

<b><i>These clinical study results are supplied for informational purposes only, in the interest of scientific disclosure. These results are not intended to substitute for the package insert or other labeling approved by your local health authority or government or other legally constituted appropriate authority, which should be the basis for all prescribing decisions.</i></b>	
<b>Title of Study:</b>	Crossover Study of the Decongestant Effect of Phenylephrine Compared With Placebo and Pseudoephedrine as Active Control in SAR Subjects Exposed to Pollen in the Vienna Challenge Chamber (Protocol No. P04579).
<b>Studied Period:</b>	09 JAN 2006 to 01 FEB 2006
	<b>Clinical Phase:</b> 3
<b>Objective(s):</b>	The <b>primary</b> objective of this study was to evaluate the effect of a phenylephrine 12-mg immediate-release capsule on nasal congestion compared with that of placebo in subjects with seasonal allergic rhinitis (SAR) who have been exposed to pollen for 6 hours in the Vienna Challenge Chamber (VCC). The key <b>secondary</b> objective of this study was to estimate the effect of a pseudoephedrine (PSE) 60 mg immediate-release tablet on nasal congestion over a 6-hour observation period relative to placebo. Another secondary objective was to evaluate the safety profile of postdose adverse events and vital signs compared with predose evaluations.
<b>Methodology:</b>	This was a randomized, investigator-blind, placebo-controlled, three-way crossover, single-center study of phenylephrine, PSE, and placebo in subjects with SAR, conducted in conformance with Good Clinical Practices. After a screening period of up to 28 days, subjects were to arrive at the VCC on the mornings of each of 3 treatment days. Dose administration was to be separated by a washout interval of at least 5 days between each of the three periods. Approximately 39 adult subjects were to be enrolled to ensure that 30 subjects would receive all three treatment sequences assigned according to a computer-generated random code supplied by the sponsor. Grass pollen was to be fed continuously and dispensed homogeneously into the VCC to induce an allergic reaction. Subjects were to complete symptom evaluations at 15-minute intervals, were to be evaluated within 120 minutes to determine if they qualify and, if qualified, were to receive study medication and remain in the VCC for 7.5 hours after dosing. Adverse events and vital signs were to be collected throughout the study to assess safety and tolerability.
<b>Number of Subjects:</b>	Thirty-nine subjects received at least one dose of treatment; 38 subjects completed treatment, receiving all three treatment sequences.
<b>Diagnosis and Criteria for Inclusion:</b>	Subjects were to be between 18 and 55 years of age, of any race, with at least a 2-year history of SAR due to grass pollen. Additionally, subjects were to meet the following key inclusion criteria: <ul style="list-style-type: none"> <li>• Skin test positive for the grass pollen allergen used in the chamber at Screening or within the prior 12 months.</li> <li>• A negative urine pregnancy test at Screening and at monthly intervals for female subjects of childbearing potential.</li> <li>• The following minimum scores at an evaluation time point during each of the 120-minute screening period challenge sessions: <ol style="list-style-type: none"> <li>1. Nasal Congestion Score of at least 2 (moderate);</li> <li>2. Total Nasal Symptoms Score (rhinorrhea, nasal congestion, sneezing, nasal itching) of at least 6;</li> <li>3. Total Non-nasal Symptoms Score (eye itching/burning, eye tearing, itching of ears/palate) of at least 2.</li> </ol> </li> <li>• Freedom from any clinically significant disease, other than SAR, that would interfere with the study evaluations.</li> </ul> <p>Subjects meeting any of the following <b>Key Exclusion Criteria</b> were not eligible for entry into this study:</p> <ul style="list-style-type: none"> <li>• An upper or lower respiratory tract infection within 4 weeks before screening.</li> <li>• Dependence upon nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal steroids, in the opinion of the investigator.</li> <li>• A known potential for hypersensitivity, allergy, or idiosyncratic reaction to the study drug or excipients.</li> </ul>

**Duration of Treatment:** After a screening phase of 1 to 28 days, subjects were to receive one dose of study drug at each of three treatment visits. There was to be at least a 5-day washout period between each treatment visit.

**Test Product, Dose, Mode of Administration:** Phenylephrine immediate-release 12 mg capsules for oral administration (purchased commercially in the UK).

**Reference Therapy, Dose, Mode of Administration:**

Placebo capsules supplied by SPRI.

PSE 60 mg immediate-release tablets for oral administration (purchased commercially in the UK).

**Criteria for Evaluation:** The **primary efficacy comparison** was of phenylephrine with placebo in the subjectively evaluated nasal decongestant effect, expressed as an average change from baseline over the first 6-hour evaluation period post-dosing.

The **key secondary comparison** was an estimate of average change from baseline in nasal congestion between PSE and placebo over the first 6-hour evaluation period post-dosing.

**Other secondary comparisons** included:

- Average change from baseline in total symptoms, total symptoms minus congestion, total nasal symptoms, total nasal symptoms minus congestion, total non-nasal symptoms, and individual symptoms scores over the first 6-hour period post-dosing and at each time point.
- Onset of action: defined as the first time point at which a consistent statistically significant ( $P \leq 0.05$ ) reduction in total symptoms score is achieved (active vs placebo) relative to predose baseline symptoms scores.
- Average change from baseline in PNIF (peak nasal inspiratory flow) scores over the first 6-hour period post-dosing and at each time point.
- Average change from baseline in nasal airflow as measured by rhinomanometry scores over the first 6-hour period post-dosing at each time point.
- Average change from baseline in nasal secretion weights over the first 6-hour period and at each time point.

**Statistical Methods:** With at least 30 subjects completing all three treatment phases, this crossover design would assure 80% power to detect a difference of at least 0.36 points in change from baseline of nasal congestion score between phenylephrine and placebo at an  $\alpha = 0.05$ , 2-sided test, assuming a pooled standard deviation of 0.50 on change from baseline in nasal congestion score. In a previous four-way crossover chamber study, the observed difference was 0.41 points between PSE and placebo.

For primary and secondary variables, pairwise comparisons were to be made using linear contrasts of the treatment means obtained from an analysis of variance model that extract sources of variation due to treatment, subject, and phase. Summary statistics for the primary variable were to be provided for the following subject subgroups: sex and race (Caucasians vs non-Caucasians). The primary comparison of phenylephrine vs placebo was to be tested at two-sided  $\alpha = 0.05$ . This was the only primary comparison for the study. PSE was included as a positive control and was also to be compared with placebo. The comparison of PSE vs placebo was to be performed at unadjusted  $\alpha = 0.05$ . The purpose of this comparison was primarily to validate the trial results. Additionally, phenylephrine was to be compared with PSE to assess relative efficacy.

**SUMMARY-CONCLUSIONS:**

**RESULTS:**

**Efficacy:** The average first 6-hour post-baseline mean percent change from baseline in nasal congestion score was -7.1% for phenylephrine treatment compared with -2.2% for placebo treatment ( $P = 0.56$ ). Phenylephrine was not significantly different from placebo in decreasing nasal congestion scores at any evaluation time. Comparatively, PSE, with an average 6-hour mean percent decrease from baseline in nasal congestion score of -21.7%, was significantly more effective than placebo ( $P < 0.01$ ) and phenylephrine ( $P = 0.01$ ) in decreasing nasal congestion scores.

Overall, phenylephrine showed 17% of the decongestant activity demonstrated by PSE over placebo. However, when results were evaluated by phase, the phase 1 difference between phenylephrine and placebo (0.31-0.10) was 64% of the difference between PSE and placebo (0.43-0.10). This result is similar to what would be expected in a parallel-group design, since the result is free of phase effect. Given these observed results for the first phase and based on observed results for phenylephrine in sequence groups when phenylephrine preceded PSE, it is hypothesized that crossover study designs that include PSE may not accurately reflect the treatment-effect sizes that would be seen if the study were run as a parallel-group design.

**Safety:** Treatment with a single dose of phenylephrine 12 mg or PSE 60 mg in male and female subjects with SAR, ages 19 to 46 years, was safe and well tolerated. There were no reports of adverse events. Clinical laboratory evaluations were performed only at baseline. No treatment differences were observed in vital signs.

**CONCLUSIONS:**

- In subjects with SAR in this study, a single dose of 12 mg phenylephrine was not shown to be significantly superior to placebo in reducing nasal congestion scores from baseline; PSE at a dose of 60 mg was superior to placebo. It is possible that recall biases inherent in the crossover design may have influenced the result for phenylephrine.
- Treatment with a single dose of phenylephrine 12 mg in male and female subjects with SAR, ages 19 to 46 years, is safe and well tolerated.

**Date of the Report:** 31 OCTOBER 2006