. Multiplicity of statistical testing on the primary and key secondary end points was controlled with a step-down method, starting from the comparison of the high dose of AIT treatment with placebo, followed by the lower dose on the ordered end points, from primary to key secondary, in a sequential manner.

Prespecified subgroup analyses of the primary efficacy end point included subjects with or without reported local application-site effects. Descriptive summary statistics (eg, mean, mean difference from placebo, 95% CI for mean

difference from placebo) for average TCS over peak RS were calculated for subgroups.

The software used for statistical analysis was SAS version 9.2 (SAS Institute, Cary, NC) in Windows XP.

## RESULTS

Between September 21, 2009, and May 25, 2010, 1604 subjects were screened at 114 sites in 5 countries. Of 784 subjects meeting eligibility criteria, 198 were randomly assigned to receive placebo, 197 to receive AIT of 1.5 Amb a 1-U, 195 to receive AIT of 6 Amb a 1-U, and 194 to receive AIT of 12 Amb a 1-U (see Fig E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). One subject was randomly assigned to the 1.5 Amb a 1-U group but left the study before receiving any study medication. Overall, 657 subjects (84%) had diary data for peak RS and were included in the analyses of TCS, DSS, and DMS during this period, and 675 subjects (86%) provided data and were included in analyses of TCS, DSS, and DMS during the entire RS. Treatment groups showed similar demographics at baseline; most subjects were sensitized to multiple allergens (Table I). Overall treatment compliance was high (see this article's Results section in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). The trial concluded when the last subject made the final visit on May 20, 2011.

The 2010 pollen season lasted approximately 46 days; overall, the average daily short ragweed pollen count was approximately 228 and 127 grains/m<sup>3</sup> during the peak and entire RS respectively.

## TCS

The 6- and 12-Amb a 1-U doses of ragweed AIT were significantly superior to placebo in the primary end point of TCS

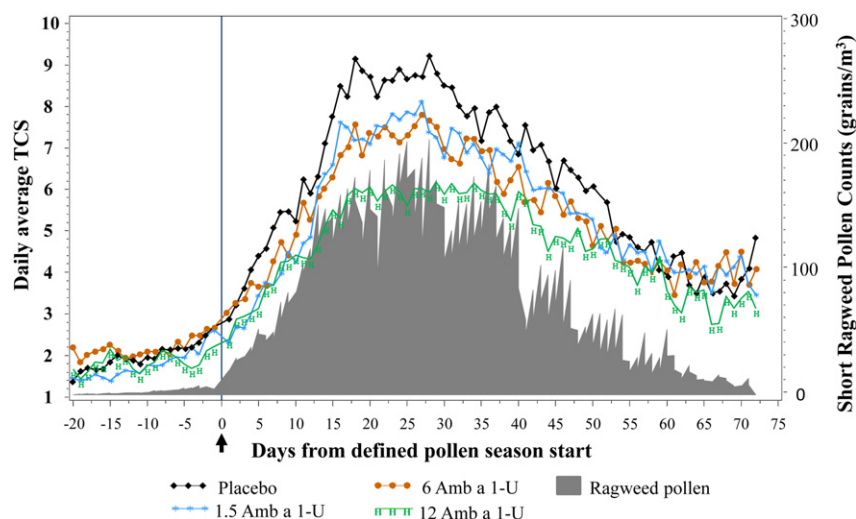


FIG 1. TCS plotted against pollen count (averaged across all regions).

over peak RS and in TCS over entire RS. TCS for each treatment group is plotted against daily average pollen count in Fig 1.

During peak RS, when symptoms can be expected to be most severe, the ragweed AIT 1.5-, 6-, and 12-Amb a 1-U groups showed respective reductions (improvement) of 9% ( $-0.76$ ; 95% CI,  $-1.98$  to  $0.45$ ;  $P = .22$ ), 19% ( $-1.58$ ; 95% CI,  $-2.80$  to  $-0.36$ ;  $P = .01$ ), and 24% ( $-2.04$ ; 95% CI,  $-3.30$  to  $-0.79$ ;  $P = .002$ ) in TCS compared with placebo (Fig 2, A). During the entire RS, the ragweed AIT 1.5-, 6-, and 12-Amb a 1-U groups showed respective reductions in TCS of 12% ( $-0.88$ ; 95% CI,  $-1.88$  to  $0.13$ ;  $P = .09$ ), 18% ( $-1.28$ ; 95% CI,  $-2.29$  to  $-0.28$ ;  $P = .01$ ), and 27% ( $-1.92$ ; 95% CI,  $-2.95$  to  $-0.88$ ;  $P < .001$ ) compared with placebo.

## DSS

During the peak RS, symptom scores in the 1.5 Amb a 1-U ( $-0.26$ ; 95% CI,  $-0.96$  to  $0.45$ ;  $P = .48$ ) and 6 Amb a 1-U ( $-0.50$ ; 95% CI,  $-1.21$  to  $0.21$ ;  $P = .17$ ) groups were numerically 5% and 9%, respectively, lower than placebo, whereas the DSS for 12 Amb a 1-U ( $-0.94$ ; 95% CI,  $-1.67$  to  $-0.21$ ;  $P = .01$ ) was significantly lower than placebo by 18% (Fig 2, B). During the entire RS, the DSS for 1.5 Amb a 1-U ( $-0.34$ ; 95% CI,  $-0.93$  to  $0.25$ ;  $P = .26$ ) and 6 Amb a 1-U ( $-0.40$ ; 95% CI,  $-0.99$  to  $0.20$ ;  $P = .19$ ) showed numeric 7% and 9% reductions, respectively, whereas the DSS for 12 Amb a 1-U ( $-0.96$ ; 95% CI,  $-1.57$  to  $-0.35$ ;  $P = .002$ ) showed significant 21% superiority to placebo. Table E1 (in the Online Repository available at [www.jacionline.org](http://www.jacionline.org)) shows nasal and ocular symptoms (and chest symptoms in asthmatic subjects). Symptomatic advantages seen for ragweed AIT in DSS were also reflected in improved VAS scores (see this article's Results section in the Online Repository).

## DMS

During the peak RS, the 1.5-, 6-, and 12-Amb a 1-U doses yielded reductions of 16% ( $-0.51$ ; 95% CI,  $-1.26$  to  $0.25$ ;  $P = .19$ ), 35% ( $-1.08$ ; 95% CI,  $-1.84$  to  $-0.32$ ;  $P = .005$ ), and 36% ( $-1.10$ ; 95% CI,  $-1.89$  to  $-0.32$ ;  $P = .006$ ) in DMS compared with placebo, respectively (Fig 2, C). During the entire RS,

the 1.5-, 6-, and 12-Amb a 1-U doses yielded 21% ( $-0.54$ ; 95% CI,  $-1.14$  to  $0.07$ ;  $P = .08$ ), 35% ( $-0.89$ ;  $-1.49$  to  $-0.28$ ;  $P = .004$ ), and 38% ( $-0.95$ ;  $-1.57$  to  $-0.33$ ;  $P = .003$ ) reductions in DMS compared with placebo, respectively.

In all AIT groups, use of rescue medication was lower than in the placebo group over peak and entire RS. Fig 3 shows percentages of subjects who used loratadine, olopatadine, and mometasone during peak RS. Use of prednisone was low ( $<3\%$ ) in all treatment groups.

## Prespecified subgroup analysis

Among subjects with local application-site reactions, peak-season TCS in the 12-Amb a 1-U group ( $n = 62$ ) was 23% ( $-1.97$ ; 95% CI,  $-4.90$  to  $0.95$ ) lower than in the placebo group ( $n = 17$ ); among subjects without local application-site reactions, peak-season TCS in the 12-Amb a 1-U group ( $n = 90$ ) was 33% ( $-2.80$ ; 95% CI,  $-4.38$  to  $-1.22$ ) lower than in the placebo group ( $n = 152$ ).

## Ragweed-specific antibody measurements

*Ambrosia artemisiifolia*-specific IgE,  $\log_{10}$  IgE, IgG<sub>4</sub>, and  $\log_{10}$  IgG<sub>4</sub> values in the ragweed AIT and placebo groups were similar at baseline. Higher  $\log_{10}$ -transformed IgE values were seen for ragweed AIT versus placebo at preseason, in season, and with a slight decrease after the season ( $P < .001$  for each) (see Fig E3 in this article's Online Repository at [www.jaci.org](http://www.jaci.org)). Higher  $\log_{10}$ -transformed IgG<sub>4</sub> values were seen for ragweed AIT versus placebo at preseason, in season, and end of season ( $P < .001$  for each AIT group at each time point) (Fig 4).

## Safety

No occurrences of deaths, life-threatening events, anaphylactic shock, systemic allergic reactions, treatment-related serious AEs, or asthma exacerbations were observed.

Table II lists treatment-emergent (new or worsening reported on or after treatment start date through 30 days after treatment stop date) and treatment-related (assessed as possibly or probably related to treatment) AEs with an incidence of 5% or greater. The

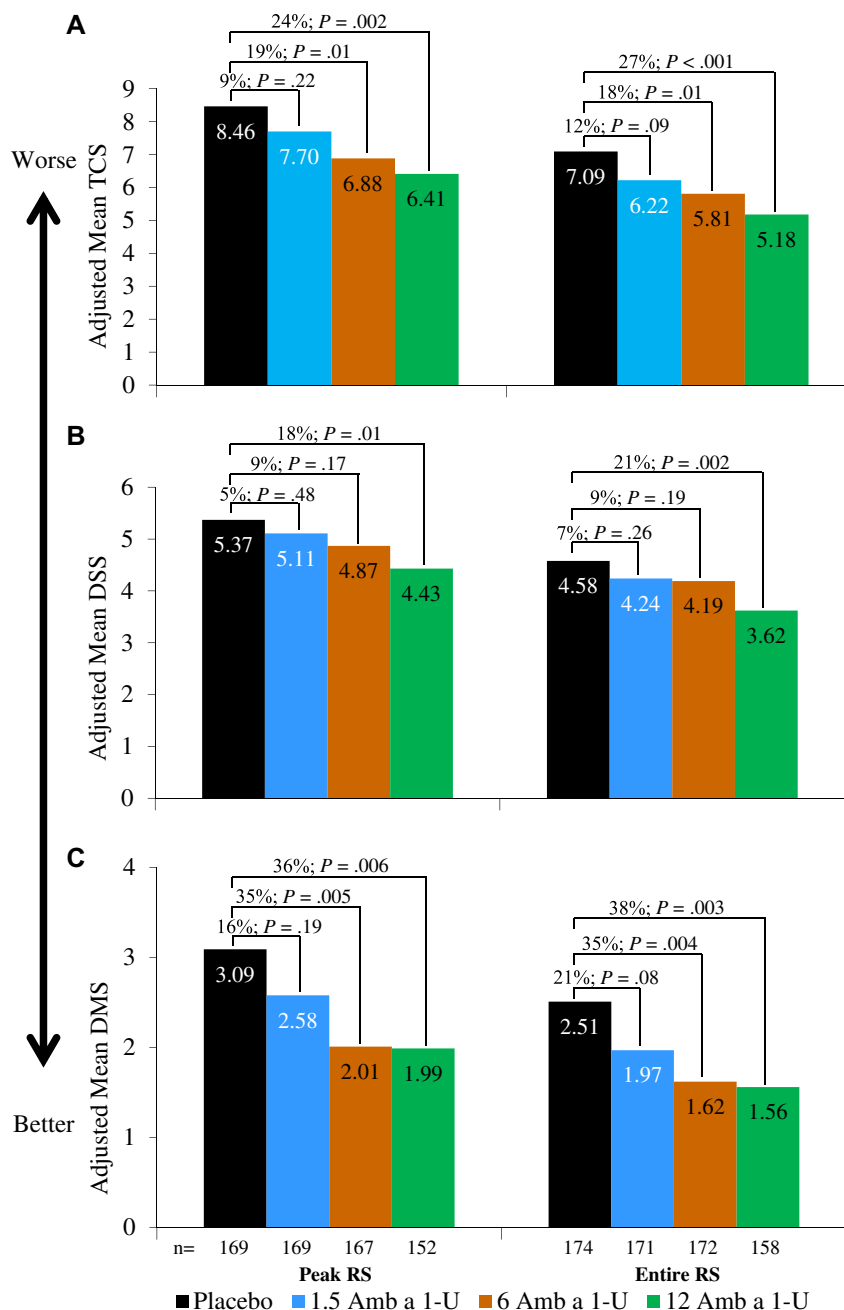


**FIG 2.** TCS (A), DSS (B), and DMS (C) over peak and entire RS. DMS, Daily medication score; DSS, daily symptom score; RS, ragweed pollen season; TCS, total combined score.

overall safety profiles of 6 and 12 Amb a 1-U were comparable. Treatment-related AEs were experienced by 23%, 40%, 52%, and 54% of subjects in the placebo and 1.5-, 6-, and 12-Amb a 1-U groups, respectively. Most subjects reporting related AEs (316/330, 96%) experienced events of mild-to-moderate severity; 241 of 330 subjects (73%) experienced application-site reactions in the mouth, throat, and ear. Local application-site reaction severity is shown in Table E2 (in the Online Repository available at [www.jacionline.org](http://www.jacionline.org)). Severe treatment-related AEs were reported by 12 and 2 subjects who received AIT and placebo, respectively. In 5 of the subjects who received AIT the severe related AE was a local application-site reaction or reactions. None of these events

resulted in airway obstruction or respiratory compromise, nor was epinephrine required.

Discontinuations due to treatment-emergent AEs were infrequent (6/198, 3%; 10/196, 5%; 16/195, 8%; and 16/194, 8% of placebo and AIT 1.5-, 6-, and 12-Amb a 1-U groups, respectively); the most frequently reported AE leading to discontinuation was tongue edema ( $n = 10$ , all assessed as mild or moderate in severity). Most local application-site reactions occurred within the first week of treatment or were reported during the first weeks of treatment.

One use of epinephrine was recorded during the trial: the subject, a 50-year-old man in the 12-Amb a 1-U group, used

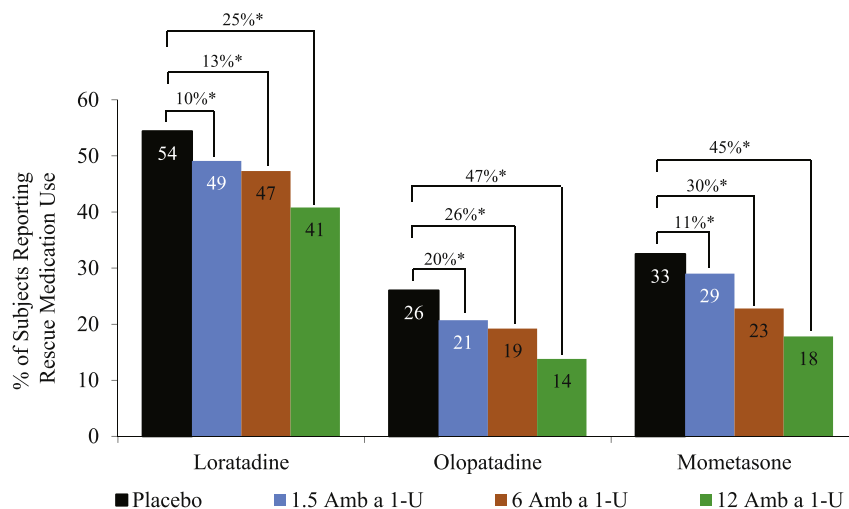


**FIG 3.** Percentages of patients in each treatment group reporting use of rescue medication during peak RS.  
\*Differences between active and placebo.

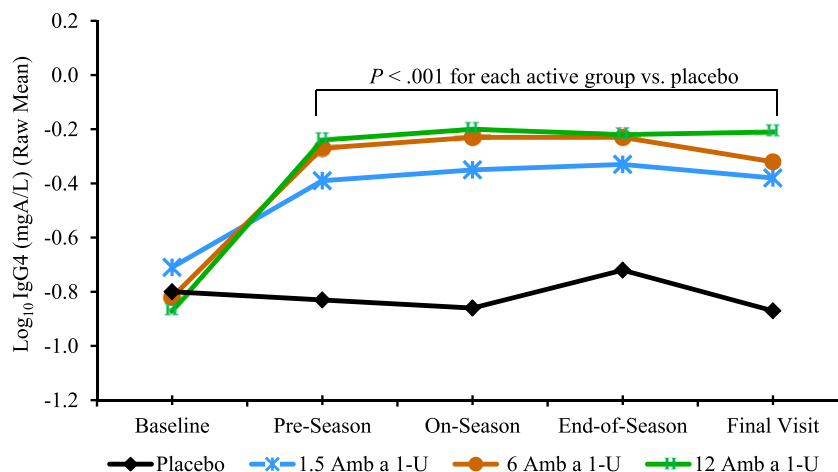


**FIG 4.** Log<sub>10</sub>-transformed *Ambrosia artemisiifolia*-specific IgG<sub>4</sub> levels.

epinephrine in response to an unrelated allergic reaction. This subject had a known history of food hypersensitivity to almonds and had an accidental ingestion, which triggered the event. The subject continued in the trial after the food allergic reaction.

Safety results were similar between asthmatic and nonasthmatic subjects; the most common AEs in asthmatic subjects were not asthma-related events but local application-site reactions. In all groups, severe AEs occurred infrequently in asthmatic and nonasthmatic subjects. Severe treatment-related AEs in the asthmatic subjects did not include exacerbations of asthma. Asthma event rates in the asthmatic subpopulation were similar among treatment groups: 94%, 97%, 90%, and 95% of subjects in placebo and 1.5-, 6-, and 12-Amb a 1-U groups, respectively; cough was the most frequently reported symptom.

## DISCUSSION

In this evaluation of short ragweed AIT for treatment of AR/C, the daily dose of AIT of 12 Amb a 1-U showed statistically significant reductions in the primary end point and all key

secondary end points; the 6-Amb a 1-U dose significantly reduced TCS and DMS during peak and entire season, and the 1.5-Amb a 1-U dose was ineffective. These results establish a dose-response relationship of AIT in the largest clinical trial to date of this therapeutic modality's use in subjects with ragweed-induced AR/C.

Several design aspects of this trial are noteworthy. The design included characteristics recommended by Casale et al<sup>25</sup> for producing high-quality evidence to establish efficacy of sublingual immunotherapy. In fact, the study was designed with greater rigor than was recommended, because subjects were required to show sensitization via both skin test and ragweed-specific IgE. The primary end point of combined symptom and medication score (TCS) allowed for adjustment of symptom scores on the basis of symptomatic medication use; this is consistent with the report from Casale et al<sup>25</sup> as well as recommendations from the World Allergy Organization<sup>26</sup> and the European regulatory agency.<sup>27</sup>

Short ragweed AIT showed significant reductions in TCS despite the trial population including subjects with multiple sensitizations, asthma, and/or preseasonal treatment duration

**TABLE II.** AEs (%) reported by  $\geq 5\%$  of subjects in any treatment group

| Event, %           | Treatment-emergent |                            |                          |                           | Treatment-related |                            |                          |                           |
|--------------------|--------------------|----------------------------|--------------------------|---------------------------|-------------------|----------------------------|--------------------------|---------------------------|
|                    | PBO<br>(n = 198)   | 1.5 Amb a 1-U<br>(n = 196) | 6 Amb a 1-U<br>(n = 195) | 12 Amb a 1-U<br>(n = 194) | PBO<br>(n = 198)  | 1.5 Amb a 1-U<br>(n = 196) | 6 Amb a 1-U<br>(n = 195) | 12 Amb a 1-U<br>(n = 194) |
| Any AE             | 63                 | 76                         | 76                       | 77                        | 23                | 40                         | 52                       | 54                        |
| Ear pruritus       | 1                  | 7                          | 14                       | 13                        | 1                 | 7                          | 13                       | 12                        |
| Oral pruritus      | 1                  | 6                          | 15                       | 8                         | 1                 | 5                          | 14                       | 8                         |
| Oral paresthesia   | 3                  | 5                          | 8                        | 5                         | 3                 | 5                          | 8                        | 5                         |
| Swollen tongue     | 1                  | 6                          | 6                        | 8                         | 1                 | 6                          | 6                        | 7                         |
| Tongue edema       | 0                  | 4                          | 8                        | 6                         | 0                 | 4                          | 8                        | 6                         |
| Tongue pruritus    | 2                  | 7                          | 10                       | 9                         | 2                 | 7                          | 10                       | 9                         |
| Nasopharyngitis    | 18                 | 16                         | 14                       | 17                        | 0                 | 0                          | 1                        | 1                         |
| Sinusitis          | 4                  | 6                          | 5                        | 4                         | 1                 | 1                          | 1                        | 0                         |
| URTI               | 5                  | 5                          | 9                        | 5                         | 0                 | 1                          | 1                        | 0                         |
| Headache           | 10                 | 8                          | 6                        | 9                         | 2                 | 3                          | 1                        | 2                         |
| Cough              | 3                  | 6                          | 5                        | 6                         | 0                 | 2                          | 2                        | 3                         |
| Oropharyngeal pain | 2                  | 7                          | 3                        | 5                         | 0                 | 2                          | 1                        | 2                         |
| Sneezing           | 2                  | 5                          | 3                        | 4                         | 2                 | 2                          | 2                        | 3                         |
| Throat irritation  | 6                  | 14                         | 22                       | 21                        | 4                 | 12                         | 21                       | 21                        |
| Skin pruritus      | 3                  | 2                          | 5                        | 2                         | 2                 | 2                          | 4                        | 2                         |

PBO, Placebo; URTI, upper respiratory tract infection.

<16 weeks. The clinical efficacy of ragweed AIT of 12 Amb a 1-U was similar to the effect sizes observed in replicated trials of timothy grass AIT, which has shown  $\geq 20\%$  differences in TCS versus placebo against a background of rescue medications.<sup>11,18,19</sup> Noteworthy reductions in symptomatic medication use were seen; 18% of subjects receiving 12 Amb a 1-U used intranasal corticosteroids during peak RS compared with 33% receiving placebo, a 45% reduction. Because mometasone was only to be used if symptoms were uncontrolled by loratadine/olopatadine, these findings suggest the ability of ragweed AIT to lessen the need for pharmacotherapy in patients with problematic symptoms.

Ragweed AIT was generally well tolerated over 1 year of treatment. The AEs reported were similar to those reported in trials of timothy grass AIT, with mainly mild and moderate local application-site reactions and few severe reactions ( $\leq 5\%$ ).<sup>19,28</sup> No serious local or systemic allergic reactions were observed, corresponding to the evidence-based World Allergy Organization and Allergic Rhinitis and its Impact on Asthma (ARIA) characterization of sublingual immunotherapy as safe for at-home administration.<sup>26,29</sup>

The immunologic data generated in this study are consistent with results from previous clinical trials of subcutaneous<sup>30,31</sup> and sublingual<sup>18,19,28</sup> immunotherapy. As seen in previous literature, increased ragweed-specific IgG<sub>4</sub> in active groups was accompanied by symptom reduction compared with subjects receiving placebo, who failed to show increases in this antibody.

This study's limitations include the inherent variability of pollen exposure. As noted by the ARIA-Global Allergy and Asthma European Network group,<sup>32</sup> large multicenter designs, as used here, are of particular use in immunotherapy trials because they minimize the risk of treatment effect being obscured by low regional pollen count. A previously suggested limitation of AIT trials is bias introduced by compromised blinding from local application-site reactions experienced by subjects receiving active treatment. However, *post hoc* examination of subgroups without local application-site reactions in previous AIT trials showed consistent treatment effect, suggesting a lack of relevant bias.<sup>33</sup> Further, in a prespecified subgroup analysis of this study, subjects

without local reactions showed more pronounced improvement than subjects with local reactions (treatment effect between AIT of 12 Amb a 1-U and placebo of  $-1.97$  vs  $-2.80$  in subjects with or without local reactions, respectively). The present study is also limited by its 1-year duration, because full courses of immunotherapy typically continue over 3 to 5 years. In long-term follow-up of a European clinical trial, 3 years' treatment with timothy grass AIT significantly reduced symptom and medication scores compared with placebo, even 2 years after end of treatment.<sup>11</sup> By the same scoring used here, timothy grass AIT reduced symptoms by 25% compared with placebo at the second-year posttreatment follow-up. The duration of AIT treatment achieving this disease-modifying effect was consistent with the duration of subcutaneous allergy immunotherapy treatment that appears necessary for disease modification.<sup>34-36</sup>

Because immunotherapy for ragweed-induced AR/C is typically given subcutaneously, it would be desirable to compare the effects of AIT in this study with results seen with injection immunotherapy; however, differences in study design complicate direct comparisons. The efficacy of subcutaneous immunotherapy for ragweed allergy was established by relatively small, single-center trials that included the pioneering evaluations by the Lichtenstein-Norman group,<sup>9,10,35,37,38</sup> in comparison with the present large multinational, multicenter study.

## Conclusions

In this trial, ragweed AIT of 12 Amb a 1-U effectively reduced symptoms and rescue medication use in subjects with ragweed-induced AR/C and was well tolerated. This study's efficacy and safety findings support the use of self-administered ragweed AIT in the treatment of AR/C induced by this prevalent aeroallergen.

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**Clinical implications: Ragweed AIT of 12 Amb a 1-U may provide an effective and well-tolerated treatment option for ragweed pollen-induced allergic rhinitis with or without conjunctivitis.**

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## METHODS

The allergy immunotherapy tablets (AITs) were supplied as neutral-tasting oral lyophilisates that dissolve within seconds after being administered under the tongue. Patients were advised to avoid swallowing for approximately 1 minute, and food or beverages were not to be taken for the next 5 minutes. Placebo was indistinguishable from the AIT in appearance and packaging but contained no ragweed pollen extract. Each subject was to take 1 tablet daily. The starting dose is the maintenance dose, and there was no dose titration before or during the season. Doses are expressed in Food and Drug Administration reference units; 1 Amb a 1-U equals approximately 1  $\mu$ g of the major short ragweed allergen Amb a 1<sup>E1</sup>; thus, a subject who received AIT 12 Amb a 1-U daily for 52 weeks would receive a cumulative dose of 4380  $\mu$ g of Amb a 1.

In addition to the inclusion criteria listed in the body of the article, subjects' safety laboratory tests and vital signs at screening had to be within normal limits or clinically acceptable to the investigator/sponsor; subjects needed to be willing to give informed written consent and to adhere to dose and visit schedules; and female subjects of childbearing potential were required to use an acceptable form of birth control, to be counseled in its appropriate use, and to provide a negative pregnancy test at screening.

In addition to the exclusion criteria listed in the body of the article, any subject who was breast-feeding, pregnant, or intended to become pregnant; who had history of allergy, hypersensitivity, or intolerance to the ingredients of the rescue medications, self-injectable epinephrine, or AIT (except for *Ambrosia artemisiifolia*); who had any clinically significant condition or situation that the investigator judged would interfere with participation or study evaluations; who had used any investigational drugs within 30 days of screening; who was participating in any other clinical trial; who was a family member of the investigational study staff; who was unable to meet medication washout requirements; who was unlikely to be able to complete the trial or likely to travel for extended periods during the season; who had any clinically significant abnormal vital sign or laboratory value; who was unable to or would not comply with the use of self-injectable epinephrine or was at a greater risk of developing adverse reactions after its use; or who had a history of self-injectable epinephrine use was ineligible. Participating subjects could not have participated in the same study at another site or have been randomly assigned more than once.

Subjects were enrolled by the investigator or qualified representative. Randomization was conducted by an external randomization group with the use of an interactive voice response system. The sponsor created 2 sets of randomization schedules: one for subject randomization numbers and the other for kit numbers; randomization was stratified by study site and asthma status. Treatments were provided in identical packaging numbered according to the randomization schedule; the sponsor, subjects, investigators, and study personnel were blinded to treatment. Blinding was maintained until database lock. No interim analyses were planned.

Details of immunologic testing were as follows. Blood samples were analyzed by ALK-Abelló (Hørsholm, Denmark) and measured with the

following assays: specific IgE, ImmunoCAP Specific *Ambrosia artemisiifolia* IgE assay; specific IgG<sub>4</sub>, ImmunoCAP Specific *Ambrosia artemisiifolia* IgG<sub>4</sub> Assay (both Phadia AB). IgE and IgG<sub>4</sub> values were log<sub>10</sub>-transformed to obtain approximately normal distributions; all statistical analyses of immunologic parameters were performed on log<sub>10</sub>-transformed data.

Adverse events (AEs) were graded as mild (awareness of sign, symptom, or event, but easily tolerated), moderate (discomfort enough to cause interference with usual activity; may warrant intervention), severe (incapacitating with inability to do usual activities or significantly affects clinical status; warrants intervention), or life-threatening (immediate risk of death). In addition, investigators assessed AEs for relationship to treatment as follows: unlikely related (no temporal association, or the cause of the event has been identified, or the study medication cannot be implicated), possibly related (temporal association, but other etiologies are likely to be the cause; however, involvement of the study medication cannot be excluded), or probably related (temporal association; other etiologies are possible, but unlikely). Asthma safety was assessed both by symptom reporting and AE reporting; an asthma event was defined as any report of asthma, chest tightness/discomfort, cough, dyspnea, wheezing, and exercise-induced symptoms on the electronic symptom diary or as an AE on the paper diary.

## RESULTS

### Compliance

Among all treated subjects in the placebo and 1.5-, 6-, and 12-Amb a 1-U groups, mean compliance, which was computed as  $([\text{total number dispensed} - \text{total number returned}]/\text{expected number taken}) \times 100$ , was 94%, 93%, 94%, and 92%, respectively.

### VAS score

During the peak RS, the VAS scores in the 1.5-Amb a 1-U (−2.09; 95% CI, −6.57 to 2.38;  $P = .36$ ) and 6-Amb a 1-U (−1.86; 95% CI, −6.35 to 2.63;  $P = .42$ ) groups were numerically 9% and 8% lower than placebo, whereas the DSS for the 12-Amb a 1-U group (−4.75; 95% CI, −9.38 to −0.12;  $P = .04$ ) was significantly 21% lower than placebo. During the entire RS, the VAS for 1.5 Amb a 1-U (−2.37; 95% CI, −6.21 to 1.47;  $P = .23$ ) and 6 Amb a 1-U (−1.54; 95% CI, −5.37 to 2.30;  $P = .43$ ) showed numeric 12% and 8% reductions, whereas the VAS for 12 Amb a 1-U (−4.52; 95% CI, −8.46 to −0.57;  $P = .02$ ) showed significant 22% superiority to placebo.

## REFERENCE

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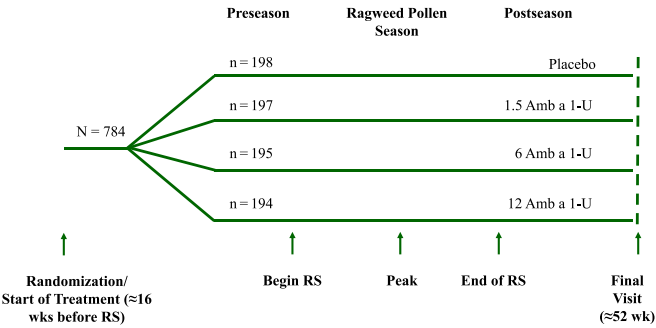


FIG E1. Study design. *RS*, Ragweed pollen season.

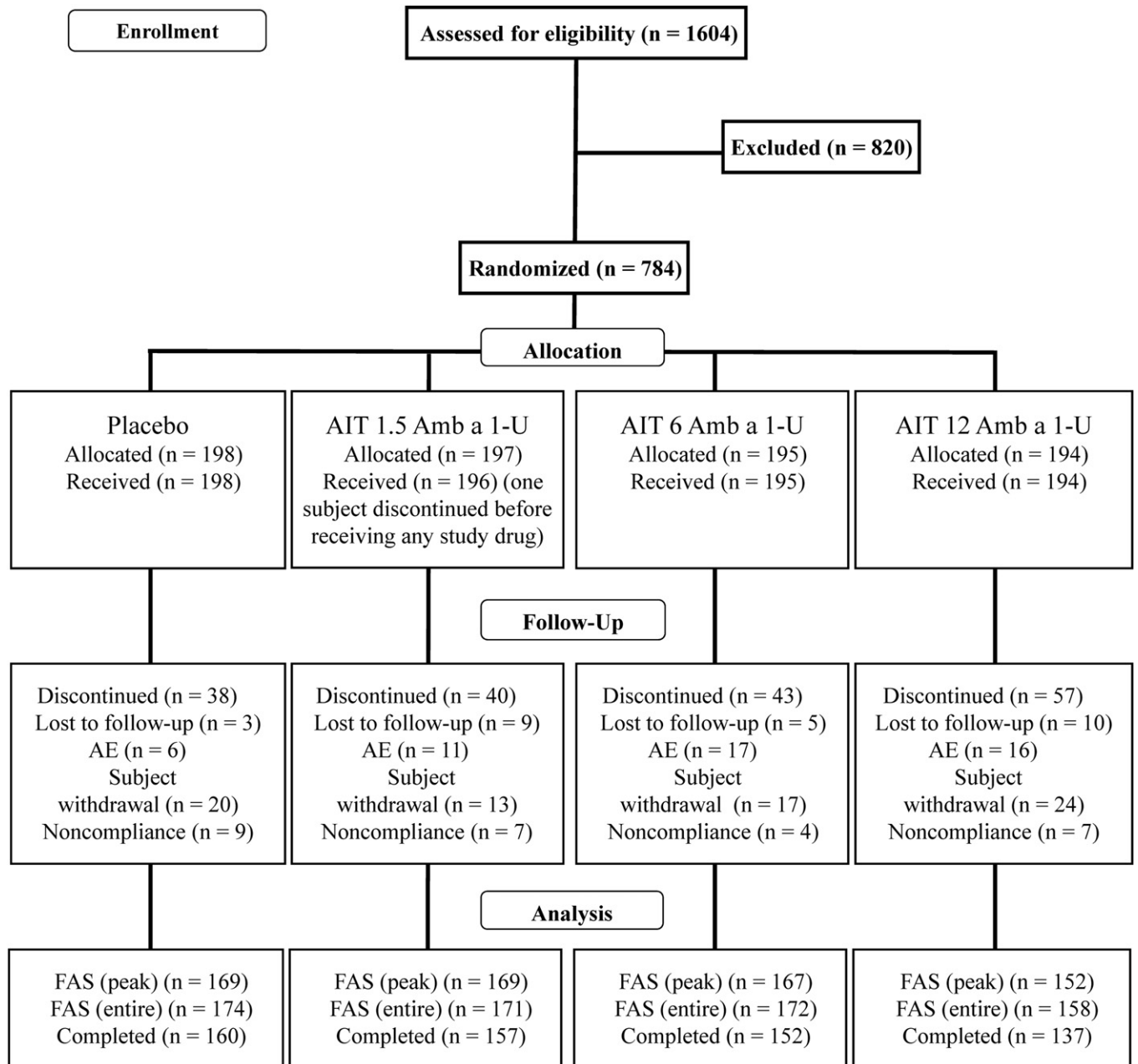


**FIG E2.** Disposition of subjects. Some subjects discontinued after providing diary entry during RS and thus are included both in "discontinued" and "full analysis set." FAS, Full analysis set.

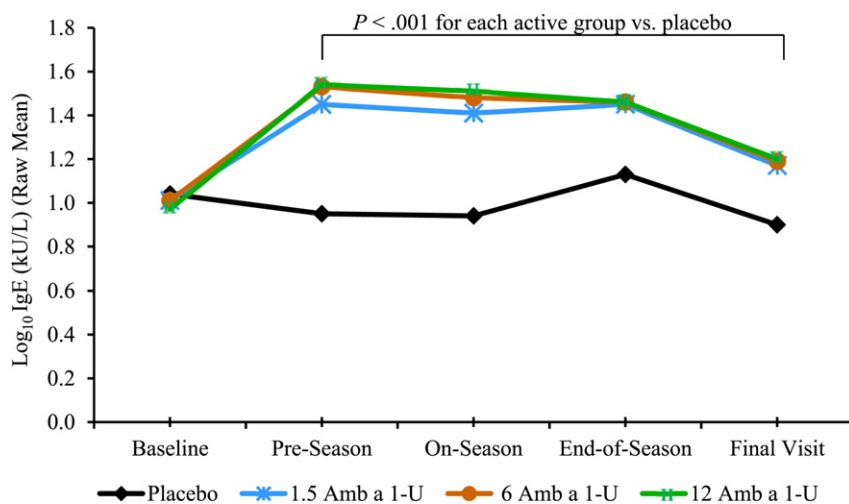


**FIG E3.** Log<sub>10</sub>-transformed *Ambrosia artemisiifolia*-specific IgE levels.

TABLE E1. Individual symptoms

|                            | Peak season |                       |                       |                        | Entire season |                       |                       |                        |
|----------------------------|-------------|-----------------------|-----------------------|------------------------|---------------|-----------------------|-----------------------|------------------------|
|                            | Placebo     | 1.5 Amb a 1-U         | 6 Amb a 1-U           | 12 Amb a 1-U           | Placebo       | 1.5 Amb a 1-U         | 6 Amb a 1-U           | 12 Amb a 1-U           |
| Subjects, no.              | 169         | 169                   | 167                   | 152                    | 174           | 171                   | 172                   | 158                    |
| Nasal symptom score*       | 3.76        | 3.64                  | 3.45                  | 3.19                   | 3.25          | 3.06                  | 2.97                  | 2.65                   |
| Treatment effect (95% CI)* |             | -0.12 (-0.61 to 0.37) | -0.32 (-0.81 to 0.17) | -0.57 (-1.08 to -0.07) |               | -0.20 (-0.61 to 0.21) | -0.28 (-0.70 to 0.18) | -0.61 (-1.03 to -0.18) |
| P value*                   |             | .62                   | .21                   | .03                    |               | .35                   | .18                   | .005                   |
| Reduction vs placebo, %*   |             | 3                     | 8                     | 15                     |               | 6                     | 9                     | 19                     |
| Ocular symptom score*      | 1.61        | 1.47                  | 1.43                  | 1.24                   | 1.33          | 1.19                  | 1.22                  | 0.97                   |
| Treatment effect (95% CI)* |             | -0.13 (-0.40 to 0.13) | -0.18 (-0.45 to 0.08) | -0.37 (-0.64 to -0.09) |               | -0.14 (-0.36 to 0.08) | -0.11 (-0.33 to 0.11) | -0.36 (-0.58 to -0.13) |
| P value*                   |             | .32                   | .18                   | .009                   |               | .21                   | .32                   | .002                   |
| Reduction vs placebo, %*   |             | 8                     | 11                    | 23                     |               | 11                    | 8                     | 27                     |
| Subjects with asthma, no.  | 28          | 31                    | 29                    | 31                     | 29            | 31                    | 29                    | 32                     |
| Asthma symptom score†      | 1.32        | 0.97                  | 0.81                  | 0.98                   | 1.20          | 0.79                  | 0.75                  | 0.88                   |
| Treatment effect (95% CI)† |             | -0.35 (-1.01 to 0.32) | -0.51 (-1.14 to 0.12) | -0.34 (-0.93 to 0.26)  |               | -0.41 (-0.99 to 0.18) | -0.45 (-1.00 to 0.11) | -0.32 (-0.84 to 0.20)  |
| P value†                   |             | .30                   | .11                   | .26                    |               | .17                   | .11                   | .22                    |
| Reduction vs placebo, %†   |             | 26                    | 39                    | 26                     |               | 34                    | 37                    | 27                     |

\*Adjusted means, confidence intervals and *P* values are based on an analysis of variance model including asthmatic condition and pollen region as covariates and treatment group as a fixed effect.

†Subjects with asthma only. Adjusted means, confidence intervals and *P* values are based on an analysis of variance model including pollen region as a covariate and treatment group as a fixed effect.

**TABLE E2.** Number of local application-site reactions, by severity

|                  | Treatment-emergent   |                            |                          |                           | Treatment-related    |                            |                          |                           |
|------------------|----------------------|----------------------------|--------------------------|---------------------------|----------------------|----------------------------|--------------------------|---------------------------|
|                  | Placebo<br>(n = 198) | 1.5 Amb a 1-U<br>(n = 196) | 6 Amb a 1-U<br>(n = 195) | 12 Amb a 1-U<br>(n = 194) | Placebo<br>(n = 198) | 1.5 Amb a 1-U<br>(n = 196) | 6 Amb a 1-U<br>(n = 195) | 12 Amb a 1-U<br>(n = 194) |
| Mild             | 20                   | 86                         | 136                      | 122                       | 16                   | 84                         | 134                      | 118                       |
| Moderate         | 2                    | 13                         | 31                       | 23                        | 1                    | 10                         | 28                       | 22                        |
| Severe           | 1                    | 1                          | 3                        | 4                         | 0                    | 0                          | 3                        | 4                         |
| Life-threatening | 0                    | 0                          | 0                        | 0                         | 0                    | 0                          | 0                        | 0                         |

A local application-site reaction was any instance of oral pruritus, mouth edema, throat irritation, ear pruritus, lip swelling, oral hypoesthesia, oral discomfort, palatal edema, dysphagia, tongue edema, oral paresthesia, swollen tongue, lip edema, glossodynia, pharyngeal edema, face swelling, stomatitis, larynx irritation, oropharyngeal swelling, or throat tightness.



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## 1.0 TITLE PAGE

10 JAN 2008 - FINAL  
05 SEP 2008 - AMENDMENT #1  
10 DEC 2009 - AMENDMENT #2  
17 AUG 2010 - AMENDMENT #3  
**12 JAN 2011 - AMENDMENT #4**

### **C O N F I D E N T I A L S T U D Y P R O T O C O L**

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STUDY TITLE: 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.: P05234

IND NO.: 12,970

SCH NO.: 39641

EUDRACT NO. 2008-003864-20

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## 2.0 SYNOPSIS

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| <b>Title of Study:</b> A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Long-Term Safety of Ragweed ( <i>Ambrosia artemisiifolia</i> ) Sublingual Tablet (SCH 39641) in Adult Subjects With a History of Ragweed-Induced Rhinoconjunctivitis With or Without Asthma (Protocol No. P05234)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                  |
| <b>Study Sites:</b> Approximately 100 sites                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                  |
| <b>Duration of Study:</b> Approximately 60 weeks                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <b>Clinical Phase:</b> Phase 2/3 |
| <b>Objectives</b><br><br><b>Primary Objective:</b> 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 <b>peak</b> ragweed season (RS).<br><br><b>Key Secondary Objectives:</b> To assess overall long-term safety and to compare the following between the SCH 39641 and placebo groups: <ol style="list-style-type: none"> <li>1. <b>The average combined (sum of) rhinoconjunctivitis DSS and rhinoconjunctivitis DMS for the entire RS.</b></li> <li>2. <b>The average rhinoconjunctivitis DSS for the peak RS.</b></li> <li>3. <b>The average rhinoconjunctivitis DSS for the entire RS.</b></li> <li>4. <b>The average rhinoconjunctivitis DMS for the peak RS.</b></li> </ol>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                  |
| <b>Rationale:</b> <a href="#">Redacted</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                  |
| <b>Methodology:</b> This is 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 will be treated once daily with either ragweed sublingual tablet (1.5, 6, and 12 Amb a 1-U) or placebo, approximately 16 weeks prior to and during an entire RS and following the RS so that the subject will be exposed to investigational medicinal product (IMP) for approximately 52 weeks. Prior to treatment initiation, each subject will be supplied with self-injectable epinephrine for treatment of acute severe systemic reactions, together with instructions on how and when to use it. Open-label rescue medications for the rhinoconjunctivitis symptoms will be supplied at the beginning of the RS and will consist of a stepwise approach of predefined medications (oral antihistamine, antihistamine eye drop, nasal corticosteroid spray, and oral corticosteroid). Subjects will visit the study site for at least 11 visits: Screening, Randomization (3 visits), Off-season, Pre-season, On-season, End-of-season, Post-season (2 visits), and Final Visit, and at Unscheduled Visits as appropriate. The first three doses of IMP will be administered at the study site, and the subject will be monitored at the site for 30 minutes following dosing. Subsequent administration of IMP will be done once daily at home at approximately the same time each day. A follow-up telephone call between the site and the subjects will be 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 may be scheduled depending on how early the subjects attend the Randomization Visit, in relation to the anticipated start of the RS.<br><br>This study will be conducted in conformity with Good Clinical Practice. A data safety monitoring committee (DSMC) will be established prior to the start of the treatment phase. The purpose of the DSMC is to |                                  |



**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. P05234)

evaluate adverse event data and to provide recommendations regarding the conduct of the study to ensure the safety of the subjects.

**Type of Blinding:** Double-blind. The active treatment SCH 39641 and placebo will be identical in appearance and taste.

**Sample Size (Including Ratio of Subjects Assigned to Treatments)/Power:** Approximately 800 subjects will be randomized in an equal ratio to one of the four treatments: 1.5, 6, and 12 Amb a 1-U of the SCH 39641, or placebo. With approximately 200 subjects per group, the study will be able to detect the following difference in the primary endpoint between an active dose group and the placebo group with **90%** power at a 5% level of significance (2-sided test).

|                                                                                           | Difference (%) of Effect From<br>Placebo to Be Detected | Estimates of        |                           |
|-------------------------------------------------------------------------------------------|---------------------------------------------------------|---------------------|---------------------------|
|                                                                                           |                                                         | Mean Placebo Effect | Pooled Standard Deviation |
| Combined Rhinoconjunctivitis<br>Symptom and Medication<br>Score <b>During the Peak RS</b> | <b>1.80 (25)</b>                                        | <b>7.10</b>         | <b>5.51</b>               |

Estimates of standard deviations and placebo effects are derived from **the two US studies, P05238 and P05239** (grass sublingual tablet).

**Subject Replacement Strategy:** There will be no replacement of discontinued subjects.

**Randomization:** Subjects will be randomized in a 1:1:1:1 ratio to either 1.5, 6, 12 Amb a 1-U of SCH 39641 or placebo by means of a computer-generated random schedule, in appropriately sized blocks.

**Stratification:** Randomization will be stratified based on study site and asthmatic status (asthmatic and non-asthmatic) of the subjects.

**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) will be selected for this study.

**Key Inclusion Criteria**

1. Subject must be 18 to 50 years of age, of either sex, and of any race.
2. Subject must have a clinical history of significant ragweed-induced allergic rhinoconjunctivitis of 2 years duration or more, with or without asthma (history of physician diagnosis), and have received treatment for the disease during the previous RS.
3. Subject must have a positive skin prick test response to *Ambrosia artemisiifolia* at the Screening Visit.
4. Subject must be positive for specific IgE against *Ambrosia artemisiifolia* ( $\geq$  IgE Class 2) at the Screening Visit.
5. Subject must have an FEV<sub>1</sub> 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 with a clinical history of symptomatic seasonal allergic rhinitis and/or asthma due to another allergen during or potentially overlapping the RS who has received regular medication for these conditions.
2. Subject with a clinical history of significant symptomatic perennial allergic rhinitis and/or asthma 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. Subjects with asthma requiring medium or high-dose inhaled corticosteroids.
6. Subject with a history of anaphylaxis with cardiorespiratory symptoms.
7. Subject with a history of chronic urticaria and angioedema.



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8. Subject with a clinical history of chronic sinusitis during the 2 years prior to the Screening Visit.
9. Subject with current severe atopic dermatitis.
10. Female subject who is breast-feeding, pregnant, or intending to become pregnant.
11. Subject who has had previous immunotherapy treatment with ragweed allergen or any other allergen within the 5 years prior to the Screening Visit.
12. Subject with 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 with a history of self-injectable epinephrine use.

**Test Product, Dose, Mode of Administration:** SCH 39641 – 1.5 Amb a 1-U, 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.

**Reference Therapy, Dose, Mode of Administration:** Matching placebo administered sublingually once daily, preferably at approximately the same time each day.

**Duration of Treatment:** Approximately 52 weeks. Subjects will be treated for approximately 16 weeks prior to start of the RS, during the entire RS, and following the RS so that the subject will be exposed to the IMP for approximately 52 weeks. The start and end of the RS will be determined based on the regional ragweed pollen count. The RS is defined as the first day of 3 consecutive recorded days with a pollen count of  $\geq 10$  grains/m<sup>3</sup>, to the last day of the last occurrence of 3 consecutive recorded days with a pollen count of  $\geq 10$  grains/m<sup>3</sup>, and will be determined after the site completes the last subject/End of Season Visit. A period of 15 consecutive recorded days with the highest moving average is defined as the peak RS.

#### Criteria for Evaluation

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

The combined score for each subject will be 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 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.**

**Safety:** Adverse events, vital signs, and safety laboratory assessments (hematology, blood chemistry, and urine analyses) will be summarized by treatment group.

#### Statistical Methods

**For the Primary Endpoints:** The primary efficacy endpoint of combined (sum of) rhinoconjunctivitis DSS and DMS averaged over the **peak** RS will be evaluated using an ANOVA model with baseline strata effects (asthmatic condition and **pollen region**) and treatment group as fixed effect in the model. Based on the ANOVA model, comparison of each active dose versus placebo will be conducted using a step-down method, starting from the comparison of the highest dose of SCH 39641 versus placebo, followed by the next lower dose and so forth in a sequential manner. Each lower dose comparison against placebo is to be carried out only if the previous comparison is statistically significant ( $P < 0.05$ ).

For the primary endpoint, subjects with at least one post-**randomization** diary record for **the** symptom **score** within the defined **peak** RS will be included. For each subject, DSS and DMS will be based on all available data during the **peak** RS and the combined score will be calculated as the sum of rhinoconjunctivitis DSS and DMS during the **peak** RS, divided by the duration of the **peak** RS.

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

**For the Key Secondary Efficacy Endpoints:** The secondary endpoints will be evaluated using the above



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mentioned ANOVA model. For the key secondary endpoints, the type I error rate will be controlled. For each dose comparison against placebo which meets the primary endpoint, testing of the key secondary endpoints will be conducted in a stepwise manner **as described in Section 8.3.2**.

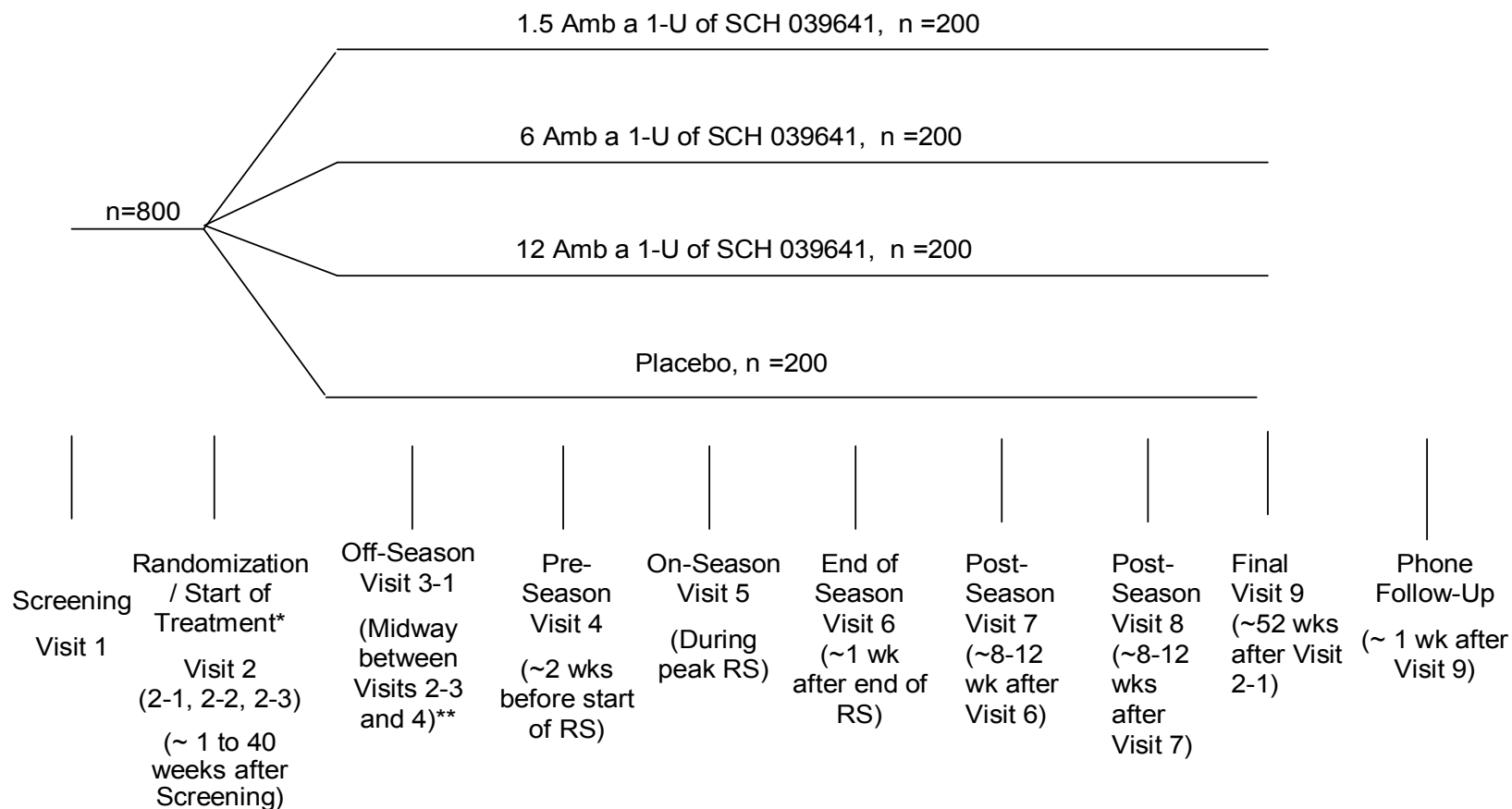
**Safety Analysis:** The number of subjects reporting any AEs, the incidence of specific AEs, and discontinuations due to AEs will be tabulated by treatment group. Laboratory and vital sign data will be listed and summarized and values outside the reference ranges will be flagged.

**Missing Data:** For the primary analysis, there will be no imputation of missing data. The average DSS and DMS will be based on the available number of days of data. The primary analysis will be supplemented by sensitivity analyses using various imputation techniques, which will be specified in the statistical analysis plan.

**Phase and Visit Schedule:** At Visit 1, subjects will be screened for eligibility. At Visit 2-1 (approximately 1 to 40 weeks after Visit 1), eligible subjects will be randomized to either SCH 39641 or placebo. The first three doses of IMP will be given on site at Visits 2-1, 2-2 and 2-3. The first three doses of IMP will be administered at the study site, and the subject will be monitored at the site for 30 minutes following dosing. Subsequent administration of IMP will be done once daily at home at approximately the same time each day. A telephone contact between the investigator/designee and the subject will occur once daily for the first 4 doses of at-home administration of IMP and approximately 1 week after the Final Visit. Visit 3-1 will occur midway between Visits 2-3 and 4. Additional Off-season Visits (Visits 3-2 and 3-3) may be scheduled depending on how early the subjects attend the Randomization Visit (Visit 2-1). Visit 4 will occur about 2 weeks prior to start of the RS (pre-season), followed by Visit 5 (anticipated peak period of the RS) and Visit 6 (end-of-the-season). Visits 7 and 8 will occur post-season and Visit 9 will occur approximately 52 weeks following the initiation of dosing. See **Section 2.2** for the Study Flow Chart for further details.



## 2.1 Study Design Diagram



Abbreviations: RS = ragweed season; Wk(s) = Week(s).

\*A telephone contact between the investigator or designee and the subjects will occur daily for the first 4 doses of at-home IMP administration.

\*\*Additional Visit 3 (3-1 and 3-3) can occur.



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## 2.2 Study Flow Chart

| Visit Name                                     | 1              | 2-1                              | 2-2 | 2-3 | 3-1, 3-2,<br>3-3 <sup>a</sup>   | 4                               | 5                       | 6                           | 7                        | 8                        | 9                        |                      |                    |
|------------------------------------------------|----------------|----------------------------------|-----|-----|---------------------------------|---------------------------------|-------------------------|-----------------------------|--------------------------|--------------------------|--------------------------|----------------------|--------------------|
| Visit Description                              | Screening      | Randomization <sup>b</sup>       |     |     | Off-Season                      | Pre-Season                      | On-Season               | End-of-Season               | Post-Season              | Post-Season              | Final                    | Phone Follow-Up      | Uns <sup>c,d</sup> |
| Time Point                                     |                | Approx 1 to 40 Wks After Visit 1 |     |     | Midway Between Visits 2-3 and 4 | Approx 2 Wks Before Start of RS | In Peak RS <sup>e</sup> | Approx 1 Wk After End of RS | Approx 8-12 Wks After V6 | Approx 8-12 Wks After V7 | Approx 52 Wks After V2-1 | Approx 1 Wk After V9 |                    |
| Week <sup>f</sup>                              | -40 to -1      | 1                                |     |     | 5-7                             | 10-14                           | 19-20                   | 26-27                       | 35-39                    | 47-51                    | 52                       | 53                   |                    |
| Informed Consent <sup>g</sup>                  | X              |                                  |     |     |                                 |                                 |                         |                             |                          |                          |                          |                      |                    |
| Inclusion/Exclusion Criteria                   | X              | X                                |     |     |                                 |                                 |                         |                             |                          |                          |                          |                      |                    |
| Demography                                     | X              |                                  |     |     |                                 |                                 |                         |                             |                          |                          |                          |                      |                    |
| Body Height and Weight                         | X              |                                  |     |     |                                 |                                 |                         |                             |                          |                          | X                        |                      |                    |
| Medical History                                | X              |                                  |     |     |                                 |                                 |                         |                             |                          |                          |                          |                      |                    |
| Assess/Record Concomitant Medications          | X              | X                                | X   | X   | X                               | X                               | X                       | X                           | X                        | X                        | X                        | X                    | X <sup>h</sup>     |
| Physical Examination                           | X              |                                  |     |     |                                 |                                 |                         |                             |                          |                          | X                        |                      | X <sup>h</sup>     |
| Vital Signs                                    | X              | X                                | X   | X   | X                               | X                               | X                       | X                           | X                        | X                        | X                        |                      | X <sup>h</sup>     |
| Pulmonary Function Tests                       | X              | X                                |     |     |                                 | X                               | X                       | X                           | X                        | X                        | X                        |                      | X <sup>h</sup>     |
| Safety Laboratory Assessments                  | X <sup>i</sup> |                                  |     |     |                                 |                                 |                         | X                           |                          |                          | X                        |                      | X <sup>h</sup>     |
| Urine Pregnancy Test <sup>l</sup>              | X <sup>i</sup> | X                                |     |     | X                               | X                               | X                       | X                           | X                        | X                        | X                        |                      | X <sup>h</sup>     |
| Skin Prick Test                                | X              |                                  |     |     |                                 |                                 |                         |                             |                          |                          |                          |                      |                    |
| Specific IgE                                   | X <sup>i</sup> |                                  |     |     |                                 |                                 |                         |                             |                          |                          |                          |                      |                    |
| Other Immunological Assessments                | X              |                                  |     |     |                                 | X                               | X                       | X                           |                          |                          | X                        |                      |                    |
| Pharmacogenetic Sample Collection <sup>k</sup> |                |                                  |     |     |                                 |                                 |                         | X                           |                          |                          |                          |                      |                    |



| Visit Name                                                                                                                               | 1              | 2-1                              | 2-2 | 2-3 | 3-1, 3-2,<br>3-3 <sup>a</sup>   | 4                               | 5                       | 6                           | 7                        | 8                        | 9                        |                      |                    |
|------------------------------------------------------------------------------------------------------------------------------------------|----------------|----------------------------------|-----|-----|---------------------------------|---------------------------------|-------------------------|-----------------------------|--------------------------|--------------------------|--------------------------|----------------------|--------------------|
| Visit Description                                                                                                                        | Screening      | Randomization <sup>b</sup>       |     |     | Off-Season                      | Pre-Season                      | On-Season               | End-of-Season               | Post-Season              | Post-Season              | Final                    | Phone Follow-Up      | Uns <sup>c,d</sup> |
| Time Point                                                                                                                               |                | Approx 1 to 40 Wks After Visit 1 |     |     | Midway Between Visits 2-3 and 4 | Approx 2 Wks Before Start of RS | In Peak RS <sup>e</sup> | Approx 1 Wk After End of RS | Approx 8-12 Wks After V6 | Approx 8-12 Wks After V7 | Approx 52 Wks After V2-1 | Approx 1 Wk After V9 |                    |
| Week <sup>f</sup>                                                                                                                        | -40 to -1      | 1                                |     |     | 5-7                             | 10-14                           | 19-20                   | 26-27                       | 35-39                    | 47-51                    | 52                       | 53                   |                    |
| IVRS                                                                                                                                     | X <sup>i</sup> | X                                |     |     | X                               | X                               | X                       | X                           | X                        | X                        |                          | X                    | X <sup>h</sup>     |
| Issue/Review Subject's Paper Diary Comments Card                                                                                         | X              | X                                | X   | X   | X                               | X                               | X                       | X                           | X                        | X                        | X                        |                      | X <sup>h</sup>     |
| Issue/Instruct in the Use of Electronic Diaries <sup>l</sup>                                                                             |                | X                                |     |     |                                 |                                 |                         |                             |                          |                          |                          |                      |                    |
| Review /Discuss Electronic Diary Recordings                                                                                              |                |                                  | X   | X   | X                               | X                               | X                       | X                           |                          |                          |                          |                      | X <sup>h</sup>     |
| Discontinue Electronic Diary                                                                                                             |                |                                  |     |     |                                 |                                 |                         | X                           |                          |                          |                          |                      |                    |
| Assess/Record AEs                                                                                                                        |                | X                                | X   | X   | X                               | X                               | X                       | X                           | X                        | X                        | X                        | X                    | X <sup>h</sup>     |
| Examination of Oral Cavity                                                                                                               |                | X                                | X   | X   | X                               | X                               | X                       | X                           | X                        | X                        | X                        |                      | X <sup>h</sup>     |
| Dispense Self-Injectable Epinephrine, Instruct in Its Use, Provide Educational Information and Written Anaphylaxis Emergency Action Plan |                | X                                |     |     |                                 |                                 |                         |                             |                          |                          |                          |                      |                    |
| Verify That Subject Possesses Self-Injectable Epinephrine/ Instruct in Its Use                                                           |                |                                  | X   | X   | X                               | X                               | X                       | X                           | X                        | X                        |                          |                      | X <sup>h</sup>     |
| Dispense IMP                                                                                                                             |                |                                  |     | X   | X                               | X                               | X                       | X                           | X                        | X                        |                          |                      | X <sup>h</sup>     |
| On-site dosing of IMP <sup>m,n</sup>                                                                                                     |                | X                                | X   | X   |                                 |                                 |                         |                             |                          |                          |                          |                      |                    |



| Visit Name                                                                                                      | 1         | 2-1                              | 2-2 | 2-3 | 3-1, 3-2,<br>3-3 <sup>a</sup>   | 4                               | 5                       | 6                           | 7                        | 8                        | 9                        |                      |                    |
|-----------------------------------------------------------------------------------------------------------------|-----------|----------------------------------|-----|-----|---------------------------------|---------------------------------|-------------------------|-----------------------------|--------------------------|--------------------------|--------------------------|----------------------|--------------------|
| Visit Description                                                                                               | Screening | Randomization <sup>b</sup>       |     |     | Off-Season                      | Pre-Season                      | On-Season               | End-of-Season               | Post-Season              | Post-Season              | Final                    | Phone Follow-Up      | Uns <sup>c,d</sup> |
| Time Point                                                                                                      |           | Approx 1 to 40 Wks After Visit 1 |     |     | Midway Between Visits 2-3 and 4 | Approx 2 Wks Before Start of RS | In Peak RS <sup>e</sup> | Approx 1 Wk After End of RS | Approx 8-12 Wks After V6 | Approx 8-12 Wks After V7 | Approx 52 Wks After V2-1 | Approx 1 Wk After V9 |                    |
| Week <sup>f</sup>                                                                                               | -40 to -1 | 1                                |     |     | 5-7                             | 10-14                           | 19-20                   | 26-27                       | 35-39                    | 47-51                    | 52                       | 53                   |                    |
| Dispense PEF Meter, Train/Perform Measurements, Review Results (asthmatic subjects in countries where required) |           | X                                | X   | X   | X                               | X                               | X                       | X                           | X                        | X                        | X                        |                      | X <sup>h</sup>     |
| Dispense Allergy Rescue Medication                                                                              |           |                                  |     |     |                                 | X                               | X                       |                             |                          |                          |                          |                      | X <sup>h</sup>     |
| Check/Collect IMP, Assess Compliance                                                                            |           |                                  |     |     | X                               | X                               | X                       | X                           | X                        | X                        | X                        |                      | X <sup>h</sup>     |
| Check/Collect Allergy Rescue Medication, Assess Compliance                                                      |           |                                  |     |     |                                 |                                 | X                       | X                           |                          |                          |                          |                      | X <sup>h</sup>     |
| Collect Self-Injectable Epinephrine                                                                             |           |                                  |     |     |                                 |                                 |                         |                             |                          |                          | X                        |                      |                    |

<sup>a</sup> All subjects must complete a minimum of one Visit 3 (ie, Visit 3-1) approximately 4 to 6 weeks following Visit 2-1. However, if the time between Visit 3-1 and Visit 4 is estimated to be beyond a 4- to 6-week interval, then the subject must return to the site for Visit 3-2 and possibly Visit 3-3 (if the interval between Visit 3-2 and Visit 4 is estimated to be beyond a 4 to 6 week interval). A maximum of 3 'Visit 3' can be completed for each subject.

<sup>b</sup> Visit 2-1 is the Randomization Visit where the first dose is administered at the site. Doses 2 and 3 are to be administered at Visits 2-2 and 2-3 respectively, at the site.

<sup>c</sup> After a visit following exacerbation of asthma, a telephone contact between the site and the subject should be made 2 to 4 days after the visit in order to ensure that asthma symptoms are improving. A follow-up Visit 7 to 10 days after the visit should take place in order to review the symptoms and to measure vital signs and spirometry. At this follow-up visit, the investigator/designee may decide whether or not the subject should adjust his/her asthma medication (including rescue medication).

<sup>d</sup> Unscheduled Visits as necessary.

<sup>e</sup> The visit must take place in the anticipated peak ragweed pollen season.

<sup>f</sup> The weeks are estimates, and will vary for each site depending on the presumed duration of each site's RS.

<sup>g</sup> To be obtained before any trial related procedures are performed.



| Visit Name        | 1         | 2-1                              | 2-2 | 2-3 | 3-1, 3-2,<br>3-3 <sup>a</sup>   | 4                               | 5                       | 6                           | 7                        | 8                        | 9                        |                      |                    |
|-------------------|-----------|----------------------------------|-----|-----|---------------------------------|---------------------------------|-------------------------|-----------------------------|--------------------------|--------------------------|--------------------------|----------------------|--------------------|
| Visit Description | Screening | Randomization <sup>b</sup>       |     |     | Off-Season                      | Pre-Season                      | On-Season               | End-of-Season               | Post-Season              | Post-Season              | Final                    | Phone Follow-Up      | Uns <sup>c,d</sup> |
| Time Point        |           | Approx 1 to 40 Wks After Visit 1 |     |     | Midway Between Visits 2-3 and 4 | Approx 2 Wks Before Start of RS | In Peak RS <sup>e</sup> | Approx 1 Wk After End of RS | Approx 8-12 Wks After V6 | Approx 8-12 Wks After V7 | Approx 52 Wks After V2-1 | Approx 1 Wk After V9 |                    |
| Week <sup>f</sup> | -40 to -1 | 1                                |     |     | 5-7                             | 10-14                           | 19-20                   | 26-27                       | 35-39                    | 47-51                    | 52                       | 53                   |                    |

<sup>h</sup> To be performed if deemed necessary by the investigator.

<sup>i</sup> A telephone contact between the investigator/designee and the subject will occur when the results of the safety laboratory assessments, urine pregnancy test, and specific IgE are available. Subjects who continue to be eligible for randomization will be told to attend Visit 2-1. Subjects who are no longer eligible will be discontinued.

<sup>j</sup> Urine pregnancy tests should be performed for all female subjects of childbearing potential.

<sup>k</sup> Informed consent for pharmacogenetic samples must be obtained before the DNA sample collection. Pharmacogenetic sampling can be performed at Visit 6 or thereafter.

<sup>l</sup> See [Section 7.6](#) for assessment.

<sup>m</sup> The investigator or designee must review the instructions in [Appendix 1](#) with the subject on how to open up the blister pack before dispensing the IMP.

<sup>n</sup> A telephone contact between the investigator/designee and the subject will occur once daily for the first 4 doses of at-home administration of IMP, and once approximately 1 week after the End-of-season Visit. The telephone call will be recorded on the site's source document and the AE assessment on the CRF.

Abbreviations: AE = adverse event; IMP = investigational medicinal product; IVRS = interactive voice response system; OTE = overall treatment effect (a 2-item global questionnaire that measures a patient's overall assessment of therapy); RS = ragweed season; Uns = unscheduled; Wk(s) = Week(s)



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## 4.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

**Table 1**                      **Glossary of Abbreviations and Terms**

Protocol No. P05234

|                  |                                                                                                                                                |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Amb a 1-U        | FDA reference unit (1 Amb a 1-U equals 1 mcg of the major short ragweed allergen [Amb a 1])                                                    |
| AE               | adverse event                                                                                                                                  |
| ALT              | alanine aminotransferase (SGPT)                                                                                                                |
| AST              | aspartate aminotransferase (SGOT)                                                                                                              |
| BID              | twice a day                                                                                                                                    |
| BUN              | blood urea nitrogen                                                                                                                            |
| CFR              | Code of Federal Regulations                                                                                                                    |
| CSR              | clinical study report                                                                                                                          |
| CTD              | Clinical Trial Directive                                                                                                                       |
| DMS              | daily medication score                                                                                                                         |
| DSS              | daily symptom score                                                                                                                            |
| eCRF             | Electronic case report form                                                                                                                    |
| FDA              | Food and Drug Administration, USA                                                                                                              |
| FEV <sub>1</sub> | forced expiratory volume in 1 second                                                                                                           |
| FVC              | forced vital capacity                                                                                                                          |
| GCP              | Good Clinical Practice                                                                                                                         |
| GMP              | Good Manufacturing Practice                                                                                                                    |
| IATA             | International Air Transport Association                                                                                                        |
| ICH              | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use                          |
| ICMJE            | International Committee of Medical Journal Editors                                                                                             |
| IEC              | Independent Ethics Committee                                                                                                                   |
| IMP              | investigational medicinal product                                                                                                              |
| IMPQC            | investigational medicinal product quality complaint                                                                                            |
| IND              | Investigational New Drug Application; legal instrument in the USA that allows study of unapproved, investigational new drugs in human subjects |
| IRB              | Institutional Review Board                                                                                                                     |
| IVRS             | interactive voice response system                                                                                                              |
| LDH              | lactate dehydrogenase                                                                                                                          |
| PR               | packaging request                                                                                                                              |
| PRN              | as needed                                                                                                                                      |
| QD               | once daily                                                                                                                                     |
| RBC              | red blood cell                                                                                                                                 |
| RQLQ(S)          | Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities                                                                 |
| RS               | Ragweed season                                                                                                                                 |
| SAE              | serious adverse event                                                                                                                          |



**Table 1                      Glossary of Abbreviations and Terms**

Protocol No. P05234

|         |                                                                          |
|---------|--------------------------------------------------------------------------|
| SGOT    | serum glutamic oxaloacetic transaminase (AST)                            |
| SGPT    | serum glutamic pyruvic transaminase (ALT)                                |
| SOP     | Standard Operating Procedure                                             |
| SPRI    | Schering-Plough Research Institute, a division of Schering Corporation   |
| TAAL    | Test Article Accountability Ledger                                       |
| TASIR   | Test Article Summary Inventory Record                                    |
| TCS     | Total Combined Score (sum of rhinoconjunctivitis DSS+DMS)                |
| UNS     | Unscheduled                                                              |
| USA     | United States of America                                                 |
| VAS     | visual analogue scale                                                    |
| WBC     | white blood cell                                                         |
| Wk      | week                                                                     |
| WPAI-AS | Work Productivity and Activity Impairment-Allergy Specific Questionnaire |
| Yr      | year                                                                     |

## 5.0 INTRODUCTION

Redacted



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## 6.0 STUDY OBJECTIVES

During this study, subjects will be screened for ragweed-induced rhinoconjunctivitis (with or without asthma) several months before the anticipated start of the ragweed season. If subjects meet all of the study inclusion criteria and no exclusion criteria, subjects will be randomized to receive either sublingual *Ambrosia artemisiifolia* or matching placebo tablets. The administration of double-blind therapy will begin approximately 16 weeks before the anticipated start of the ragweed season. This approximate 16-week period is considered a pre-seasonal treatment period. Double-blind dosing of IMP will begin at Visit 2-1.

### 6.1 Primary Objective

The primary objective of this study is 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).

## 6.2 Secondary Objective(s)

### Key Secondary Objectives

The key secondary objectives are to assess overall long-term safety and compare the following between the SCH 39641 and placebo groups:

1. ***The average combined (sum of) rhinoconjunctivitis DSS and rhinoconjunctivitis DMS averaged over the entire ragweed season (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.***

## 6.3 Other Objectives

Other study objectives are to assess and compare the following immunologic variables between the SCH 39641 and placebo groups:

1. IgE level against *Ambrosia artemisiifolia*
2. IgG4 level against *Ambrosia artemisiifolia*

## 7.0 INVESTIGATIONAL AND ANALYSIS PLAN

### 7.1 Overall Study Design and Plan: Description

This is 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.

Refer to the Study Design Diagram ([Section 2.1](#)) and the Study Flow Chart ([Section 2.2](#)) for additional information.



## **7.2 Discussion of the Study Design**

### **7.2.1 Design of the Study**

This is a multicenter, double-blind, randomized, placebo-controlled, parallel-group study of SCH 39641 in subjects 18 to 50 years of age, of either sex, and of any race, with a history of ragweed-induced rhinoconjunctivitis with or without asthma to be conducted in conformance with Good Clinical Practices.

A total of approximately 800 subjects will be randomized in a 1:1:1:1 ratio to receive either 1.5, 6, 12 Amb a 1-U of SCH 39641, or placebo once daily for approximately 16 weeks prior to and during the RS and following the RS so that the subject will be exposed to IMP for approximately 52 weeks. Subjects will visit the study site for at least 11 visits: Screening, Randomization, (3 Visits, administration of the first IMP dose at the Randomization Visit, followed by two on-site IMP administrations for next two doses), Off-season, Pre-season, On-season, End-of-season, Post-season (2 visits), Final Visit, and at Unscheduled Visits as appropriate. A telephone contact between the investigator/designee and the subject will occur once daily for the first 4 doses of at-home administration of IMP, and once approximately 1 week after the Final Visit.

Safety evaluations will include monitoring of subject-reported AEs, measurement of vital signs, and assessment of the safety laboratory data.

Approximately 8 to 30 subjects per site will be randomized. Assuming a screen failure rate of 33%, approximately 1200 subjects will be screened in order to ensure a total of approximately 800 randomized subjects. Sites will be supplied with extra treatment kits and rescue medications, as needed, to enable specific sites to randomize additional subjects if requested to do so by the sponsor.

### **7.2.2 Participation in and Completion of the Study**

The subject is considered to be enrolled in the study when the subject (or the subject's legal representation) provides written informed consent.

The subject is considered to have completed the study upon the completion of the last protocol-specified contact (eg, visits or telephone contacts).

Subject participation may be terminated prior to completion for the reasons described in [Section 7.3.3](#). For those subjects who do not complete the study, subject participation will be considered terminated upon the completion of the last visit or contact (eg, telephone contact with the investigator or qualified designee).



The overall study ends when the last remaining subject has completed or has been discontinued from the study.

Once a subject has ended participation in the study, SCH 39641 will no longer be available to the subject, and he/she will revert to usual care according to his/her own personal physician.

### 7.3 Study Population

Subjects 18 to 50 years of age, of either sex, and of any race, with a history of significant ragweed-induced allergic rhinoconjunctivitis with or without asthma will be selected for the study. Subjects must meet all of the inclusion criteria and none of the exclusion criteria to participate in the study.

#### 7.3.1 Subject Inclusion Criteria

The subject must meet **ALL** the criteria listed below for entry:

1. Subject must be 18 to 50 years of age, of either sex, and of any race.
2. Subject must have a clinical history of significant ragweed-induced allergic rhinoconjunctivitis of 2 years duration or more, with or without asthma (history of physician diagnosis), and have received treatment for the disease during the previous RS.
3. Subject must have a positive skin prick test response to *Ambrosia artemisiifolia* at the Screening Visit (see [Section 7.6](#) for the definition of a positive skin test).
4. Subject must be positive for specific IgE against *Ambrosia artemisiifolia* ( $\geq$  IgE Class 2) at the Screening Visit.
5. Subject must have an FEV<sub>1</sub> 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
7. A subject must be willing to give written informed consent and be able to adhere to dose and visit schedules.
8. Female subjects of childbearing potential must be using a medically acceptable and adequate form of birth control. These include:
  - a. hormonal contraceptives as prescribed by a physician (oral, hormonal vaginal ring, hormonal implant or depot injectable);



- b. medically prescribed intra-uterine device;
  - c. medically prescribed topically-applied transdermal contraceptive patch;
  - d. double-barrier method (eg, condom in combination with a spermicide).
9. Female subjects of childbearing potential should be counseled in the appropriate use of birth control while in the study. Female subjects who are not currently sexually active must agree and consent to use one of the above-mentioned methods if they become sexually active while participating in the study.
10. Female subjects of childbearing potential must have a negative urine pregnancy test at the Screening Visit in order to be considered eligible for enrollment. Women who have been surgically sterilized or at least 1 year postmenopausal are not considered to be of childbearing potential.

### 7.3.2 Subject Exclusion Criteria

The subject will be excluded from entry if **ANY** of the criteria listed are met:

- 1. Subject with 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 with a clinical history of significant symptomatic perennial allergic rhinitis and/or asthma 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. Subjects with asthma requiring medium or high-dose inhaled corticosteroids.
- 6. Subject with a history of anaphylaxis with cardiorespiratory symptoms.
- 7. Subject with a history of chronic urticaria and angioedema.
- 8. Subject with a clinical history of chronic sinusitis during the 2 years prior to the Screening Visit.
- 9. Subject with current severe atopic dermatitis.
- 10. Female subject who is breast-feeding, pregnant, or intending to become pregnant.
- 11. Subject who has had previous treatment by immunotherapy with ragweed allergen or any other allergen within 5 years prior to the Screening Visit.
- 12. Subject with 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 with any clinically significant condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with the study evaluations or optimal participation in the study. Specific examples include but are not limited to hypertension being treated with beta blockers, coronary artery disease, arrhythmia, stroke, ocular conditions requiring topical beta blockers, any condition requiring the use of beta blockers, and systemic disease affecting the immune system ie, autoimmune diseases, immune complex diseases or immune deficiency diseases.
14. Subject who has used any investigational drugs within 30 days of the Screening Visit.
15. Subject who is participating in any other clinical study.
16. Subject who is a family member of the investigational study staff conducting this study.
17. Subject who is unable to meet medication washout requirements as listed in **Table 3**.
18. Subject who is unlikely to be able to complete the trial, for any reason, or likely to travel for extended periods of time during the RS, which in the opinion of the investigator will compromise the data.
19. Subject with clinically significant abnormal vital sign or laboratory value that would preclude participation in the study.
20. A subject participating in this study may not participate in this same study at another investigational site.
21. A subject must not be randomized into this study more than once.
22. A subject who is unable to or will not comply with the use of self-injectable epinephrine.
23. Subjects who may be at greater risk of developing adverse reactions after epinephrine administration.
24. Subject with a history of self-injectable epinephrine use.

### 7.3.3 Subject Discontinuation Criteria

Subject participation **may be** terminated during the study for a serious adverse event (SAE).

Subject participation **must be** terminated during the study for the following reasons:

- Life-threatening, treatment-related AE.
- Failure to comply with the dosing, evaluations, or other requirements of the study, despite documentation at the site of repeated efforts to reinforce compliance and continued discussions between the investigator and the sponsor.



- An investigator-based assessment of the subject's current asthma condition indicating that there is clinically relevant poor control with the current asthma medication.
- Acute severe, treatment-related asthmatic reaction.
- Treatment-related anaphylactic reactions such as arrhythmia, hypotension, severe urticaria, and severe angioedema.
- Subject inability to tolerate the study medication as perceived by the investigator or subject.
- Investigator perception that the subject continuation in the trial will be detrimental to the subject's well-being.
- Other intolerable AEs as determined by the investigator or subject. These may include but are not limited to vomiting, diarrhea, abdominal pain, and severe site allergic reactions.
- Request of the subject (subjects have the right to discontinue treatment at any time for any reason).
- Pregnancy (should a pregnancy test become positive during the study, the subject will be withdrawn from the study and the pregnancy will be followed to completion).
- In case of unblinding.

It is the right and the duty of the investigator or sub-investigator to interrupt treatment of any subject if he/she feels that study discontinuation is necessary to protect the subject, or that there are unmanageable factors, that may interfere significantly with the study procedures and/or the interpretation of results.

If a randomized subject discontinues prior to completion of the study, the reason for the discontinuation should be obtained. The date of the last dose of IMP and the date of the last assessment and/or contact should be obtained. This information should be documented in the appropriate section of the eCRF. A follow-up contact (telephone or visit) will be arranged as appropriate.

At the time of discontinuation, every effort should be made to ensure that all procedures and evaluations scheduled for the final study visit (Visit 9) are performed ([Section 2.2](#), Study Flow Chart and [Section 7.5](#) Study Schedule). For all discontinued subjects, AEs should be recorded, IMP and rescue medication compliance assessed, and any returned IMP and rescue medication inventoried.

Treatment should be temporarily stopped for up to 7 days under the following conditions:



1. In case of oral surgery, including dental extraction, to allow healing of the oral cavity.
2. Other reasons as deemed necessary by the investigator.

### **7.3.4 Replacement of Subjects**

Randomized subjects who discontinue treatment early will not be replaced.

## **7.4 Treatments**

### **7.4.1 Study Treatments**

#### **7.4.1.1 Investigational Treatments**

##### **7.4.1.1.1 IMP**

SCH 39641 and placebo will be supplied to the study site by the sponsor. The active treatment (SCH 39641) is a ragweed (*Ambrosia artemisiifolia*) pollen allergen extract. SCH 39641 is formulated as a rapidly dissolving tablet to be administered sublingually once daily. The placebo treatment is identical to the active treatment except that no allergen extract is included in the placebo rapidly dissolving tablet.

The first three doses of IMP will be administered at the study site at Visits 2-1, 2-2, and 2-3, and the subject will be required to stay at the study site for approximately 30 minutes after each administration for observation of any AEs. Prior to administration of the first dose of IMP, the investigator should discuss well known immediate application site reactions with the subjects and severe AEs requiring the use of self-injectable epinephrine. The investigator/designee will complete the Anaphylaxis Emergency Action Plan ([Appendix 2](#)) for each subject, provide a copy to the subjects, and keep a copy for the site's records. If any significant AE such as wheezing, dyspnea, severe oral swelling or signs of generalized anaphylactic reaction occurs, the investigator must evaluate the subject to determine whether treatment of the adverse reaction should be initiated. In such cases the observation period should be extended for at least an additional 30 minutes. When the subject leaves the study site, instructions should be given to contact the study site immediately if the reaction reoccurs or a new reaction appears. If the investigator determines that a subject cannot leave the study site but needs further attention not otherwise available at the study site, the subject will be transferred to an appropriate facility such as an emergency room.

Subjects not experiencing clinically significant reactions may leave the study site approximately 30 minutes after each of the first three doses of IMP has been given.



Subjects will be instructed to contact the study site immediately if any reaction occurs after leaving the study site.

Subsequent dosing of IMP will be done once daily at home at approximately the same time each day. Subjects will be instructed how to open the blister pack and administer the tablet. In addition, subjects will be provided with a written description of the procedure ([Appendix 1](#)). The tablet is to be placed under the tongue for approximately 1 minute, and is then to be swallowed. Eating and drinking are not allowed for approximately 5 minutes after tablet administration.

A telephone contact between the investigator or designee and the subject will occur daily for the first 4 doses of at-home administration to determine if a subject has experienced an AE. If an AE occurs, the investigator will determine if the subject needs to return to the study site for an Unscheduled Visit. In case of a medical emergency at home, the subject will be instructed to dial the local emergency telephone number.

An Unscheduled Visit must take place if a subject develops asthma or if a subject has an exacerbation of his/her known asthma and a change in asthma rescue medication is required (see [Section 7.4.1.1.2.2](#) for further details). An Unscheduled Visit may take place at any time, as deemed necessary by the investigator.

#### **7.4.1.1.2 Rescue Medications**

##### **7.4.1.1.2.1 Allergy Rescue Medications for Rhinoconjunctivitis Symptoms**

Subjects may experience allergy symptoms that require additional treatment during the RS. Thus, rescue medication will be provided by the sponsor or designee to the study site to be given to the subjects as predefined, open-label medication to be taken in a step-wise fashion depending on the persistence, severity, and type of symptoms during the ragweed season. The subject will be advised **not** to take the allergy rescue medications regularly in anticipation of ragweed-induced symptoms but rather to call the site to obtain permission of the investigator or designee. The step-wise schedule for use of allergy rescue medication is provided in [Table 2](#).

The amount of allergy rescue medication, including self-injectable epinephrine, dispensed to and returned by each subject will be recorded on the Test Article Accountability Ledger (TAAL) or an equivalent document, and the number of doses taken will be recorded by the subject on the electronic diary. The allergy rescue medications will be supplied to a subject at Visit 4, and also at other visits following Visit 4 (either scheduled or unscheduled), as deemed necessary by the investigator up to Visit 6.



Any use of allergy medications before Visit 4 or after Visit 6 should be recorded as concomitant medications on the eCRF, and after Visit 4 until Visit 6 on the electronic diary. In addition, any use of allergy or asthma medications that were not supplied by the sponsor as a rescue medication should be recorded as concomitant medication on the eCRF.

**Table 2**                      **Schedule for Rescue Medication**

Protocol No. P05234

| RHINOCONJUNCTIVITIS |                                                     |                                                                                                  |                                                                                                                                                          |                                |
|---------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| STEP                | Rescue Medications                                  | Subject Dosing Instruction                                                                       | Requirements for Start of Use                                                                                                                            | Dispensed at Visits            |
| 1                   | Loratadine 10 mg RediTabs tablet <sup>a</sup>       | 1 tablet QD                                                                                      | Total symptom score of $\geq 4$ and start of RS confirmed by site                                                                                        | 4                              |
| 1b                  | Olopatadine hydrochloride 0.1% ophthalmic solution  | 1 drop in each affected eye BID                                                                  | In addition to loratadine for control of persistent eye symptoms                                                                                         | 4                              |
| 2                   | Mometasone furoate monohydrate nasal spray 50 mcg   | 2 sprays in each nostril QD                                                                      | Total symptom score of $\geq 4$ despite loratadine. Use in addition to loratadine                                                                        | 4                              |
| 3                   | Prednisone tablet 5 mg (or prednisolone equivalent) | Day 1: 1 mg/kg/day (maximum 50 mg/day);<br>Days 2 and forward: 0.5 mg/kg/day (maximum 25 mg/day) | Total symptom score of $\geq 4$ despite loratadine and mometasone furoate nasal spray. Use in addition to loratadine and mometasone furoate nasal spray. | Unscheduled Visit <sup>b</sup> |

<sup>a</sup> An alternate formulation of loratadine will be provided in countries where RediTabs are not available.

<sup>b</sup> To be dispensed only at Unscheduled Visits taking place between Visit 4 and Visit 6. In countries where prednisone is not available, prednisolone will be dispensed in a clinically equivalent dosage.

Allergy rescue medications for rhinoconjunctivitis symptoms will be provided for use during the RS according to the following steps (for dosage instructions, [Table 2](#)):

1. Step 1: Loratadine 10 mg RediTabs tablet<sup>a</sup>
2. Step 1b: Olopatadine hydrochloride 0.1% ophthalmic solution
3. Step 2: Mometasone furoate monohydrate nasal spray 50 mcg
4. Step 3: Prednisone 5 mg tablet, or an equivalent dose of prednisolone

<sup>a</sup> **An alternate formulation of loratadine will be provided in countries where RediTabs are not available.**



The use of allergy rescue medication is subject to the following step-wise requirements:

### **Step 1**

Loratadine 10 mg Reditabs tablet or comparable formulation will be dispensed to the subject at Visit 4 but must not be used before the investigator or designee has confirmed that in his/her opinion the RS has started and the subject has an adequate level of symptoms as evaluated in accordance with the following procedure:

The subject must be instructed to contact the investigator in case of rhinoconjunctivitis symptoms and the need for allergy rescue medication. The investigator will then ask the subject to score his/her nose and eye symptoms (ie, runny nose, blocked nose, sneezing, itchy nose, gritty feeling/itchy/red eyes, and watery eyes) using a scale from 0 to 3 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms) ([Section 7.6](#), Electronic Diary Recording).

Once the investigator or designee has confirmed a total symptom score of  $\geq 4$  and the RS has started, the subject may be authorized to start using Step 1 medication. The total symptom score and the date of this authorization must be recorded in the source documents as required by the sponsor.

Once symptoms are improved, the subjects should reduce or stop use of allergy rescue medication. Subjects may restore use of the allergy rescue medications without contacting the study site.

### **Step 1b**

Olopatadine hydrochloride 0.1% ophthalmic solution will be dispensed to the subject at Visit 4 but should only be used in addition to Step 1 loratadine Reditabs tablet if eye symptoms persist in spite of Step 1 treatment. The subject must be instructed to contact the investigator for authorization to use olopatadine hydrochloride 0.1% ophthalmic solution. The date of this authorization must be recorded in the source documents as required by the sponsor.



Once symptoms are improved, the subjects should reduce or stop use of this allergy rescue medication. Subjects may restore use of the allergy rescue medications without contacting the study site.

## **Step 2**

Mometasone furoate monohydrate nasal spray 50 mcg will be dispensed to the subject at Visit 4 but should only be used if symptoms are not satisfactorily controlled by Step 1 medication as evidenced by a persisting minimum total symptom score of  $\geq 4$ . The subject should again call the investigator for authorization to use mometasone furoate monohydrate nasal spray to be taken in addition to Step 1 medication. The date of this authorization must be recorded in the source documents as required by the sponsor.

Once symptoms are improved, the subjects should reduce or stop use of this allergy rescue medication. Subjects may restore use of the allergy rescue medications without contacting the study site.

## **Step 3**

If symptoms are not satisfactorily controlled by Step 1 and Step 2 medications, the subject should call the study site for an Unscheduled Visit. The investigator should confirm the persisting minimum total symptom score of  $\geq 4$ . Upon confirmation, and if the investigator considers appropriate, the subject will be supplied with up to 50 mg prednisone or equivalent dose of prednisolone to be taken orally at the time of the visit, and with a 7-day supply of prednisone to be taken in addition to Step 1 and Step 2 medications. If symptoms are severe, treatment can be extended at the investigator's discretion.

Once symptoms are improved, the subject must call the investigator to reduce or stop use of this allergy rescue medication.

### **7.4.1.1.2.2 Medications for Asthma Symptoms**

Medications for asthma, including rescue medications, will not be provided. Subjects who are taking low dose inhaled corticosteroids for asthma management at screening will be allowed to continue with the same medications during the study. These subjects must have been using a low daily dose of inhaled corticosteroid for at least 12 weeks and must have been on a stable regimen (daily dose unchanged)



for at least 2 weeks prior to Screening. Low daily doses of inhaled corticosteroids are defined as follows:

- 200 to 500 mcg beclomethasone CFC
- 100 to 250 mcg beclomethasone HFA
- 200 to 600 mcg budesonide DPI
- 500 to 1000 mcg flunisolide
- 100 to 250 mcg fluticasone
- 200 mcg mometasone furoate
- 400 to 1000 mcg triamcinolone acetonide
- 80 to 160 mcg ciclesonide

If a subject requires additional asthma medications, the subject should follow recommendations regarding medication adjustments provided by his/her physician. Medication use should be recorded on the eCRF and relevant questions related to asthma medication should be responded to in the electronic diary between Visits 4 and 6. If symptoms are severe and asthma control cannot be attained, the subject should be discontinued from the study.

Subjects who experience an asthma exacerbation or development of asthma symptoms (wheeze, etc) without a history of asthma at screening should call the study site and request an unscheduled visit to be performed. The subject's symptoms should be evaluated and appropriate medications prescribed according to the investigator's judgment. There should be a telephone contact 2 to 4 days after the Unscheduled Visit in order to ensure that asthma symptoms are improving. A follow-up visit 7 to 10 days after the Unscheduled Visit should take place in order to review the symptoms and to measure vital signs and spirometry. At this Follow-up Visit, the investigator may decide whether the subject should reduce or stop use of asthma medication.

#### **7.4.1.1.2.3 Rescue Medication for Severe Allergic Reactions (Self-Injectable Epinephrine)**

Self-injectable epinephrine is intended for immediate self-administration for an anaphylactic reaction. Anaphylaxis is likely when respiratory compromise and/or reduced blood pressure occur and/or when multiple organ systems are involved following exposure to an allergen. A list of symptoms that may be present during anaphylaxis include flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, vomiting, diarrhea and abdominal cramps, wheezing, dyspnea due to laryngeal spasm, lower airway



obstruction, pruritus, rashes (such as urticaria), or angioedema. Self-injectable epinephrine should be administered promptly when significant respiratory and/or cardiovascular symptoms accompany an allergic reaction.

Randomized subjects will be provided with self-injectable epinephrine at the Randomization Visit (Visit 2-1). The investigator or designee will instruct the subject on how to administer self-injectable epinephrine. The investigator or designee will provide and explain to the subject the written instructions regarding when to administer self-injectable epinephrine. The investigator/designee will complete the Anaphylaxis Emergency Action Plan for each subject, provide a copy to the subjects, and keep a copy for the site's records ([Appendix 2](#), Anaphylaxis Emergency Action Plan).

In the event that self-injectable epinephrine is used, the subject must immediately call the local emergency number and the 24-hour investigational site emergency number indicated in the Anaphylaxis Emergency Plan, informed consent and/or diary. An Unscheduled Visit will be arranged to further evaluate the subject.

The investigator or designee must notify the sponsor within 1 working day of first becoming aware of the use of self-injectable epinephrine. The symptoms and/or circumstances that triggered the use of self-injectable epinephrine must be clearly recorded on the eCRF. Further doses of IMP should not be administered to the subject without prior approval of the sponsor. If the investigator, sponsor, and subject agree that the subject can continue the trial, then the subsequent two doses of IMP must be administered in the investigator's office. The subject will be required to stay at the study site for approximately 30 minutes after each IMP administration. Provided that the subject does not have further clinically significant reactions, the subject may continue further dosing of the IMP at home. The investigator will provide additional self-injectable epinephrine to the subject and a telephone contact between the investigator or designee and the subject will occur approximately 24 hours following the second IMP dose.

#### **7.4.1.2 Method of Treatment Assignment, Randomization, and/or Stratification**

After informed consent is obtained, the subject will be assigned a screening number at the Screening Visit (Visit 1). These numbers will be used to identify the subject during the screening period of the study.

Following completion of the Screening Period, subjects who continue to qualify for the study will be randomized at Visit 2-1 to receive either 1.5, 6, or 12 Amb a 1-U SCH 39641 or placebo in a 1:1:1:1 ratio according to a computer-generated randomization schedule, in appropriately sized blocks.



Randomization will be conducted by an external randomization group using an interactive voice response system (IVRS). The sponsor will create two sets of randomization schedules: one for subject randomization numbers and the other for kit numbers. Randomization will be stratified by study site and asthmatic status of the subject (yes/no).

Case report forms are to be completed for all subjects who receive a randomization number and for all screen failures who had an SAE within the screening period.

#### **7.4.1.3 Selection and Timing of Dose for Each Subject**

The treatment assigned to each subject is based on the randomization code. IMP should be administered daily at approximately the same time each day starting at Visit 2-1. The first three doses of the IMP will be administered at the site and the subjects will be monitored for 30 minutes on site for observation of any AEs. Subsequent administration of IMP will be done once daily at home at approximately the same time each day.

#### **7.4.1.4 Blinding of Study Treatments**

A double-blind technique will be used, ie, SCH 39641 and its matching placebo rapidly dissolving tablet will be identical in appearance and will be packaged identically so that treatment blind is maintained. The placebo tablet is similar to the IMP in appearance, smell and taste. Neither the subject nor the investigational staff (investigator and evaluators) will know which treatment the subject is receiving.

Unblinding should occur only in the event of an emergency or AE for which it is necessary to know the study treatment to determine an appropriate course of therapy for the subject. If the investigator must identify the treatment assignment of an individual subject, the investigator or qualified designee is to call IVRS. A written explanation as to why the investigator felt it necessary to break the blind must be filed in the subject's source document and the statement provided to the sponsor.

#### **7.4.1.5 Investigational Product and Rescue Medications**

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and usage of these materials in accordance with the protocol and any applicable laws and regulations.



#### **7.4.1.5.1 Identity of Investigational Medicinal Product and Rescue Medications**

Investigational medicinal product will be dispensed to the subject at Visit 2-3. Hereafter, additional IMP will be dispensed as needed at each subsequent visit as per the study flow chart, [Section 2.2](#).

#### **Active Treatment: SCH 39641 Rapidly Dissolving Tablet**

Active ingredients: *Ambrosia artemisiifolia* allergen extract.

Dosage form: Rapidly dissolving tablet administered sublingually once daily.

Dose/strength: 1.5 Amb a 1-U, 6 Amb a 1-U, and 12 Amb a 1-U.

The complete list of ingredients in the SCH 39641 rapidly dissolving tablet is provided in the Investigator's Brochure.

#### **Placebo Treatment**

Active ingredients: None.

Dosage form: Rapidly dissolving tablet administered sublingually once daily.

#### **Allergy Rescue Medication**

See [Section 7.4.1.1.2](#) for the list of provided allergy rescue medications.

#### **Rescue Medication for Severe Allergic Reactions (Self-Injectable Epinephrine) for US and Canada (and Other Countries Where Allowed by Local Regulations)**

Active ingredient: Epinephrine.

Dosage form: For intramuscular use.

Dose/strength: 0.3 mg



#### **7.4.1.5.2 Source**

The sponsor will provide all IMP. Allergy rescue medication, including self-injectable epinephrine, will be supplied by the sponsor and/or sponsor designee (or purchased locally for ex-USA countries), and provided to the subjects by the investigator.

#### **7.4.1.5.3 Labeling**

Labeling of IMP is handled in a double-blind fashion. The IMP and matching placebo will be labeled in accordance with Good Manufacturing Practice (GMP) and local regulations, and will include the following information:

- Protocol number
- Packaging Request (PR) number
- Packaging Lot number
- Kit number
- Contents
- Subject number (to be handwritten in by investigator or designee following IMP assignment via IVRS)
- Storage requirements: Store up to 25°C (77°F). Do not freeze or refrigerate.
- Direction for administration:
  - Take 1 tablet once daily. Peel back the foil to remove the tablet. Do not push the tablet through the foil. Place the tablet under the tongue and keep there for 1 minute before swallowing. Eating and drinking are not allowed for 5 minutes after tablet intake.
- Caution and warning statements
- Sponsor: Schering Corporation, Kenilworth, NJ 07033 or as per local requirements

All allergy rescue medication supplied will have the original labels as supplied by the manufacturer. Additional ancillary labeling for investigational use may be required based on the local regulations. Dosing information for allergy rescue medications is presented in [Table 2](#).



#### **7.4.1.5.4 Packaging**

The IMP and matching placebo will be supplied in blister cards containing 10 tablets each. The blister cards will be packaged in kits, and four blister cards will be placed in each kit. The IMP and matching placebo will be identified by PR number and kit number. All rescue medications including self-injectable epinephrine will be supplied in their original commercial packaging.

#### **7.4.1.5.5 Storage**

The IMP must be stored in a secure, limited-access location under the storage conditions specified on the IMP supply label. Also, all rescue medications must be stored in a secure, limited access location and storage conditions must be in accordance with the manufacturer's instructions.

#### **7.4.1.5.6 Dispensing**

A subject who meets the eligibility criteria at Visit 2-1 will be dispensed IMP from Visits 2-3 to 8, as needed. The investigator agrees neither to dispense the study drug from, nor store it at, any site(s) other than those listed on the Investigator's Statement of Good Clinical Research (Form FDA 1572 or local health authority equivalent). The investigator agrees that study drug(s) will be dispensed by the investigator or sub-investigator(s) named on the Investigator's Statement of Good Clinical Research (Form FDA 1572 or local health authority equivalent), or their designees.

#### **7.4.1.5.7 Replacement Units**

If the IMP and allergy rescue medications, are lost or damaged, additional supplies will be provided via IVRS.

#### **7.4.1.5.8 Drug Accountability**

Subjects will be instructed to return all empty, unused, and partially used IMP and rescue medications (including self-injectable epinephrine) at all protocol-specified visits for assessment of subject compliance.



An accurate and current accounting of the dispensing and return of IMP and rescue medications for each subject will be maintained on an ongoing basis by a member of the study site staff in the TAAL or an equivalent document and will be verified by the sponsor's study monitor. The original TAAL or equivalent document shall be approved by the investigator and retained at the study site and a copy supplied to the sponsor when the study is complete.

All study supplies, including all containers of IMP and rescue medications, whether empty or containing unused IMP or rescue medications, must be returned to the sponsor or its designee, unless investigators are instructed otherwise by the sponsor or its designee. The sponsor's study monitor will provide instructions on the return of all IMP and rescue medication supplies. Under instructions from the sponsor, the investigator or designee may destroy unused or partially used IMP, rescue medications, and provided the investigator retains sufficient record of the destruction. A final inventory of the total amount of IMP and rescue medication received at each study site against the amount used and returned or destroyed by the site must be recorded in the Test Article Summary Inventory Record (TASIR) or equivalent document.

A complete review and recording of IMP and all rescue medications used will be recorded at Visit 2-1 onwards and at all unscheduled visits.

Inventory records must be readily available for inspection by the study monitor and/or auditor, and open to government inspection at any time.

## **7.4.2 Nonstudy Treatments**

### **7.4.2.1 Prior and Concomitant Medications**

Concomitant medications are all medications being continued by a subject on entry to the trial and all medications taken in addition to the IMP and rescue medications.

All medications taken by the subject within 3 months prior to the Screening Visit and all concomitant therapies taken by the subject during the study are to be recorded on the eCRF. The identity of the therapy, dose, route, and regimen, the dates started and stopped (or notation of "continuing" if that is the case), and the reason for use must be recorded on the eCRF. The use of any concomitant medication must relate to an AE or the subject's medical history.

Concomitant medications should be kept to a minimum during the trial. However, if considered necessary for the subject's well-being and if they are unlikely to interfere with the IMP or rescue medications, they may be given at the discretion of the investigator according to the local standard of care.



At each visit, the investigator or designee will ask the subject about concomitant medications in conjunction with the diary comment card. All concomitant medications must be documented in the subject's medical records and in the eCRF. Furthermore, each change in concomitant medication (eg, new treatment, discontinuation of treatment, and change in dosage/routine) during the trial must be documented in the same way.

#### 7.4.2.1.1 Medications Prohibited During the Study

The medications prohibited and washout times (with the exception of the provided allergy rescue medications) are listed in [Table 3](#).

Certain types of medications will be allowed after Visit 6, including: short-acting parenteral corticosteroids, long-acting parenteral (intra-articular or intramuscular) corticosteroids, oral corticosteroids, nasal corticosteroids, leukotriene antagonists/synthase inhibitors, inhaled, topical or oral nedocromil or cromolyn sodium, oral or topical antihistamine or nasal decongestants, tricyclic antidepressant medications with antihistaminic effects (eg, doxapin, mianserin), antipsychotic medications with antihistaminic effects (eg, chlorpromazine, levomepromazine, clozapine, olanzapine, thioridazine) (refer to [Table 3](#) for details).

**Table 3 Prohibited Concomitant Medications and Duration of Washout Period Prior to Visit 4**

Protocol No. P05234

| Prohibited Medications                                                    | Washout Time Before Visit 4 | Restart Medications                           |
|---------------------------------------------------------------------------|-----------------------------|-----------------------------------------------|
| Short-acting parenteral corticosteroids                                   | 30 days                     | after v6                                      |
| Long-acting parenteral (intra-articular or intramuscular) corticosteroids | 90 days                     | after v6                                      |
| Oral corticosteroids                                                      | 60 days                     | after v6                                      |
| Nasal corticosteroids                                                     | 30 days                     | after v6                                      |
| Inhaled corticosteroids <sup>a</sup>                                      | 30 days                     | prohibited for duration of study (refer to a) |
| Leukotriene antagonists/synthase inhibitors                               | 30 days                     | after v6                                      |
| Inhaled, topical or oral nedocromil or cromolyn sodium                    | 14 days                     | after v6                                      |
| Oral or topical antihistamine or nasal decongestants                      | 7 days                      | after v6                                      |
| Long-acting inhaled $\beta$ -agonists                                     | 30 days                     | prohibited for duration of study              |
| Beta blockers, regardless of route of administration                      | 7 days                      | prohibited for duration of study              |
| Anti IgE treatment (eg, Xolair)                                           | At any time                 | prohibited for duration of study              |
| Immunotherapy                                                             | 5 years <sup>b</sup>        | prohibited for duration of study              |
| Self-injectable epinephrine                                               | At any time                 | prohibited for duration of study              |



**Table 3 Prohibited Concomitant Medications and Duration of Washout Period Prior to Visit 4**

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|                                                                                                                                  |                      |                                  |
|----------------------------------------------------------------------------------------------------------------------------------|----------------------|----------------------------------|
| Tricyclic antidepressant medications with antihistaminic effects (eg, doxapin, mianserin)                                        | 14 days              | after v6                         |
| Antipsychotic medications with antihistaminic effects (eg, chlorpromazine, levomepromazine, clozapine, olanzapine, thioridazine) | 7 days               | after v6                         |
| Monoamine oxidase inhibitors                                                                                                     | 14 days              | prohibited for duration of study |
| Investigational drugs                                                                                                            | 30 days <sup>b</sup> | prohibited for duration of study |

<sup>a</sup> Subject maintained on low-dose inhaled corticosteroid will be allowed to continue on his/her medication during the study. A subject must have been using a low daily dose of inhaled corticosteroid for at least 12 weeks and must have been on a stable regimen (daily dose unchanged) for at least 2 weeks before Screening (Visit 1).

Low daily doses of inhaled corticosteroids are defined as follows:

- ≤500 mcg beclomethasone CFC
- ≤250 mcg beclomethasone HFA
- ≤600 mcg budesonide DPI
- ≤1000 mcg flunisolide
- ≤250 mcg fluticasone
- 200 mcg mometasone furoate
- ≤1000 mcg triamcinolone acetonide
- ≤160 mcg ciclesonide

**Note:** Dose delivery by method or modality other than those noted above must be equivalent.

<sup>b</sup> Washout prior to Screening (Visit 1).

#### 7.4.2.1.2 Medications Allowed During the Study

Subjects may take any medication that is not restricted by the protocol and that would not be expected to interfere with the conduct of the study. Refer to [Table 3](#) for medications that are allowed to be administered following Visit 6. Chronic medication should be dosed on a stable regimen. Acetaminophen may be taken as needed for appropriate indications. All concomitant medications must be appropriately documented on the eCRF.

#### 7.4.2.2 Other Treatments

No other treatments other than those previously described in this protocol are permitted in this study.



### **7.4.3 Procedures for Monitoring Subject Compliance**

The subject must take the first three doses of IMP at the study site under the supervision of the investigator or designee. Subjects are to record compliance deviations with IMP on the paper diary comment card. At all protocol-specified visits, the investigator or qualified designee is to note in the appropriate section of the eCRF whether treatment had been taken per protocol in the preceding interval. If not, the date(s) and reason for each deviation must be recorded. In addition, the study staff will maintain an ongoing record of the dispensing and return of all IMP and rescue medications for each subject on the TAAL or equivalent document that will be verified by the sponsor's study monitor.

Study staff will instruct each subject to bring all IMP and rescue medications, (including self-injectable epinephrine) to each protocol-specified visit. The IMP and rescue medications (empty, partially used, and unused), will be inspected at all protocol-specified visits.

The investigator or qualified designee will ensure that any relevant comments on the paper subject comment diary card which refer to possible compliance issues are discussed or clarified with the subject and are captured on the eCRF.

Compliance with electronic diary and paper diary comment card completion regarding IMP and rescue medication usage is essential. Therefore, any noncompliance noted upon review will result in documented consultation with the subject on corrective measures needed to ensure compliance.

### **7.5 Study Schedule**

An overview of the study is provided in the Study Design Diagram in [Section 2.1](#), and the study schedule is shown in the Study Flow Chart in [Section 2.2](#). The timing of each visit is relative to Visit 2-1. Every attempt should be made to re-schedule as closely as possible to the original visit date.

The order in which the procedures are listed below is the approximate order in which they should be performed at the site.



## **Visit 1 (Screening-May Take Place Over Several Days)**

The following procedures will be performed:

- Obtain written informed consent
- Demography
- Body height and weight
- Medical history (including allergy and asthma medical history, tobacco use, self-injectable epinephrine use and other relevant history)
- Record concomitant medications (including allergy and asthma medications)
- Physical examination
- Vital signs
- Pulmonary function tests
- Safety laboratory assessments
- Urine pregnancy test for female subjects of childbearing potential
- Skin prick test
- Blood collection for specific IgE
- Blood collection for other immunological assessments
- Assess compliance with inclusion and exclusion criteria
- Call into IVRS
- Issue and instruct in the use of paper diary comment cards
- Plan a telephone contact between the investigator/designee and the subject to assess continued participation in the study
- Schedule Visit 2-1

## **Visit 2-1 (Randomization)**

Visit 2-1 (Day 1) will occur approximately 1 to 40 weeks after Visit 1 and approximately 16 weeks before the anticipated start of the RS.

The following procedures will be performed:

- Re-evaluation of inclusion/exclusion criteria [repetition of skin prick test, safety laboratory assessments (except pregnancy tests) and specific IgE are not necessary]
- Vital signs



- Urine pregnancy test for female subjects of childbearing potential
- Pulmonary function tests
- Review paper diary comment cards
- Issue and instruct in the use of electronic diaries
- Record changes to concomitant medications
- Assessment of AEs
- Randomization (via IVRS)
- Dispense self-injectable epinephrine, instruct in its use, and provide subject with educational information, including the written Anaphylaxis Emergency Action Plan
- Examination of oral cavity before and after dosing
- On-site administration of IMP followed by 30 minutes of on-site monitoring
- Dispense PEF meter, train subjects in proper use, perform PEF measurements (for asthmatic subjects if needed per country requirements)
- Schedule Visits 2-2, 2-3

### **Visits 2-2, 2-3**

Visit 2-2 and 2-3 will occur to correspond with the second and third doses of IMP.

The following procedures will be performed:

- Vital signs
- Review paper diary comment cards
- Discuss electronic diary recordings and compliance
- Record changes to concomitant medication
- Assessment of AEs
- Examination of oral cavity before and after dosing
- On-site administration of IMP followed by 30-minutes of on-site monitoring
- Dispense IMP for at-home administration (Visit 2-3 only)
- Verify that subject possesses self-injectable epinephrine and instruct in its use
- Review PEF values recorded since last visit; PEF measurement (in asthmatic subjects if needed per country requirements)
- Schedule time for daily telephone contact for the first 4 doses of at-home administration of IMP, and schedule Visit 3.



### **Visit 3 (Off-Season)**

Visit 3-1 will occur approximately mid-way between Visit 2-3 and 4. Two additional visits (Visits 3-2 and 3-3) may be scheduled depending on how early subjects attend Visit 2-1. The following procedures will be performed at all Visit 3s:

- Vital signs
- Urine pregnancy test for female subjects of childbearing potential
- Review paper diary comment cards
- Discuss electronic diary compliance and instructions
- Record changes to concomitant medications
- Assessment of AEs
- Examination of oral cavity
- Call into IVRS for re-supply information
- Verify that subject possesses self-injectable epinephrine and instruct in its use
- Review PEF values recorded since last visit; PEF measurement (in asthmatic subjects if needed per country requirements)
- Check/collect IMP (empty, partially used, and unused), dispense as necessary, and assess compliance
- Schedule Visit 4

### **Visit 4 (Pre-Season)**

Visit 4 will occur approximately 2 weeks before the anticipated start of the RS. The following procedures will be performed:

- Vital signs
- Pulmonary function tests
- Urine pregnancy test for female subjects of childbearing potential
- Blood collection for immunological assessments
- Review paper diary comment cards
- Discuss electronic diary compliance and instructions
- Record changes to concomitant medications
- Assessment of AEs



- Examination of oral cavity
- Call into IVRS for re-supply information
- Verify that subject possesses self-injectable epinephrine and instruct in its use
- Review PEF values recorded since last visit; PEF measurement (in asthmatic subjects if needed per country requirements)
- Check/collect IMP (empty, partially used, and unused), dispense as necessary, and assess compliance
- Dispense allergy rescue medication
- Schedule Visit 5

### **Visit 5 (On-Season)**

Visit 5 will occur at the time of the anticipated peak period of the RS. The following procedures will be performed:

- Vital signs
- Pulmonary function tests
- Urine pregnancy test for female subjects of childbearing potential
- Blood collection for immunological assessments
- Review paper diary comment cards
- Discuss electronic diary compliance and instructions
- Record changes to concomitant medications
- Assessment of AEs
- Examination of oral cavity
- Call into IVRS for re-supply information
- Verify that subject possesses self-injectable epinephrine and instruct in its use
- Check/collect IMP (empty, partially used, and unused), dispense as necessary, and assess compliance
- Check/collect rescue medications (empty, partially used, and unused), dispense as necessary and assess compliance
- Review PEF values recorded since last visit; PEF measurement (in asthmatic subjects if needed per country requirements)
- Schedule Visit 6



## **Visit 6 (End-of-Season)**

Visit 6 will occur approximately 1 week after the RS has ended. The following procedures will be performed:

- Vital signs
- Pulmonary function tests
- Urine pregnancy test for female subjects of childbearing potential
- Safety laboratory assessments
- Blood collection for immunological assessments
- Blood collection for pharmacogenetic sample (optional) and informed consent for DNA sample collection
- Review paper diary comment cards
- Discuss electronic diary compliance
- Discontinuation of electronic diary
- Record changes to concomitant medications
- Assessment of AEs
- Examination of oral cavity
- Call into IVRS for re-supply information
- Check/collect IMP (empty, partially used, and unused) dispense as necessary, and assess compliance
- Collect all remaining allergy rescue medications (empty, partially used, and unused), dispensed at the previous visits and assess compliance
- Verify that subject possesses self-injectable epinephrine and instruct in its use
- Review PEF values recorded since last visit; PEF measurement (in asthmatic subjects if needed per country requirements)
- Schedule Visits 7 and 8

## **Visits 7 and 8 (Post-Season)**

The Post-season Visits (Visits 7 and 8) are to be scheduled so that intervals between visits are of approximately the same length (ie, Visit 7 is approximately 8 to 12 weeks after Visit 6, and Visit 8 is approximately 8 to 12 weeks after Visit 7). The following procedures will be performed:

- Record changes to concomitant medications



- Vital signs
- Pulmonary function tests
- Urine pregnancy test for female subjects of childbearing potential
- Review paper diary comment cards
- Assessment of AEs
- Examination of oral cavity
- Call into IVRS for re-supply information
- Check/collect IMP (empty, partially used, and unused) dispense as necessary, and assess compliance
- Verify that subject possesses self-injectable epinephrine and instruct in its use
- Review PEF values recorded since last visit; PEF measurement (in asthmatic subjects if needed per country requirements)

### **Visit 9 (Final Visit)**

Subjects should continue treatment until they can attend the Final Visit, which should be scheduled within approximately 1 week after the subject has received IMP for approximately 52 weeks. The following procedures will be performed:

- Physical examination
- Body height and weight
- Vital signs
- Pulmonary function tests
- Urine pregnancy test for female subjects of childbearing potential
- Safety laboratory assessments
- Blood collection for immunological assessments
- Blood collection for pharmacogenetic sample (optional) if not obtained at Visit 6.
- Review and collect paper diary comment cards
- Record changes to concomitant medications
- Assessment of AEs
- Examination of oral cavity
- Collect all remaining IMP (empty, partially used, and unused) dispensed at the previous visits and assess compliance
- Collect self-injectable epinephrine



- Review PEF values recorded since last visit; PEF measurement (in asthmatic subjects if needed per country requirements)
- Schedule date and time for the follow-up telephone contact; plan to call IVRS following this phone contact to note subject's completion of the study

### **Unscheduled Visit**

The following procedures will be performed as deemed necessary by the investigator:

- Physical examination
- Vital signs
- Pulmonary function tests
- Urine pregnancy test for female subjects of childbearing potential
- Safety laboratory assessments (if clinically warranted)
- Review paper diary comment cards
- Discuss electronic diary compliance and instructions
- Record changes to concomitant medications
- Discontinue electronic diary and paper diary comment cards (in case of subject's withdrawal)
- Assessment of AEs
- Examination of oral cavity
- Dispense and/or verify that subject possesses self-injectable epinephrine and instruct in its use, as necessary
- Check/collect IMP, self-injectable epinephrine and rescue medications, dispense as necessary and assess compliance
- Call into IVRS
- Review PEF values recorded since last visit; PEF measurement (in asthmatic subjects if needed per country requirements)

### **Follow-Up Telephone Contact Procedures**

A telephone contact between the investigator/designee and the subject will occur when the results of the safety laboratory assessments, urine pregnancy test, and specific IgE are available. Subjects who continue to be eligible for randomization will be told to attend Visit 2-1. Subjects who are no longer eligible will be discontinued.



A telephone contact between the investigator or designee and the subjects will occur daily for the first 4 doses of at-home administration of IMP for AE assessment, and 2 to 4 days after an Unscheduled Visit. In addition, the investigator/designee will contact the subject within 24 hours of re-initiation of IMP following dose interruption after the use of epinephrine for treatment of an AE.

A telephone contact between the investigator/designee and the subjects also will occur approximately 1 week after the last dose of IMP (Visit 9). If an AE was ongoing at the previous visit, or if a new AE is identified during the telephone contact, or if one of the safety laboratory parameters measured at the previous visit showed a clinically significant abnormality, the subject may be asked to return to the study site. Following completion of the Visit 9 follow-up telephone contact, the investigator or designee will call into IVRS to note the subject's completion of the study.

All telephone contact between the investigator/designee and the subjects will be recorded on the site's source document and the AE assessment on the eCRF.

## 7.6 Study Procedures

The Study Flow Chart in [Section 2.2](#) summarizes the study procedures to be performed at each visit. Individual study procedures are described below. For details of the procedures for assessment and reporting of AEs, [Section 7.7.2.2](#), Assessment and Reporting of AEs.

In order to minimize variability of evaluations, it is preferred that the same individuals perform the same types of evaluations for all subjects at each study site.

- **Explain Study and Obtain Written Informed Consent:** Visit 1.

The investigator or qualified designee will explain the study to the subject, answer all of their questions, and obtain written informed consent before performing any study-related procedures (including required washout of medications). A copy of the informed consent will be given to the subject or subject's legal representative and this will be documented in the source.

For tracking purposes, a subject who signs an informed consent will be given a Screening number.

This study includes a pharmacogenetic assessment that requires documented approval of this component of the study from an IRB/IEC as well as a separate consent if the subject (and the subject's legal representative, if appropriate) agrees to participate. Provided IRB/IEC approval is obtained for this component of the study, it is required as part of this protocol that the investigator present this



option to the subject. An additional separate informed consent will be obtained for the pharmacogenetic sample collection procedure and analysis. The process for obtaining informed consent should be exactly the same as for the main informed consent.

Declining to participate in this pharmacogenetic assessment will in no way affect the subject's ability to participate in the main research study.

- **Review Inclusion/Exclusion Criteria:** Visits 1 and 2-1.

Inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study.

A telephone contact between the investigator/designee and the subject will occur when the results of the safety laboratory assessments, urine pregnancy test, and specific IgE are available. Subjects who continue to be eligible for randomization will be told to attend Visit 2-1. Subjects who are no longer eligible will be discontinued.

- **Demographics:** Visit 1.

Record the subject demographics: sex, date of birth (month and year), and ethnic origin.

- **Body Height and Weight:** Visits 1 and 9.

- **Medical History:** Visit 1.

**General Medical History:** Subject history will be obtained by the investigator or qualified designee. History should include information on personal (to be recorded on the eCRF), smoking (to be recorded on the eCRF), and family history (to be recorded only on the source document). A full medical history for the 5 years prior to Visit 1 must be obtained and findings recorded on the eCRF as appropriate.

**Allergy and Asthma Medical History:** Record history of allergy and asthma symptoms including the duration and intensity (mild, moderate, severe). Subjects will be asked a series of detailed questions that will cover medical history topics such as perennial allergic rhinitis, smoking, self-injectable epinephrine use, and asthma, and responses will be recorded on the eCRF.

- **Concomitant Medication Review:** All Visits and Unscheduled Visits.

At Visit 1, concomitant medications should be checked against the list of prohibited medications ([Section 7.4.2.1.1](#)). If the subject does not meet medication washout requirements, some of the procedures performed at this visit may be rescheduled. Screening procedures may take place over several days.

Record all medications (including allergy and asthma medications, and immunosuppressive therapy) taken by the subject during at least the 3 months prior to Visit 1 on the eCRF.

Use of concomitant medications should be reviewed at each visit by the investigator or designee. The identity of the therapy, dose, route, and frequency of use, the dates started and stopped (or notation of "continuing" if that is the case), and the reason for use must be recorded on the eCRF. Generic names should be used whenever possible; for combination products, a trade name



should be used. Use of PRN (as needed) medication should be summarized and recorded on the eCRF.

If a subject requires chronic medication, the medication and supporting data should be recorded. It is only necessary to document this medication again during the course of the study if the dose or frequency of dosing is discontinued or changed.

Any information on concomitant medications recorded on the paper diary comment card by the subject should be transferred to the eCRF. If the concomitant medication was taken for an AE, the AE must be reported on the appropriate section of the eCRF.

- **IVRS:** Visits 1, 2-1, 3, 4, 5, 6, 7, 8, and Unscheduled Visits.

The investigator or designee will call into IVRS following each subject's Screening Visit (Visit 1). Upon confirmation of a subject's eligibility at Visit 2-1, the investigator or designee will call back into IVRS to randomize the subject. Subjects who do not continue to meet the eligibility criteria at Visit 2-1 will be screen-failed via IVRS. For all randomized subjects, the investigator or designee will continue to call into IVRS at Visits 3, 4, and 5, 6, 7, and 8 to obtain additional IMP assignments and allergy rescue medication supplies for each randomized subject as needed. The investigator or designee will make the final call into IVRS following completion of each randomized subject's telephone follow-up at the end of the study.

- **Physical Examination:** Visits 1, 9, and Unscheduled Visits.

All subjects will undergo a standard physical examination at Visits 1 and 9, and at any Unscheduled Visit if deemed necessary by the investigator. Physical findings at Screening will be recorded on the medical history page of the eCRF. Abnormal findings from other visits will be recorded on the AE section of the eCRF.

The examination should be based on the following body systems: general appearance, head (oral inspection, ears, eyes, nose, and throat), respiratory (auscultation/stethoscopy examination of the lungs), heart (auscultation/stethoscopy examination of the heart), lymph nodes and skin. Subjects with evidence of current, clinically significant, intercurrent illness (eg, significant cold or flu) may be rescheduled for rescreening on resolution of illness.

For the following body systems, questioning regarding symptoms may be sufficient: abdomen, urogenital, musculoskeletal, and neurological. If deemed necessary by the investigator, a physical examination of these body systems will be performed.

If the subject is discontinued for any reason during the treatment phase, every attempt should be made to perform a final physical examination as part of the Visit 6 procedures.

- **Vital Signs:** All Visits.

Vital signs will be measured at all visits. Vital signs will include temperature, blood pressure (mmHg), heart rate (beats/minute), and respiratory rate



(breaths/minute) (measured while in a seated position after  $\geq 3$  minutes of seated inactivity).

- **Pulmonary Function Tests:** Visits 1, 2-1, 4, 5, 6, 7, 8, 9, and Unscheduled Visits.

Pulmonary function tests will include measurements of FEV<sub>1</sub> and FVC and will be performed at Visits 1, 2-1, 4, 5, 6, 7, 8, 9. FEV<sub>1</sub> and FVC measurements should also be performed at Unscheduled Visits, if deemed necessary by the investigator.

- **Safety Laboratory Assessments:** Visits 1, 6, 9, and Unscheduled Visits.

All laboratory assessments will be performed centrally at a laboratory selected by the sponsor.

Blood and urine samples for clinical laboratory evaluation will be collected at Visits 1, 6, 9 and at any Unscheduled Visits as necessary.

The clinical laboratory values will be reported to the investigator by the laboratory and he/she will review them for significance.

Blood samples should be taken using standard venipuncture techniques.

The laboratory variables specified in [Table 4](#) will be measured.

**Table 4 Laboratory Variables to be Measured**

| Hematology                   | Chemistry                 | Urinalysis       |
|------------------------------|---------------------------|------------------|
| RBC                          | Total protein             | pH               |
| Hematocrit                   | Albumin                   | Specific gravity |
| Hemoglobin                   | Calcium                   | Protein          |
| Platelets                    | Inorganic phosphorus      | Glucose          |
| WBC (total and differential) | Blood urea nitrogen (BUN) | Ketones          |
|                              | Total Bilirubin           | Blood            |
|                              | Alkaline phosphatase      | Color            |
|                              | AST (SGOT)                | Microscopic exam |
|                              | ALT (SGPT)                |                  |
|                              | LDH                       |                  |
|                              | Creatinine                |                  |
|                              | Glucose                   |                  |
|                              | Potassium                 |                  |
|                              | Sodium                    |                  |
|                              | Chloride                  |                  |
|                              | Bicarbonate               |                  |



- **Urine Pregnancy Test:** All Visits except Visits 2-2 and 2-3.  
A female subject of childbearing potential must have a negative urine pregnancy test at Visit 1 in order to be eligible to participate in the study. Pregnancy tests should be repeated at all visits per the study flow chart, [Section 2.2](#).
- **Skin Prick Testing:** Visit 1.  
Skin prick testing (SPT) will be performed to confirm hypersensitivity to the ragweed allergen extract (*Ambrosia artemisiifolia*). Skin test solutions will be applied two times to the inner forearm. A histamine positive control and saline negative control will also be applied. For each of the two wheals produced by the ragweed allergen extract, the wheal size will be determined by averaging the horizontal and vertical diameters 15 to 20 minutes after application. The average of the two wheals sizes must be at least 5 mm larger than the saline control to be considered positive. Subjects should wait an appropriate time before departing from the study site following the test and should be counseled to call the study site if any untoward symptoms occur.  
All skin prick testing supplies will be provided by the sponsor or designee.
- **Specific IgE:** Visit 1.  
A blood sample will be taken at Visit 1 for the determination of specific IgE against *Ambrosia artemisiifolia*, grasses (dependent upon region), trees (dependent upon region), weeds (dependent upon region), cat hair, dog, alternaria, cladosporium, and dust mites (D. pter and D. far).
- **Pharmacogenetic Sample Collection:** Visit 6.  
At Visit 6 or any time during the study (with approval by the sponsor), an 8.5 mL blood sample will be collected for genomic DNA extraction. Informed consent specific for pharmacogenetic sampling must be obtained prior to collection. Samples will be obtained and shipped according to instructions provided in [Appendix 7](#). DNA samples will be de-identified and stored for a period up to 20 years for genetic analysis as specified in [Appendix 8](#).
- **Other Immunological Assessments:** Visits 1, 4, 5, 6, and 9.  
Other Immunological tests for *Ambrosia artemisiifolia* will be performed on blood collected at Visits 1, 4, 5, 6, and 9.  
Blood samples will be kept in a sponsor's designated facility during the trial, hereafter they will be transferred to the sponsor or the sponsor's designee for analysis. If any samples are left after this analysis, they may be kept for future immunological testing. Subjects will be asked to approve this sample storage by signing an informed consent form designed for this purpose.
- **Subject Diary Comment Cards:** All visits (except Visit 10), and Unscheduled Visits.  
The subject will receive a separate paper diary comment card to assist in capturing information between visits regarding IMP and rescue medication compliance, AEs, and use of concomitant medications. The paper diary comment card will be returned at each visit and the information discussed with the investigator and/or qualified designee.



If the data from the paper diary comment card reflect a change in concomitant medications, occurrence of an AE(s), explanation of non-compliance, or other relevant information pertaining to the subject's involvement in this study, they will be captured in the appropriate section of the eCRF. Comments that are not considered to be relevant, in the investigator's or designee's judgment, will be indicated as such on the paper diary comment card in the space provided. All paper diary comment cards should be initialed and dated by the reviewer at the time of collection from the subject. The paper diary comment cards will remain at the site as a source document.

- **Electronic Diary Recording**

**Rhinoconjunctivitis and Asthma Symptoms:** Visits 2-1 to 6.

Subjects will be required to record allergy and asthma symptoms in an electronic diary once daily in the evening before bedtime from Visits 2-1 to 6. Instructions on how to complete entries and electronic diary findings will be reviewed with the subjects at all visits.

A total of nine symptoms, six rhinoconjunctivitis symptoms (runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes) and three asthma symptoms (cough, wheeze, and chest tightness/shortness of breath [dyspnea]), will be measured on a scale of 0 to 3 as follows:

|                       |                                                                                                           |
|-----------------------|-----------------------------------------------------------------------------------------------------------|
| 0 = no symptoms       | No sign/symptom evident.                                                                                  |
| 1 = mild symptoms     | Sign/symptom is clearly present but minimal awareness; easily tolerated.                                  |
| 2 = moderate symptoms | Definite awareness of sign/symptom, which is bothersome but tolerable.                                    |
| 3 = severe symptoms   | Sign/symptom is hard to tolerate; may cause interference with activities of daily living and/or sleeping. |

Rescue medication usage:

Subjects will be asked to record any intake of rescue medication in the e-diary from Visit 4 through to Visit 6.

**Assessment of Rhinoconjunctivitis Symptoms by Visual Analogue Scale (VAS):** Visits 2-1 to 6.

From Visits 2-1 to 6, the overall severity of rhinoconjunctivitis symptoms will be registered in the electronic diary daily in the evening by the subject indicating a point on a visual analogue scale (VAS) between 'no symptoms' and 'severe symptoms'.

**Baseline Subject Pharmacoeconomic Assessment:** Visit 2-1.

At Visit 2-1, subject will complete a pharmacoeconomic assessment of prior allergy season's impact on his or her productivity and economic costs ([Appendix 3](#)). The assessment will be administered via the electronic diary.



**Rhinoconjunctivitis Quality of Life Questionnaire With Standardised Activities:** Visits 2-1, 4, 5, and 6.

The RQLQ(S) will be completed in the electronic diary by the subject at Visit 2-1, and weekly from Visits 4 to 6 ([Appendix 4](#)). The RQLQ(S) data from this study are collected separately from symptom severity and AE data, and no reconciliation of RQLQ(S) data, symptoms, and AEs data will occur.

Assessments will include only subjects in participating countries in which validated translated questionnaires are available.

**Work Productivity and Activity Impairment-Allergy Specific Questionnaire (WPAI-AS):** Visits 2-1, 5, and 6.

The WPAI-AS will be completed in the electronic diary by subject at Visits 2-1, 5, and 6 ([Appendix 5](#)). The WPAI-AS data from this study are collected separately from symptom severity and AE data, and no reconciliation of WPAI-AS data and AE data will occur. Assessments will include only subjects in participating countries in which validated translated questionnaires are available.

**Overall Treatment Effect (OTE) Global Questionnaire:** Visits 4, 5 and 6.

The overall treatment effect global questionnaire will be completed in the electronic diary by subject at Visits 4, 5 and 6 ([Appendix 6](#)). The OTE data are collected separately from symptom severity and AE data, and no reconciliation of OTE data and AE data will occur. Assessments will include only subjects in participating countries in which validated translated questionnaires are available.

- **Review of Electronic Diary Data:** Visits 2-2, 2-3, 3, 4, 5, 6, and Unscheduled Visits.

At all visits from Visit 2-1 through Visit 6, electronic diary data will be reviewed by the investigator or qualified designee. The review will include an assessment of:

- Rhinoconjunctivitis and asthma symptoms,
- Completeness of responses to the pharmacoeconomic assessment, RQLQ(S), WPAI-AS, and OTE,
- Rescue medication usage against rescue medication usage criteria,
- Overall completeness and accuracy of all recorded entries.

Deficiencies will be immediately discussed with the subject in order to improve the quality of information subsequently recorded on the electronic diaries.

- **Adverse Event Evaluation:** All Visits (except Visit 1) and Unscheduled Visits.

The investigator or designee will question the subject about AEs and intercurrent illnesses since the last visit (as applicable) and will record the pertinent information on the eCRF ([Section 7.7.2.2](#)).

Any information regarding AEs and intercurrent illnesses recorded by the subject on the paper diary comment card should be transferred to the eCRF, as appropriate.

Any events related to signs and symptoms of rhinoconjunctivitis and/or asthma will not be noted as an AE until after Visit 6 on the eCRF.

See [Section 7.7.2.2](#), Assessment and Reporting of AEs, and [Section 7.4.2](#), Nonstudy Treatments.



- **Examination of Oral Cavity:** All Visits (except Visit 1).  
The oral cavity will be inspected for signs of mouth irritation, edema and any other abnormalities at all visits. At Visits 2-1, 2-2 and 2-3, the oral cavity examination should be done before and after dosing. All abnormal findings considered AEs must be recorded on the AE module of the eCRF.
- **On-Site Administration, Dispense and/or Collect IMP:** Visits 2-1, 2-2, 2-3, 3, 4, 5, 6, 7, 8, and Unscheduled Visits.  
A subject who meets the eligibility criteria at Visit 2-1 will have the first three doses of IMP taken at the study site at Visits 2-1, 2-2, and 2-3. The subject will remain at the site for approximately 30 minutes following each dose of IMP administered on site. IMP will be dispensed from Visits 2-3 to 8. A telephone contact between the investigator or designee and the subject will occur daily for the first 4 doses of at-home administration of IMP to determine if the subject has experienced any AEs and if any follow-up measure is required. All telephone contacts will be recorded on the site's source document and the AE assessment on the eCRF. All doses of IMP are to be taken at approximately the same time of the day. IMP will be checked at all visits and re-dispensed as necessary. Unused IMP will be collected at Visit 9 and at Unscheduled Visits if the subject discontinues.
- **Dispense and/or Collect Rescue Medications:** Visits 4, 5, 6, and Unscheduled Visits.  
Rescue medications will be dispensed at Visits 4, 5, and at Unscheduled Visits as necessary. Unused rescue medications will be collected at Visits 5 and 6. The investigator or designee will demonstrate proper technique of delivery of the nasal spray.
- **Dispense, Check Self-Injectable Epinephrine, Instruct in Its Use, and/or Collect Self-Injectable Epinephrine:** Visits 2-1, 2-2, 2-3, 3, 4, 5, 6, 7, 8, 9, and Unscheduled Visits.  
The investigator or designee will dispense self-injectable epinephrine, instruct in its use, and provide subject with educational information including the written Anaphylaxis Emergency Action Plan ([Appendix 2](#)) at Visit 2-1 and at Unscheduled Visits as necessary. The Anaphylaxis Emergency Plan may be modified outside the US to meet local standards.  
The subject will be instructed to bring the self-injectable epinephrine to all visits. The investigator or designee will verify that the subject has self-injectable epinephrine and will instruct in its use at Visit 2-1 through Visit 8 and at Unscheduled Visits. Unused self-injectable epinephrine will be collected at Visit 9.
- **Evaluate IMP Compliance:** Daily from Visits 2-1 to 6 and Unscheduled Visits.  
The subject will be asked to record whether he/she has taken IMP on the subject comment diary card. Any problems with compliance will be reviewed with the subject, and gross compliance problems should be discussed with the sponsor.



- **Evaluate Rescue Medication Compliance:** Daily from Visits 4 to 6.  
The subject will be asked to record any intake of rescue medication in the electronic diary on a daily basis from Visits 4 to 6.
- **PEF Measurements:** Daily from Visits 2-1 through Visit 9 and at Unscheduled Visits.  
Daily PEF measurements will be obtained by all asthmatic subjects in countries where this evaluation is needed per the local requirements at Visits 2-1 through Visit 9 and at Unscheduled Visits. At randomization (Visit 2-1), the subject will be given a PEF meter and will be instructed as to its proper use. The subject should be instructed to bring the PEF meter to all visits to confirm that he/she is using the appropriately dispensed PEF meter, and that it is working properly. The subject also should be instructed to record PEF measurements as directed by the investigator/designee. PEF values recorded will be reviewed by the investigator/designee at each visit.
- **Pollen Counts:** Each site will obtain pollen count data an average of 5 days per week.  
Each site will obtain daily pollen count data either locally, regionally, or through a professional provider (eg, National Allergy Bureau) for ragweed and all other pollen, including tree and grass. Daily pollen counts will be recorded on a pollen count log for at least the time period from the start of tree pollen season through the end of ragweed season (site specific), which will reflect the pollen present in the area of the study site. It is expected that most subjects in the study will reside and/or work in the vicinity of the investigator's office. Therefore, subjects will be exposed to the pollen levels measured and recorded. For ragweed, these counts, expressed as counts per meter cubed, will be tabulated for each site for information purposes. Rain days should be noted. The pollen count logs will be returned to the sponsor.

## 7.7 Study Assessments

### 7.7.1 Efficacy

#### 7.7.1.1 Primary Endpoint

The primary efficacy endpoint is the combined (sum of) rhinoconjunctivitis DSS and DMS averaged over the **peak** RS.

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



### 7.7.1.2 Secondary Endpoints

The key secondary endpoints are:

1. *The combined (sum of) rhinoconjunctivitis DSS and DMS averaged over the entire RS, divided by the duration of the entire RS.*
2. *The average rhinoconjunctivitis DSS for the peak RS, calculated for each subject as the sum of the rhinoconjunctivitis DSS during the peak RS, divided by the duration of the peak RS.*
3. *The average rhinoconjunctivitis DSS averaged over the entire RS.*
4. *The average rhinoconjunctivitis DMS for the peak RS, calculated for each subject as the sum of the rhinoconjunctivitis DMS during the peak RS, divided by the duration of the peak RS.*

Additional secondary endpoints are:

1. *The average weekly rhinoconjunctivitis quality of life total score for the peak RS.*
2. *The average rhinoconjunctivitis DMS for the entire RS, calculated for each subject as the sum of the rhinoconjunctivitis DMS during the entire RS, divided by the duration of the entire RS.*
3. *The percentage of minimal symptom days for the entire RS, calculated for each subject as the sum of the observed minimal symptom days during the entire RS, divided by the duration of the entire RS. A minimal symptom day is defined as a day without use of any rescue medication and with a rhinoconjunctivitis symptom score of  $\leq 2$ .*
4. Change in the WPAI-AS sub-scale scores from randomization to peak-season and to end-of-season.
5. Overall treatment effect Global Questionnaire (scores).
6. The average rhinoconjunctivitis DSS for the entire RS and for the peak RS by VAS, calculated for each subject as the sum of the daily VAS scores during the entire or peak RS, divided by the duration of the entire or peak RS.
7. The average asthma DSS for the entire RS and for the peak RS, calculated for each **asthmatic** subject as the sum of the daily asthma symptom during the entire or peak RS, divided by the duration of the entire or peak RS.



### **7.7.1.3 Other Endpoints**

Other study endpoints will include the following immunological assessments:

1. IgE level against *Ambrosia artemisiifolia*
2. IgG4 level against *Ambrosia artemisiifolia*

### **7.7.1.4 Symptom Scores**

A total of nine symptoms, six rhinoconjunctivitis symptoms (runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes) and three asthma symptoms (cough, wheeze, and chest tightness/shortness of breath [dyspnea],) would be measured on a scale of 0 to 3 as follows:

|                       |                                                                                                           |
|-----------------------|-----------------------------------------------------------------------------------------------------------|
| 0 = no symptoms       | No sign/symptom evident.                                                                                  |
| 1 = mild symptoms     | Sign/symptom is clearly present but minimal awareness; easily tolerated.                                  |
| 2 = moderate symptoms | Definite awareness of sign/symptom, which is bothersome but tolerable.                                    |
| 3 = severe symptoms   | Sign/symptom is hard to tolerate; may cause interference with activities of daily living and/or sleeping. |

### **7.7.1.5 Rhinoconjunctivitis Rescue Medication Score**

Subjects will be provided with open-label allergy rescue medication to be used as needed for treatment of their rhinoconjunctivitis symptoms not controlled by IMP. Subjects will be instructed to report their use of specific rescue medication via the electronic diary. To transform the number of rescue medication doses used into DMS, the scoring principles detailed in [Table 5](#) are applied.

Any asthma medication usage will not be scored. Prednisone use for asthma will be included in the medication score for rhinoconjunctivitis.



**Table 5 Scoring of Rescue Medication Usage**

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| RHINOCONJUNCTIVITIS                                |                                                                                    |                      |                     |
|----------------------------------------------------|------------------------------------------------------------------------------------|----------------------|---------------------|
| STEP                                               | Rescue Medication                                                                  | Score/Dose Unit      | Maximum Daily Score |
| 1                                                  | Loratadine RediTabs <sup>a</sup> 10 mg – 1 tablet QD                               | 6 (per tablet)       | 6                   |
| 1b                                                 | 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 mcg - 2 sprays in each nostril QD    | 2 (per spray)        | 8                   |
| 3                                                  | Prednisone tablet 5 mg (Day 1 - 1 mg/kg/day, Max 50 mg/day)                        | 1.6 (per tablet)     | 16 <sup>b</sup>     |
| 3                                                  | Prednisone tablet 5 mg (Day 2+ - 0.5 mg/kg/day, Max 25 mg/day)                     | 1.6 x 2 (per tablet) | 16 <sup>b</sup>     |
| Maximum daily rhinoconjunctivitis medication score |                                                                                    |                      | 36                  |

<sup>a</sup> An alternate formulation of loratadine will be provided in countries where RediTabs are not available.

<sup>b</sup> Any use of prednisone will be counted in the rhinoconjunctivitis medication score including treatment of an asthma exacerbation. In countries where prednisone is not available, prednisolone will be dispensed in a clinically equivalent dosage.

The rhinoconjunctivitis DMS are based on the data from our studies with loratadine and mometasone furoate nasal spray in seasonal allergic rhinitis patients. Ten (10) mg loratadine led to a clinical benefit as determined by a reduction in nasal symptoms score (the sum of 4 nasal symptom scores) of approximately 30% and a reduction in total non-nasal symptoms score (the sum of 4 non-nasal symptom scores) of approximately 33% (eg, Study C92-258<sup>(5)</sup>). As these nasal symptoms are identical to those of nasal symptoms being recorded in this study, the use of 10 mg loratadine will replace a score of 4 nasal score points (ie, approximately 30% of the maximum nasal symptom score of 12). Similarly, since only 2 of the loratadine non-nasal symptoms are similar to those being recorded in this study, the use of loratadine will replace a score of 2 non-nasal points (ie, approximately 33% of the maximum non-nasal symptom score of 12 divided by 2). Olopatadine hydrochloride eye drops are expected to have a higher effect on eye symptoms as loratadine, therefore daily use of olopatadine hydrochloride will replace a score of 3 non-nasal points or 1.5 point per drop used.

In a comparable examination of the effects of mometasone furoate nasal spray 200 mcg/day in allergic rhinitis subjects with symptoms despite antihistamine treatment, a beneficial reduction in nasal symptom score of approximately 50% and a reduction in non-nasal symptom score of 30% had been observed. Hence, the use of 200 mcg mometasone furoate nasal spray will replace a nasal score of 6 points and a non-nasal score of 2 points for a total rhinoconjunctivitis score of 8 points. Since subjects may be using less than the recommended total daily dose of 4x50 mcg sprays, these 8 points are divided into 2 points per 50 mcg spray.



Oral steroids profoundly affect symptoms relating to all three organ systems. Therefore, short bursts of oral prednisone could be expected to cause a significant reduction of nose, eye and asthma symptoms (greater than the other medications), and therefore oral prednisone will replace a score of 16 for the rhinoconjunctivitis score.

#### **7.7.1.6 Pharmacogenetics**

Exploratory pharmacogenetic (PG) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) interactions are observed or unexpected adverse events are identified. Pharmacogenetic markers of disease may also be investigated. Pharmacogenetic studies will be conducted with Biostatistics input and compared to PK/PD results or clinical outcomes. Any significant PG relationships to outcome will require validation in future clinical studies.

#### **7.7.1.7 Appropriateness of Measurements**

The study design and methods of data collection, analysis, and evaluation are standard for the indication studied. Subjective symptom reporting and assessment of the nasal and non nasal symptoms are standard efficacy measurements in rhinoconjunctivitis. The pulmonary function tests are standard measures used to evaluate asthma.

### **7.7.2 Safety**

#### **7.7.2.1 Specification of Safety Variables**

Safety variables to be assessed include: AEs, vital signs, and safety laboratory assessments, and they will be summarized by treatment groups.

#### **7.7.2.2 Assessment and Reporting of Adverse Events**

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product, biologic (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.



**All AEs must be recorded in the subject's medical records and on the eCRF.**

The onset and end dates, severity and relationship to IMP will be recorded for each AE. The severity of the AE will be assessed according to specific guidelines ([Section 7.7.2.2.1](#)). Any action or outcome (eg, hospitalization, discontinuation of therapy, etc) will also be recorded for each AE.

Lab abnormalities that do not qualify as SAEs do not need to be recorded as AEs on the CRF.

Subjects will be questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.

**7.7.2.2.1 Assessment of Adverse Event Severity and Relationship to Treatment**

The severity of AEs will be graded using the following definitions:

|                   |                                                                                                                           |
|-------------------|---------------------------------------------------------------------------------------------------------------------------|
| Mild:             | awareness of sign, symptom, or event, but easily tolerated;                                                               |
| Moderate:         | discomfort enough to cause interference with usual activity and may warrant intervention;                                 |
| Severe:           | incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention; |
| Life-Threatening: | immediate risk of death.                                                                                                  |

Where determination of the relationship of the AE to the use of the IMP rests on medical judgment, the determination must be made with the appropriate involvement of the investigator or, if the investigator is not a physician, a designated subinvestigator who is a physician. The following guidelines are to be used:



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

The expectedness of an adverse reaction shall be determined according to the specified reference document containing safety information. The reference document containing safety information for the IMP in this current study is to be the most recent Investigator's Brochure for SCH 39641.

For information on rescue medications, the current package insert should be consulted.

#### **7.7.2.2.2 Monitoring Adverse Events**

Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator. The investigator or qualified designee is expected to report ongoing AEs at completion of the clinical study to the primary care physician who will determine the need for and provide standard medical care.

Any actions taken and follow-up results must be recorded on the appropriate page of the CRF. Follow-up laboratory results should be filed with the subject's source documentation.

For all AEs that require the subject to be discontinued from the study, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate or until final resolution or stabilization of the event(s).

#### **7.7.2.2.3 Known Adverse Events Relating to the Underlying Clinical Condition**

Common signs and symptoms of rhinoconjunctivitis and asthma are described below:



- **Rhinoconjunctivitis:** runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes, and watery eyes.
- **Asthma:** cough, wheeze, and chest tightness/shortness of breath.

These symptoms should not be recorded as AEs until after Visit 6 unless there is a clear temporal relationship to IMP administration or otherwise meet the definition of a SAE.

#### 7.7.2.2.4 Known Potential Toxicities of Study Drug

There is no known inherent pharmacological or chemical toxicity with oral mucosal exposure or subsequent ingestion of SCH 39641 (*Ambrosia artemisiifolia* extract). Any toxicity associated with this therapy would be related to the immunologic reactions of subjects who are sensitized to ragweed and have allergen-specific IgE fixed on tissue mast cells. Mast cell degranulation results in release of histamine and other pro-inflammatory mediators, and is the proximate cause of nasal, ocular, and bronchospastic reactions to exposure to aeroallergens such as ragweed.

Clinical experience with sublingual and other oral immunotherapies with allergenic extracts, including grass pollen and ragweed, suggest a low incidence of systemic allergic reactions.<sup>(6)</sup>

In this trial, efficacy and safety will be compared in subjects who receive sublingual immunotherapy with ragweed sublingual tablet to those receiving matching placebo. All subjects will have access to rescue medication during the RS.

Refer to the Investigator's Brochure for additional information on AEs observed to date.

#### 7.7.2.2.5 Definition of Serious Adverse Events

An SAE is any adverse drug or biologic or device experience occurring at any dose that results in any of the following outcomes:

- death;
- life-threatening AE (ie, one that places the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurs);
- persistent or significant disability/incapacity;



- requires in-patient hospitalization (ie, admission), or prolongs hospitalization;
- congenital anomaly or birth defect.

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

**All SAEs**, whether or not deemed drug-related or expected, **must be reported** by the investigator or qualified designee to the sponsor **within 1 working day after the investigator or qualified designee first becomes aware of the event**. If the report is given to the sponsor via telephone rather than in writing on the form designated for SAE reporting, a full description of the event and any sequelae, including the investigator-determined causality to the IMP must be provided, so that the appropriate written report can be completed by the designated sponsor contact. SAEs that occur at any time after the inclusion of the subject in the study up to 30 days after the subject completed or discontinued the study ([Section 7.2.2](#)) must be reported.

Reports of all **SAEs** must be communicated as soon as possible to the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and/or reported in accordance with local laws and regulations.

#### 7.7.2.2.6 Reporting of Subject Death

The death of any subject after enrollment or within 30 days of study completion ([Section 7.2.2](#)), regardless of the cause, **must be reported** by the investigator or qualified designee to the sponsor **within 1 working day after the investigator or designee first becomes aware of the death**. After the 30-day period, deaths need to be reported only for long-term survival studies. If the report is given via telephone rather than in writing on the form designated for SAE reporting, a full description of the circumstances, including the investigator-determined causality to IMP must be provided, so that the appropriate written report can be completed by the designated sponsor contact.

If an autopsy is performed, the report must be provided to the sponsor.



Reports of all deaths must be communicated as soon as possible to the appropriate IRB or IEC and/or reported in accordance with local law and regulations.

#### **7.7.2.2.7 Reporting of Pregnancies**

Pregnancy information on clinical study subjects is collected by the sponsor's Global Pharmacovigilance department. If a woman should become pregnant during the course of the study, the investigator or qualified designee must contact the sponsor within 5 working days of the investigator or qualified designee first becoming aware of the pregnancy. If an SAE occurs in conjunction with the pregnancy, then the reporting time frame for an SAE (1 working day) must be met. The sponsor will provide instructions on how to collect pregnancy information. Follow-up information on the outcome of the pregnancy should also be forwarded to the sponsor.

#### **7.7.2.2.8 Preplanned Hospitalizations or Procedures**

During the study, if a subject has a hospitalization or procedure (eg, elective surgery) that was scheduled prior to the subject entering the study (ie, before the subject [or the subject's legal representation] signed the informed consent) for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of an SAE. However, if the event/condition worsens during the study, it must be reported as an AE (or SAE, if the event/condition results in a serious outcome such as hospitalization).

#### **7.7.2.2.9 Reports of Overdose**

An overdose of SCH 39641 is a dose higher than the dose recommended in this study (higher than 12 Amb a 1-U).

Information on overdoses in clinical subjects is collected by the sponsor's Global Pharmacovigilance department. Should a subject experience an overdose during the course of the study (whether symptomatic or not), the investigator or qualified designee must contact the sponsor within 5 working days of the investigator or qualified designee first becoming aware of the overdose. Follow-up information on the outcome of the overdose should be forwarded to the sponsor.

Any event associated with, or observed in conjunction with, a product overdose (whether accidental or intentional) or a product abuse and/or withdrawal is considered an AE and should be reported as such ([Section 7.7.2.2](#)). If an SAE occurs in conjunction with the overdose, then the reporting time frame for an SAE



(1 working day) must be met. The sponsor will provide instructions on how to collect this information.

#### **7.7.2.2.10 Protocol-Specific Exceptions to SAE Reporting to Drug Safety Surveillance**

There are no exceptions to the SAE reporting standards.

#### **7.7.2.3 Reporting of Investigational Medicinal Product Quality Complaints**

Any defect or possible defect in the IMP (defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial) must be reported by the investigator or qualified designee to the sponsor **within 1 working day** of first becoming aware of the possible defect. This report to the sponsor may be made by telephone or by faxing the Investigational Medicinal Product Quality Complaint (IMPQC) form to the designated sponsor representative. The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

#### **7.7.3 Other Assessments**

None.

#### **7.7.4 Criteria for Termination of the Trial**

Since ragweed allergen extract has been used in injectable and oral formulations, it is not anticipated that this study will be terminated prematurely.

However, the study will be stopped if the following event occurs:

- Treatment-related death of a subject.
- The same or similar treatment-related SAE (hypotension, tachycardia, severe asthmatic reaction, shock) occurs in at least 2 subjects.



Study medication intake may only be resumed after the information has been presented to health authorities, and health authorities concur with continued drug intake.

In case of complete premature termination of the trial, participating investigators/subjects, the Institutional Review Board, and the relevant health authorities must be promptly informed of the termination.

## 7.8 Allergen Exposure

Pollen count data for ragweed and other allergens will be collected by each site to map the length and intensity of the pollen season and thereby quantify allergen exposure.

For the planning of subject visits, the start, peak, and end dates of the RS are defined as follows:

- Start of RS: the first day of 3 consecutive recorded days with a pollen count of  $\geq 10$  grains/m<sup>3</sup>.
- Peak of RS: a period of 15 consecutive recorded days with the highest moving average.
- End of RS: the last day of the last occurrence of 3 consecutive recorded days with a pollen count  $\geq 10$  grains/m<sup>3</sup>.

## 8.0 STATISTICAL AND ANALYTICAL PLANS

Prior to the final efficacy analysis, a detailed Statistical Analysis Plan (**SAP**) will be completed. The Statistical Analysis Plan will contain a more comprehensive explanation than described below of the methodology used in the statistical analyses. The Statistical Analysis Plan will also contain the rules and data handling conventions used to perform the analyses, and the procedure used for accounting for missing data.

For the primary analysis, there will be no imputation of missing data. The average score will be based on the available number of days of data. The primary analysis will be supplemented by sensitivity analyses using various imputation techniques, which will be specified in the **SAP**.

***The SAP will also include the planned analyses for pooling data from study P05233 and study P05234. The purpose of pooled analyses is to get a more***



***precise estimate of the treatment effect (SCH-placebo) and to have a reasonable power to detect that the treatment effect relative to placebo at a specified margin for the primary endpoint of Total Combined Score (TCS) during the peak ragweed season.***

## 8.1 Data Sets

All subjects randomized will be included in the safety analyses. For the analysis ***on the primary efficacy endpoint of the combined (sum of) rhinoconjunctivitis DSS and DMS (TCS) averaged over the peak RS averaged over the peak RS***, subjects with at least one post-baseline diary record within the ***peak*** RS will be included. For each subject, sum of DSS and DMS will be based on all available data in the ***peak*** RS.

## 8.2 Demographic and Other Baseline Characteristics

Demographic variables (sex, race, age, weight, baseline characteristics, etc) will be summarized by treatment group to assess treatment group comparability.

## 8.3 Efficacy Analyses

### 8.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint of ***TCS*** averaged over the ***peak*** RS will be evaluated using an ANOVA model with baseline strata effects (asthmatic condition and ***pollen region***) and treatment group as fixed effect in the model. Based on the ANOVA model, comparison of each active dose versus placebo will be conducted using a step-down method, starting from the comparison of the highest dose of SCH 39641 versus placebo, followed by the next lower dose and so forth in a sequential manner. Each lower dose comparison against placebo is to be carried out only if the previous comparison is statistically significant ( $p < 0.05$ ).

For the primary endpoint, subjects with at least one post-***randomization*** diary record for the symptom score within the defined ***peak*** RS will be included. For each subject, DSS and DMS score will be based on all available data during the ***peak*** RS and the combined score will be calculated as the sum of rhinoconjunctivitis DSS and DMS during the ***peak*** RS, divided by the duration of the ***peak*** RS.

For each dose comparison against placebo, a 2-sided 95% confidence interval of the difference in adjusted means between the two treatment groups will be presented. Also the difference in adjusted means between the two treatment groups relative to



the adjusted mean of the placebo group will be presented as a percentage with corresponding confidence interval.

### 8.3.2 Secondary Efficacy Endpoints

The **continuous** secondary endpoints listed in [Section 7.7.1.2](#) will be evaluated using the above mentioned ANOVA model. For the key secondary endpoints, the type I error rate will be controlled. ***The 1.5 Amb a 1-U dose will not be included in the testing procedure since the main purpose of this dose is to estimate the dose response at the lower end of the dose range; p-value will be presented but will be of descriptive nature only.***

For each dose (**12 or 6 Amb a 1-U**) comparison against placebo which meets the primary endpoint, testing of the key secondary endpoints will be conducted in a stepwise manner in the following order:

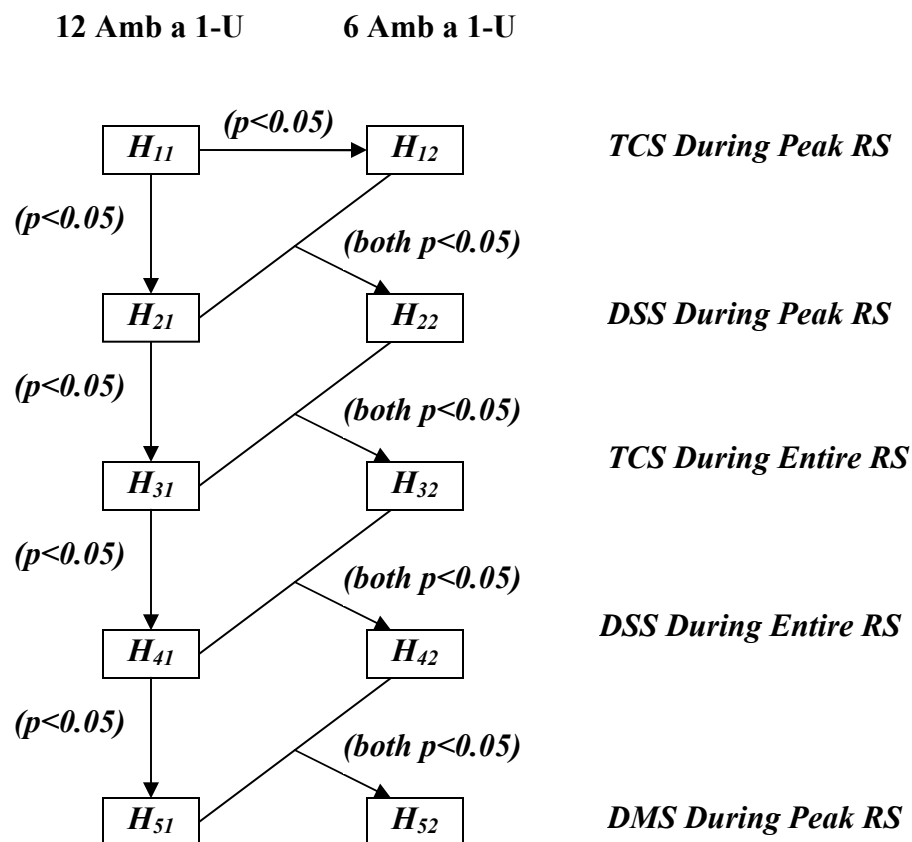
1. **SCH 39641 versus placebo on the average TCS during the entire RS.**
2. **SCH 39641 versus placebo on the average rhinoconjunctivitis DSS for the peak RS.**
3. **SCH 39641 versus placebo on the average rhinoconjunctivitis DSS for the entire RS.**
4. **SCH 39641 versus placebo on the average rhinoconjunctivitis DMS for the peak RS.**

***The 12 Amb a 1-U dose comparison for the each step will be analyzed only if the previous dose comparison for the 12 Amb a 1-U dose is statistically significant ( $p < 0.05$ ). The 6 Amb a 1-U dose comparison will be analyzed only if the 6 Amb a 1-U dose comparison for the previous step and the 12 Amb a 1-U dose comparison for the same step are both statistically significant ( $p < 0.05$ ).***

***If the 12 Amb a 1-U dose is not significantly different from placebo ( $p \geq 0.05$ ) for any step, then p-values resulting from treatment comparisons for the 12 Amb a 1-U dose for the remaining endpoints will be presented with no interpretation regarding the significance of the results. Similarly, if the comparisons for the 6 Amb a 1-U dose for the previous step or the 12 Amb a 1-U dose for the same step are not both significantly different from placebo ( $p \geq 0.05$ ) for any step, then p-values resulting from treatment comparisons for the 6 Amb a 1-U dose for the remaining endpoints will be presented with no interpretation regarding the significance of the results.***

***Additional details for the multiplicity strategy are displayed in [Figure 1](#).***





**Note:**  $H_{ij}$  is the null hypothesis for comparing the  $j^{\text{th}}$  dose to the placebo on the  $i^{\text{th}}$  endpoint;  $i = 1$  to 5 and  $j = 1, 2$ .

**TCS=Total Combined Score; DSS=Daily Symptom Score; DMS=Daily Medication Score; RS=Ragweed Season.**

**Figure 1      Multiplicity Strategy**



## Other Endpoints

Change from Baseline in immunological assessments listed in [Section 7.7.1.3](#) will be evaluated using the above mentioned ANOVA model.

## 8.4 Safety

The number of subjects reporting any AEs, the incidence of specific AEs, and discontinuations due to AEs, will be tabulated by treatment group. Laboratory data will be listed and summarized and values outside the reference ranges will be flagged.

This study will include a Data Safety Monitoring Committee (DSMC). The DSMC will be established prior to the start of the treatment phase. The purpose of the DSMC is to evaluate adverse event data and to provide any recommendations regarding the conduct of the study to ensure that the safety of the subjects participating in the study is protected. The DSMC will monitor trial conduct and safety data as outlined in a separate charter.

## 8.5 Determination of Sample Size/Power/Level of Significance

***Approximately 800 subjects will be randomized in an equal ratio to one of the four treatments: 1.5, 6, and 12 Amb a 1-U of the ragweed sublingual tablet, and placebo. Based on the original protocol primary endpoint of TCS during the entire RS, with approximately 200 subjects per group, the study would be able to detect the difference of -1.63 in the primary endpoint between an active dose group and the placebo group with 92% power at a 5% level of significance (2-sided test). The calculation was based on the original assumptions on the estimates of the standard deviation (SD=4.77) and treatment effect (-1.63) derived from ALK-Abello study GT-08 (grass sublingual tablet).***

***Based on the current (amended) protocol primary endpoint of TCS during the peak RS, with approximately 200 subjects randomized in an equal ratio to one of the four treatments: 1.5, 6, and 12 Amb a 1-U of the ragweed sublingual tablet, and placebo, the study will be able to detect the difference of -1.80 in the primary endpoint between an active dose group and the placebo group with 90% power at a 5% level of significance (2-sided test). Additional details are provided in [Table 6](#).***



**Table 6** Estimates of Differences of Effect to be Detected

Protocol No. P05233

|                                                  | Differences of <b>Effect</b><br>(%) From Placebo to<br>Be Detected | Estimates of           |                                 | <b>Power</b>      |
|--------------------------------------------------|--------------------------------------------------------------------|------------------------|---------------------------------|-------------------|
|                                                  |                                                                    | Mean Placebo<br>Effect | Pooled<br>Standard<br>Deviation |                   |
| <b><i>TCS During the Peak RS<sup>a</sup></i></b> | <b><i>-1.80 (25)</i></b>                                           | <b><i>7.10</i></b>     | <b><i>5.51</i></b>              | <b><i>90%</i></b> |

<sup>a</sup> Estimates of standard deviations and placebo effects are derived from the two US studies P05238 and P05239 (grass sublingual tablet).<sup>(3)</sup>

## 8.6 Interim Analysis

No interim analysis is planned. However, efficacy and safety data for this study will be evaluated sequentially. Since the data for the primary and secondary efficacy endpoints will be available at the end of the ragweed season, efficacy is planned to be evaluated first to facilitate decision to move forward with the program and planning of future studies. Therefore, the final efficacy analyses for primary and secondary endpoints will be conducted when all diary data are available and finalized at the end of the ragweed season. Since subjects are treated for 1 year, the final analyses for safety and immunological parameters will be conducted at a later date when 52-week safety and immunological data are available and the database is locked.

## 8.7 Pharmacogenetic Testing

In an effort to determine if DNA sequence variability in candidate genes is associated with disease status and response to study treatment, DNA samples will be collected from subjects who provide specific informed consent for pharmacogenetic analysis. In addition, genome-wide association analysis may be performed in an effort to understand other genetic factors associated with variability in response to study treatment, as well as potential for development of adverse events.

The exploratory pharmacogenetic studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests (chi-square tests, ANCOVAs, linear and logistic regression) are used for the analyses. Additional data, from subsequent clinical trials, are often needed to confirm associations. Alternatively, if the numbers of



subjects enrolled in the study are too small to complete proper statistical analyses, these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

The use of pharmacogenetics to search for biomarkers of disease and drug action is exploratory. Any results from this pharmacogenetic study will not be placed in the subject's medical records.

In all cases of genetic analysis of DNA samples provided by subjects participating in Study P05234, strict confidentiality will be maintained. To maximize confidentiality, all samples and the information associated with the samples will be double-coded to prevent the exposure of the subject's information and identity. This double-coding process will allow the sponsor to go back and destroy the sample at the subject's request. In addition, sample information is stored in one secured database while genetic data are stored in an independent secured database. Details of these procedures are described in [Appendix 8](#).

## **9.0 ADHERENCE TO ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS**

The study must be conducted in accordance with Good Clinical Practice (GCP) as outlined in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, E6 Good Clinical Practice: Consolidated Guidance and other applicable laws and regulations. In addition, the study must be conducted in accordance with: (i) the USA Code of Federal Regulations (CFR) if the study is conducted under a USA IND, regardless of the country involved; (ii) the European Union (EU) Clinical Trial Directive (CTD) and local regulations if the study is conducted in the EU; and (iii) any specific local regulations if the study is conducted elsewhere.

### **9.1 Ethical Conduct of the Study**

#### **9.1.1 Independent Ethics Committee or Institutional Review Board**

Prior to initiation of the trial at any site, the trial, including the protocol, informed consent, and other trial documents must be approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB/IEC must be constituted according to applicable regulatory requirements. As appropriate, amendments to the protocol must also be approved by the IRBs/IECs before implementation at the sites. The IRB/IEC approval should be obtained in writing, clearly identifying the trial, the documents reviewed (including informed consent), and the date of the review. The trial, as described in the protocol (or amendment),



informed consent, and other trial documentation may be implemented only after all the necessary approvals have been obtained and the sponsor has confirmed that it is acceptable for the investigator to do so.

In the event that the IRB requires changes in the protocol, the sponsor shall be advised and must approve the changes prior to implementation. The investigator shall not modify the study described in the protocol once finalized and after approval by the IRB without the prior written approval of sponsor.

Where the investigator submits the study protocol and statement of informed consent to the IRB, the investigator or qualified designee will forward the approvals to the sponsor.

### **9.1.2 Subject Information and Consent**

The details of the protocol must be discussed with each potential subject, and written informed consent must be obtained for all subjects before any study-related procedure is performed. In obtaining informed consent, the information must be provided in language and terms understandable to the subject. The subject, or the subject's legal representative, must give their written consent to participate in the trial. The signed and dated consent form itself must be retained by the investigator as part of the trial records. A copy of the signed and dated consent forms must be given to the subject. The consent form must include all of the required elements of informed consent in accordance with ICH Guidelines E6 and local laws. In addition, the sponsor specifically requests that the consent form identify it as the sponsor and state that use of the SCH 39641 is experimental and the side effects of SCH 39641 are not completely known. The consent form must be approved by the appropriate IRB/IEC and sponsor before study initiation at a study site. Any subsequent changes to the approved informed consent form must be reviewed and approved by the appropriate IRB and sponsor before implementation.

### **9.1.3 Protocol-Related Regulatory and Ethical Considerations/Issues**

There are no protocol-related regulatory or ethical issues.

## **9.2 Reporting to Sponsor**

The investigator will ensure that there are sufficient time, staff, and facilities available for the duration of the trial to conduct and record the trial as described in the protocol and according to all applicable guidances, laws, and regulations.



Any records or documents used as the source of information in the CRF (called the "subject source data") are to be retained for review by authorized representatives of the sponsor or a regulatory agency.

The investigator must maintain records and data during the trial in compliance with all applicable legal and regulatory requirements. The investigator is to provide subject data on completed Case Report Forms (CRFs), according to the sponsor's instructions and compliant with GCP practices. CRFs and the electronic database from the trial are the exclusive property of sponsor.

All data collection forms should be completed (as soon as possible) after the evaluation has occurred. All dates appearing on the sponsor's subject data collection forms for laboratory tests, cultures, and other data collected, must be the dates on which the specimens were obtained, or the procedures performed.

A CRF must be completed for all subjects who have given informed consent. The sponsor must not collect subject names, initials, or other personal information that is beyond the scope of the trial from any subject. Subjects are not to be identified by name or initials on the CRF or any trial documents. The only acceptable identification for a subject that may appear on a CRF or trial document is the unique subject identification number. The investigator must maintain contact information for each participant so that all can be quickly contacted by the investigator, if necessary.

A CRF or screening log with a minimum of the following information shall be completed for subjects who fail screening: (1) demographics, (2) subject status, (3) reason for screen failure, and (4) SAEs. Data are to be collected from the time the informed consent form is signed until the subject is determined to have failed screening.

All entries into CRFs are the responsibility of the investigator and must be completed by the investigator or a qualified designee. The investigator will acknowledge in writing that he/she has verified the accuracy of the recorded data.

## **9.3 Publications and Other Rights**

### **9.3.1 Rights to Publish by the Investigator**

The investigator has the right to publish or publicly present the results of the study in accordance with this [Section 9.3](#) of the protocol. In the event that the protocol is a part of a multi-site study, it is understood that it is the intent of the sponsor and the investigator to initially only publish or present the study results together with the other sites, unless specific written permission is obtained in advance from the sponsor to publish separate results. The sponsor shall advise as to the implications



of timing of any publication in the event clinical trials are still in progress at sites other than the investigator's site.

The investigator agrees not to publish or publicly present any interim results of the study without the prior written consent of the sponsor. The investigator further agrees to provide to the sponsor 45 days prior to submission for publication or presentation, review copies of abstracts or manuscripts for publication (including, without limitation, slides and texts of oral or other public presentations and texts of any transmission through any electronic media, eg, any computer access system such as the Internet, World Wide Web, etc) that report any results of the study. The sponsor shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts and the right to review and comment on the data analysis and presentation with regard to the following concerns:

1. proprietary information that is protected by the provisions contained in **Section 9.3.2**
2. the accuracy of the information contained in the publication; and
3. to ensure that the presentation is fairly balanced and in compliance with FDA regulations.

If the parties disagree concerning the appropriateness of the data analysis and presentation, and/or confidentiality of the sponsor's confidential information, investigator agrees to meet with the sponsor's representatives at the clinical study site or as otherwise agreed, prior to submission for publication, for the purpose of making good faith efforts to discuss and resolve any such issues or disagreement.

### **9.3.2 Use of Proprietary or Confidential Information in a Publication**

No publication or manuscript shall contain any trade secret information of the sponsor or any proprietary or confidential information of the sponsor and shall be confined to new discoveries and interpretations of scientific fact. If the sponsor believes there is patentable subject matter contained in any publication or manuscript submitted for review, the sponsor shall promptly identify such subject matter to investigator. If sponsor requests and at sponsor's expense, investigator shall use its best efforts to assist sponsor to file a patent application covering such subject matter with the USA Patent and Trademark Office or through the Patent Cooperation Treaty prior to any publication.



### **9.3.3 Use of Trial Information in a Publication**

Investigator is granted the right, subject to the provisions of this protocol, to use the results of all work provided by investigator under this protocol, including but not limited to, the results of tests and any raw data and statistical data generated for investigator's own teaching, research, and publication purposes only.

Investigator/Institution agrees, on behalf of itself and its employees, officers, trustees, and agents, not to cause said results to be knowingly used for any commercial purpose whatsoever except as authorized by the sponsor in writing.

### **9.3.4 Authorship of Publications**

Authors of publications must meet the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship and must satisfy the 3 criteria that follow:

1. Authors must make substantial contributions to the conception and design of the trial, acquisition of data, or analysis of data and interpretation of results;
2. Authors must draft the publication or, during draft review, provide contributions (data analysis, interpretation, or other important intellectual content) leading to significant revision of the manuscript with agreement by the other authors;
3. Authors must provide written approval of the final draft version of the publication prior to submission.

All contributors who do not meet the 3 criteria for authorship should be listed in an acknowledgments section within the publication, if allowed by the journal, per the ICMJE guidelines for acknowledgment.

## **9.4 Shipping of Hazardous or Dangerous Goods**

It is the responsibility of the investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens or any other hazardous or dangerous goods act in conformance with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous or dangerous goods.



## **9.5 Trial Documents and Records Retention**

During the trial and after termination of the trial – including after early termination of the trial – the investigator must maintain copies of all documents and records relating to the conduct of the trial. This documentation includes, but is not limited to, protocols, CRFs, advertising for subject participation, AE reports, subject source data, correspondence with health authorities and IRBs/IECs, consent forms, investigator's curricula vitae/biosketch, monitor visit logs, laboratory reference ranges, and laboratory certification or quality control procedures and laboratory director curriculum vitae. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, or as specified below. The study monitor must be consulted if the investigator wishes to assign the files to someone else, remove them to another location, or is unable to retain them for the specified period.

The investigator must retain trial records for the amount of time specified by applicable laws and regulations. At a minimum, trial records must be retained for the amount of time specified by ICH Guidelines or the EU Good Clinical Practices Directive, whichever is longer:

1. The ICH Guidelines specify that records must be retained for a minimum of 2 years after a marketing application for the indication is approved (or not approved) or 2 years after notifying the appropriate regulatory agency that an investigation is discontinued.
2. The EU GCP Directive specifies that trial records must be retained for 5 years after the completion of the trial.

All trial documents shall be made available if required by relevant health authorities. The investigator should consult with the study monitor prior to discarding trial and/or subject files.

Sponsor will retain all sponsor-required documentation pertaining to the trial for the lifetime of the product. Archived data may be held on microfiche or electronic record, provided that a back-up exists and that a paper copy can be obtained from it, if required.



## **10.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE**

### **10.1 Sponsor**

The sponsor of this study is Schering-Plough Research Institute indicated in [Section 1](#), Title Page.

### **10.2 Investigators**

#### **10.2.1 Selecting Investigators**

Only investigators qualified by training and experience to perform a clinical investigation with SCH 39641 are selected. The sponsor will contact and select all investigators or co-investigators (ie, the legally responsible party at each study site), who, in turn, will select their staff.

#### **10.2.2 Financial Disclosure Requirement**

In connection with the clinical study described in the protocol, the investigator certifies that, if asked, the investigator will read and answer the Clinical Investigator Financial Certification Form truthfully and to the best of investigator's ability. Investigator also certifies that, if asked, the investigator will have any other applicable party(ies) (eg, subinvestigators) read and answer the Clinical Investigator Financial Certification Form as a condition of their participation in the study.

If the financial interests reported on the Clinical Investigator Financial Certification Form change during the course of the study or within 1 year after the last subject has completed the study as specified in the protocol, the investigator and the other applicable party(ies) are obligated to inform the sponsor of such financial change.

#### **10.2.3 Clinical Study Report Coordinator Investigator**

A clinical study report (CSR) will be prepared by the sponsor or its qualified designee to describe the results of the study. One of the investigators shall be selected by the sponsor to review the CSR and provide approval of the final CSR in writing. The investigator chosen to review and approve the CSR is to be called the CSR Coordinating Investigator. A second investigator shall be selected as the Alternate CSR Coordinating Investigator. The Alternate CSR Coordinating Investigator is to review and approve the CSR should the first CSR Coordinating Investigator be unable to do so. The sponsor is to select the CSR Coordinating



Investigator and Alternate CSR Coordinating Investigator from the investigators using the following criteria:

- Must be the Principal Investigator at a study site actively enrolling subjects and participating in the study;
- Must be willing and capable of completing the necessary reviews and providing approval of the CSR in writing;

### 10.3 Central Organizations

The following responsibilities will be performed by contract research organizations: clinical monitoring, clinical study management, data management, electronic diaries, interactive voice response system, and central laboratory.

## 11.0 REFERENCES

1. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006 Feb;117(2):319-25.
2. Bousquet J, Lockey RF, Malling HJ. WHO Position Paper. Allergen immunotherapy: Therapeutic vaccines for allergic diseases. *Allergy* 1998;53(44):1-42.
3. GT-08 – A randomized, parallel group, double-blind, placebo-controlled, Phase-3 trial assessing the efficacy and safety of ALK Grass Tablet *Phleum pratense* in subjects with seasonal grass pollen induced rhinoconjunctivitis. Final Integrated Clinical Trial Report Pollen Season 2005: Version 1, 24 October 2005.  
GT 08 – Extension 2<sup>ND</sup> Year – A randomized, parallel group, double-blind, placebo-controlled, Phase-3 trial assessing the efficacy and safety of ALK Grass Tablet *Phleum pratense* in subjects with seasonal grass pollen induced rhinoconjunctivitis. Second Year Integrated Clinical Trial Report Pollen Season 2006: Version 1, 06 March 2007
4. RT-01 - A randomized, multiple dose, dose-escalation, double-blind, placebo-controlled Phase 1 trial investigating the optimal safe dose of ALK Ragweed tablet (*Ambrosia artemisiifolia*) in adult subjects with seasonal rhinoconjunctivitis caused by ragweed pollen. Final Integrated Clinical Trial Report: 27 September 2007.

