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A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY EVALUATING THE EFFICACY AND SAFETY OF SUBLINGUAL IMMUNOTHERAPY WITH SCH 697243 (*PHLEUM PRATENSE*) IN CHILDREN 5 TO <18 YEARS OF AGE WITH A HISTORY OF GRASS POLLEN INDUCED RHINOCONJUNCTIVITIS WITH OR WITHOUT ASTHMA (PROTOCOL NO. P05239)

Other Study Information:	This was an approximately 19-month study including an observational period during Year 1 2008 Grass Pollen Season (GPS) with no administration of investigational medicinal product (IMP), and a treatment period during Year 2 2009 GPS, with randomization to either SCH 697243 or placebo.
Name of Sponsor:	Schering-Plough Research Institute, a division of Schering Corporation
Included Protocols:	P05239: 14 SEP 2007 – FINAL P05239AM1: 12 FEB 2008 – AMENDMENT #1 P05239AM2: 12 AUG 2008 – AMENDMENT #2 P05239AM3: 29 JUL 2009 – AMENDMENT #3
Development Phase of Study:	3
Study Initiation Date:	07 JAN 2008
Study Completion Date:	25 SEP 2009

Sponsor's Responsible Medical Officer:	[redacted] MD Vice President Allergy/Respiratory Diseases/ Clinical Immunology Head of Therapy Area
Sponsor's Signatory:	[redacted], MD, PhD Director of Allergy/Respiratory Diseases/Clinical Immunology
Sponsor's Contact Person:	[redacted] Telephone: [redacted] FAX: [redacted]
GCP Compliance:	This study was performed in compliance with good clinical practice, including the archiving of essential documents.
Date of the FINAL Report:	12 AUG 2010
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2 SYNOPSIS

Title of Study: A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of Sublingual Immunotherapy With SCH 697243 (*Phleum Pratense*) in Children 5 to <18 Years of Age With a History of Grass Pollen Induced Rhinoconjunctivitis With or Without Asthma (Protocol No. P05239)	
Investigators: Multicenter	
Study Centers: Multicenter: 58 centers initiated in the United States and 10 centers initiated in Canada	
Publications: None	
Studied Period: 07 JAN 2008 to 25 SEP 2009	Clinical Phase: 3

Objectives:

Primary Objective: To evaluate the efficacy of grass sublingual tablet (SCH 697243) versus placebo in the treatment of grass pollen-induced rhinoconjunctivitis based on the combined (sum of) rhinoconjunctivitis daily symptom score (DSS) and rhinoconjunctivitis daily medication score (DMS) averaged over the entire grass pollen season (GPS).

Key Secondary Objectives: To assess overall safety and to compare the following between the SCH 697243 and placebo groups:

The average rhinoconjunctivitis DSS for the entire GPS.

The average rhinoconjunctivitis DMS for the entire GPS.

The average weekly rhinoconjunctivitis quality of life total score for the entire GPS.

Methodology: This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study in subjects 5 to <18 years of age of either sex and of any race with a history of grass pollen-induced rhinoconjunctivitis with or without asthma.

There was an observational grass pollen season period in year 2008 where no investigational medicinal product (IMP) was administered. Open-label rescue medications for the rhinoconjunctivitis and asthma symptoms were provided. Subjects were to visit the study site for at least 6 visits: Screening, Post-screening, Pre-season, On-season, End-of-season, and Off-season Visits, and at Unscheduled Visits as appropriate. Additional Off-season Visits were scheduled depending on the timing of the Randomization Visit (2-1) in relation to the anticipated start of the GPS. Qualified subjects were to be randomized into the treatment period. Due to low enrollment, new subjects were also enrolled after the start of the Year 1 2008 observational period GPS to meet the targeted sample size.

In the treatment period, the subjects were treated once daily with either SCH 697243 (Timothy grass allergy immunotherapy tablet [grass AIT]) or placebo for approximately 16 weeks prior to the GPS and during the GPS. At the Randomization Visit (Visit 2-1), subjects were supplied with self-injectable epinephrine together with instructions on how and when to use it. Open-label rescue medications for the rhinoconjunctivitis and asthma symptoms were to be provided. Subjects were to visit the study site for at least 9 visits: Screening (2 visits), Randomization (3 visits), Off-season, Pre-season, On-season, and End-of-season Visits, and at Unscheduled Visits as appropriate. The first three consecutive daily doses of IMP were administered at the study site, and the subjects were monitored at the site for 30 minutes following dosing. Subsequent administration of IMP was done once daily at home at a time of the day that would allow the parent/guardian to monitor the subject for adverse events (AEs) following dosing. A telephone contact between the investigator/designee and the parent/guardian occurred daily for the first 4 days of at-home administration of IMP to monitor AEs and once approximately 1 week after the End-of-season Visit. Additional Off-season Visits were scheduled depending on the timing of the Randomization Visit (2-1) in relation to the anticipated start of the GPS.

This study was conducted in conformity with Good Clinical Practice. A data safety monitoring committee (DSMC) was established prior to the start of the treatment period. The purpose of the DSMC was to evaluate adverse event data and to provide recommendations regarding the conduct of the study to ensure the safety of the subjects.

Number of Subjects: A total of 345 subjects were randomized in the treatment period (Year 2 2009); one subject was randomized, but not treated: 76 subjects were continued from the Year 1 2008 observational period GPS, and 269 subjects were enrolled directly into the treatment period. Of the 344 treated subjects who were randomized in a 1:1 ratio to either SCH 697243 or Placebo, 175 subjects were in the active group and 169 were in the placebo group.

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Diagnosis and Criteria for Inclusion: Subjects of either sex and of any race, with a clinical history of significant grass pollen-induced allergic rhinoconjunctivitis (with or without asthma) were to be selected for this study. Subjects from 5 to <18 years old who had received treatment for their disease during the previous GPS were to be recruited.

Key Inclusion Criteria

1. Subject must have been 5 to <18 years of age, of either sex and of any race.
2. Subject must have had clinical history of significant allergic rhinoconjunctivitis to grass (with or without asthma) diagnosed by a physician and have received treatment for their disease during the previous GPS.
3. Subject must have had a positive skin prick test response (average wheal diameter ≥5 mm larger than the saline control after 15 to 20 minutes) to *Phleum pratense* at the Screening Visit.
4. Subject must have been positive to specific Immunoglobulin E (IgE) against *Phleum pratense* (≥ IgE Class 2; ≥0.7 kAU/L) at the Screening Visit.
5. Subject must have had a forced expiratory volume in 1 second (FEV1) ≥70% of predicted value at the Screening Visit.
6. A subject's safety laboratory tests and vital signs conducted at the Screening Visit must have been 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, having received regular medications because of another allergen during or potentially overlapping the GPS.
2. Subject with a clinical history of significant symptomatic perennial allergic rhinitis and/or asthma having received regular medication because of an allergen to which the subject is regularly exposed.
3. Subject with sufficient pre-seasonal data in the observational period will not be eligible to continue in the treatment period if the subject: 1) does not have an increase in rhinoconjunctivitis symptom score of at least 4 above the pre-seasonal average symptom score for at least 2 days, and 2) does not use allergy rescue medication for at least 2 days during the Year 1 2008 observational period GPS.

   (Note: This exclusion criterion applied only to the treatment period and for those subjects who had participated in the observation period.)
4. Subject who has had previous immunotherapy treatment with grass pollen allergen or any other allergen within the 5 years prior to the Screening Visit.
5. Subject with a known history of allergy, hypersensitivity or intolerance to the ingredients in the IMP (except for *Phleum pratense*), rescue medications, or self-injectable epinephrine.

Test Product, Dose, Mode of Administration, Batch No: SCH 697243 (2800 Bioequivalent Allergen Units [BAU] of *Phleum pratense* extract, containing approximately 15 mcg Phl p 5), administered sublingually once daily preferably at approximately the same time each day; Batch No. K-H08514 (690066)

Duration of Treatment: Approximately 24 weeks. Subjects were to be treated for approximately 16 weeks prior to start of the GPS and during the entire GPS of the treatment period. The start and end of the GPS was to be determined on the basis of the regional grass pollen count. The GPS was defined as the first day of 3 consecutive recorded days with a pollen count of ≥10 grains/m^3, to the last day of the last occurrence of 3 consecutive recorded days with a pollen count ≥10 grains/m^3, and was to be determined after the site completed the last subject/last visit and prior to database lock for each study period. A period of 15 consecutive recorded days with the highest moving average was defined as the peak GPS.

Reference Therapy, Dose, Mode of Administration, Batch No: Matching placebo (to test product), administered sublingually once daily preferably at approximately the same time each day; Batch No. K-08509 (694705)

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Criteria for Evaluation:

Observational Period: The average DSS and DMS for the rhinoconjunctivitis and asthma symptoms for each subject was to be summarized.

In addition, the psychometric characteristics (ie, reliability, validity, responsiveness), including the minimal important difference, of the total combined score (TCS) (sum of DSS and DMS) were evaluated.

The number of subjects reporting any adverse events, the incidence of specific adverse events, and discontinuations due to adverse events were tabulated. Laboratory and vital sign data were listed and summarized, and values outside the reference ranges were to be flagged.

Treatment Period

Primary Efficacy Endpoint:

The primary efficacy endpoint was the total combined (sum of) rhinoconjunctivitis DSS and DMS averaged over the entire GPS.

(The combined score for each subject was to be calculated as the sum of rhinoconjunctivitis DSS and DMS during the entire GPS, divided by the duration of the entire GPS.)

Key Secondary Efficacy Endpoints:

1. The average rhinoconjunctivitis DSS for the entire GPS, calculated for each subject as the sum of the rhinoconjunctivitis DSS during the entire GPS, divided by the duration of the entire GPS.
2. The average rhinoconjunctivitis DMS for the entire GPS, calculated for each subject as the sum of the rhinoconjunctivitis DMS during the entire GPS, divided by the duration of the entire GPS.
3. The average weekly rhinoconjunctivitis quality of life total score for the entire GPS.

Statistical Methods:

For the Primary Endpoint: The primary efficacy endpoint of the total combined (sum of) rhinoconjunctivitis DSS and DMS averaged over the entire GPS was evaluated using a linear model with asthma status, study site, and treatment group as fixed effects. For the primary endpoint, subjects with at least one post-baseline diary record with DSS and DMS within the defined pollen season were included. The combined average score was to be based on all available data during the GPS for each subject.

A 2-sided 95% confidence interval of the difference in adjusted means between the two treatment groups was presented. Also, the difference in adjusted means between the two treatment groups relative to the adjusted mean of the placebo group was presented as a percentage with corresponding confidence intervals.

For the Secondary Efficacy Endpoints: The secondary endpoints were evaluated using a linear effect model with asthma status, treatment, and study site effects in the model. For the following key secondary endpoints, the type 1 error rate was controlled using the Hochberg's test :

1. SCH 697243 vs placebo on the average rhinoconjunctivitis DSS for the entire GPS
2. SCH 697243 vs placebo on the average rhinoconjunctivitis DMS for the entire GPS
3. SCH 697243 vs placebo on the average weekly rhinoconjunctivitis quality of life total score for the entire GPS

The secondary endpoints were adjusted for multiplicity using the Benjamini and Hochberg[15] method to control the overall alpha level of 0.05 among them. The key secondary analyses were performed only if the primary analysis was statistically significant at two-sided alpha = 0.05.

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

Missing Data: For the primary analysis, there was no imputation of missing data. The combined average score was based on the available number of days of data. The primary analysis was supplemented by sensitivity analyses using various imputation techniques, which were specified in the statistical analysis plan.

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SUMMARY-CONCLUSIONS:

RESULTS: A total of 345 subjects were randomized in the treatment period (Year 2 2009), of which 76 subjects were continued from the Year 1 2008 observational period GPS, and 269 subjects were enrolled directly into the treatment period. Of this, 344 subjects (one subject was randomized and not treated) received double-blind treatment with either 2800 BAU SCH 697243 (n=175) or placebo (n=169). A total of 282 (82%) of subjects overall completed the protocol-specified, double-blind treatment period. The median preseasonal duration of treatment was approximately 15.6 weeks. Demographic and Baseline characteristics were well matched between the treatment groups. Overall, the median age was 13 years, 65% of subjects were male, and 88% were white. Median duration of allergic rhinoconjunctivitis at Baseline was 6 years. All subjects, except for two, tested positive by serum specific IgE measurements to *Phleum pratanse* (mean *Phleum pratense* IgE 33.23 kAU/L) and all subjects, except for two, tested positive for grass pollen (*Phleum pratense*) by skin prick testing (mean wheal to *Phleum pratense* 10.65 mm; mean histamine wheal 5.52 mm) at screening. The majority of subjects (89%) also tested positive for one or more other allergens (the most predominant being tree, weeds, and cat/dog). Twenty-six percent of subjects had a diagnosis of asthma.

Efficacy*:*

For the primary efficacy variable, SCH 697243 (grass sublingual tablet; 2800 BAU) showed statistically significantly lower total combined symptom and medication score compared to the placebo group during the entire grass pollen season (26% lower, p=0.001) and during the peak grass pollen season (31% lower, p<0.001). The treatment difference is observed from the start of the GPS and is maintained throughout the season. Additionally, this improvement was confirmed in the PP analyses.

For the key secondary variables, SCH 697243 treatment demonstrated 25% lower rhinoconjunctivitis daily symptom score (DSS) during GPS when compared to placebo, which reached statistical significance (p=0.005). Perhaps due to a weak pollen season overall, rescue medication usage was low in both treatment groups. Throughout the pollen season, a favorable trend was noted for a decrease in the need for rescue medication in the SCH 697243 group over placebo (32% lower, p=0.066); however, during peak season when symptom scores were higher, a 41% (p=0.049) reduction in medication score was reported in the SCH 697243 group when compared to placebo. Additionally, nonparametric analysis of rhinoconjunctivitis DMS data showed an 81% significant improvement of SCH 697243 over placebo (p=0.006). Subjects treated with SCH 697243 demonstrated an 18% statistically significantly lower total Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score over placebo (p=0.042). The difference in RQLQ demonstrated statistical significance in favor of the grass AIT group, although the RQLQ minimal important difference (MID) of 0.5[13] was not obtained.

From the additional secondary analyses, it is clear that grass AIT is as effective at providing lower TCS, DSS, and DMS during the peak GPS when compared to the effect over the entire GPS.

A greater number and percent of minimal symptom days during the GPS was shown for subjects in the SCH 697243 group (18.07 days; 47.37%) compared to subjects in the placebo group (11.23 days; 35.33%); a 61% difference (p=<0.001). In line with the lower DSS in the SCH 697243 group, the visual analogue scale (VAS) also showed lower DSS during the entire and peak GPS in the active group over the placebo group (p=0.013 and p=0.007, respectively).

In the analyses of the immunological parameters *Phleum pratense* specific IgE, Immunoglobulin G4 (IgG4), and IgE-Blocking Factor, a significant increase in the immunological response in subjects treated with SCH 697243 compared to placebo was observed in the treatment year. The specific IgE response was similar in both treatment groups.

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Safety:

Review of the safety data demonstrates that treatment with SCH 697243 (2800 BAU) was well tolerated with no deaths, anaphylactic shock or life-threatening events. The most frequently reported treatment-related adverse events were as expected, early occurring, transient, self-limited local application site reactions of mouth, throat, and ear (primarily oral pruritus, throat irritation, stomatitis [note: stomatitis is the preferred term; however, these events were mild and described as redness or irritation under the tongue], ear pruritus, and mouth edema). The majority of the local application site reactions were reported by subjects in the SCH 697243 group (60.0% versus 8.3% in the placebo group), and were considered mild or moderate in severity. These events are the common events that have been seen in previous trials with sublingual grass AIT.

Nineteen subjects (5%) discontinued during the treatment period because of AEs, 13 subjects (7%) in the SCH 697243 group, 5 (3%) in the placebo group, and 1 subject not randomized to any treatment. Five subjects (4 subjects in the placebo group and 1 subject not randomized to any treatment) reported SAEs (4 events in 4 subjects) during the treatment period. All SAEs were considered to be unlikely related to study drug.

There was no indication of a differential response to treatment with regard to AEs between asthmatic and non-asthmatic subjects, and there were no safety signals that emerged in the asthmatic group.

Three subjects received epinephrine during the study. One of the administrations was due to an allergic reaction with predominantly moderate local application site symptoms following the first administration of study drug under the supervision of the investigator (subject was in the active group). The other two epinephrine administrations were unrelated to study medication (1 subject with viral pharyngitis in the active group; 1 subject with asthma exacerbation in the placebo group).

Two subjects each had two events on the same day that together could indicate a systemic event or reaction when applying the anaphylaxis criteria as described by Sampson, et al[16]; these subjects were on the active arm of treatment, and the events were considered either mild or moderate and probably related to grass AIT.

Additionally, no clinically relevant changes in vital signs, pulmonary function tests (forced expiratory volume in 1 second [FEV1] and forced vital capacity [FVC]), and laboratory values (hematology and blood chemistry) were observed. Finally, no new safety signals were detected.

CONCLUSIONS:

- Treatment with grass AIT (SCH 697243 2800 BAU) for approximately 16 weeks prior to the season provided significant clinical benefit to allergic rhinoconjunctivitis subjects as shown by improvement in the total combined score (26%) and by a 25% decrease in daily symptom score (DSS), despite a weak grass pollen season. The improvement was shown at the start of the grass pollen season and was maintained throughout the season, with the same treatment effect recorded during the peak pollen exposure.

- In the SCH 697243 group, the effect on daily rescue medication across the season showed a trend in lower rescue medication usage, with a DMS of 0.91 (-32%), without reaching statistical significance ($p = 0.066$). This is not an unexpected finding in a weak pollen season, since the poor utilization of allergy rescue medications for both groups explains an inability to see a significant decrease in the use of rescue medication in the SCH 697243 arm. However, the treatment effect on medication usage was significant during peak season.

- The primary and key secondary results were supported by similar findings during the peak grass pollen season and by statistically improved RQLQ scores (18% during GPS and 38% during peak season) and lower VAS scoring of rhinoconjunctivitis symptoms in the SCH 697243 group over the placebo group.

- A greater number of minimal symptom days during the GPS was shown for subjects in the SCH 697243 group (18.07 days) compared to subjects in the placebo group (11.23 days) with a difference of 61% ($p=<0.001$).

- Similar to findings with injection therapy and previous AIT grass trials (GT-08, GT-02, and GT-12), active treatment induced marked and sustained increases of *Phleum pratense* specific IgG4 and IgE-blocking factor, suggesting direct immunomodulatory effects leading to possible immune deviation and tolerance development.

- Treatment with SCH 697243 was well-tolerated for up to 33 weeks of treatment, and no new safety concerns emerged during the trial.

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- The most frequently reported treatment-related adverse events were as expected, mild or moderate local application site reactions of mouth, throat, and ear.
- There was no indication of a differential response to treatment with regard to AEs between asthmatic and non-asthmatic subjects.
- This study replicates pediatric study results from Europe (GT-12) and results in adults from another North American trial P05238.

Date of the Report: 12 AUG 2010