DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the Review Division of Office. We have brought the issue of the effectiveness of phenylephrine as an over-the-counter nasal decongestant to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Nonprescription Drugs Advisory Committee Meeting

Cold, Cough, Allergy, Bronchodilator, Antiasthmatic Drug Products for Over-the-Counter Human Use
Effectiveness and Safety of Phenylephrine Hydrochloride and Phenylephrine Bitartrate as an Oral Nasal Decongestant Drug Product

December 14, 2007

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- Clinical endpoints and General Study Design for the Evaluation of Efficacy of Nasal Decongestants
  Xu Wang, M. D., Ph.D., Medical Officer
  Division of Pulmonary and Allergy Drug Products

4. Related Submissions:

- Consumer Healthcare Products Association Final Report January 30, 2007
  "Efficacy Meta-analysis of Single-Dose 10 mg Phenylephrine vs Placebo in Adults with Acute Nasal Congestion Due to Common Cold"

- Wyeth Consumer Healthcare Phenylephrine Review, November 16, 2006 (EMC140 in Docket No. 1976N-0052N)

- Schering Plough (Study P04579)
  "Crossover Study of the Decongestant Effect of Phenylephrine Compared with Placebo and Pseudoephedrine as Active Control In SAR Subjects Exposed to Pollen the Vienna Challenge Chamber"

MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Regulation Development

Date: November 15, 2007

From: Susan Johnson, Ph.D.
Associate Director, Office of Nonprescription Products

Through: Charles Ganley, M.D.
Director, Office of Nonprescription Products

TO: Nonprescription Drugs Advisory Committee for December 14, 2007

Subject: Briefing Package Executive Summary: OTC Monograph Status of Phenylephrine

FDA received a citizen petition (CP) on February 8, 2007, from Dr. Leslie Hendeles et al. at the University of Florida regarding the dosing of immediate release formulations for oral delivery phenylephrine indicated for nasal decongestion (hence, the OTC monograph terminology "oral nasal decongestant"). The petition is contained in Tab 2. It requests that the adult dose of phenylephrine provided for in the OTC monograph be increased on the basis that the current dose is ineffective. The petition also requests that the OTC monograph be modified to withdraw recommended dosing for children under 12 years of age. The NDAC is being asked to consider only the moiety phenylephrine and the appropriate dosing for adults. Any implications that the NDAC deliberation may have on other aspects of science or regulation will be addressed via other mechanisms. Additional explanation will be provided throughout the background package and presentations to NDAC by FDA.

The following is a summary of the factors that are addressed in this background package and that we believe most pertinent for NDAC consideration.

- Regulatory Status

The OTC Drug Review process for oral nasal decongestant cough cold products is presented in Tab 3 "The Evaluation of Nonprescription Drug Products." This process of review of the available scientific data by an Advisory Panel, followed by a series of notice and comment rulemakings, established a final monograph that includes two salts of phenylephrine, hydrochloride and bitartrate in doses equivalent to 10 mg

phenylephrine hydrochloride to be dosed every 4 hours, not to exceed 60 mg (6 doses) in a 24 hour period. Phenylephrine is also available under the OTC Drug Review for topical nasal application to treat congestion, and as an ophthalmic or rectal vasoconstrictor. Phenylephrine is in prescription oral cough/cold combination products approved through the NDA/ANDA regulatory path, and is used as an injectable vasopressor.

- Pharmacology and Pharmacokinetics

Phenylephrine is a sympathomimetic, primarily with alpha-receptor agonist activity on the cardiovascular system. In oral doses it has been shown to have a short Tmax and half life, approximately 2.5 hours, as described in the review found at Tab 3 "Effectiveness and Safety." Extensive metabolism occurs in the gut wall, leading to a relatively low bioavailability of the oral dose. It is expected that the NDAC will hear additional information about the pharmacokinetics of phenylephrine, based on new research, during sponsor presentations at the December 14 meeting.

- Efficacy of Phenylephrine

Tab 3 "Review of the Effectiveness and Safety Data for Phenylephrine" contains a short summary of each of the available efficacy studies. These studies have been reviewed in various groupings, as designated in the review table of contents. Many of the studies were considered as part of the OTC Drug Review. The petitioner has conducted a meta-analysis based on a slightly different group of studies, and the Consumer Health Products Association (CHPA) has also conducted a meta-analysis on yet a different group of studies. Finally, new data have become available from two sponsors, Wyeth and Schering Plough, as part of the public response to the petitioner.

There is substantial variability among the study designs, methods, populations, endpoints, and outcomes. Most of the studies included only a very limited number of subjects. In addition, FDA has not had access to full study reports, including protocols and data sets for most of these studies. The impact of these conditions on the application of meta-analysis techniques is discussed in FDA's statistical review, Tab 3 "Statistical Review of the Meta-analyses." While the conclusions of the petitioner and CHPA about their meta-analyses differ, there are important limitations for the NDAC to consider about both.

One aspect of particular interest in evaluating the quality of available efficacy data is the use of different endpoints among the studies. Primarily, the earlier studies of the decongestant effects of phenylephrine employed nasal airway resistance (NAR), while later studies included patient- or healthcare provider- assessed symptom scores. Some studies included both types of metrics and these studies largely concluded that the outcomes correlate to some extent. A consult from the Division of Pulmonary and Allergy Drug Products is included at Tab 3 "Clinical Endpoints and General Study Design for the Evaluation of Efficacy of Nasal Decongestants" and discusses the merits of each type of endpoint. FDA currently requires that sponsors developing products for use in allergic rhinitis to study subjective symptom score endpoints, but continues to

encourage sponsors to develop validated objective measures. There is ongoing research involving NAR and recent publications are provided for reference.
Additional efficacy data are included in Tab 3, as submitted by "Consumer Healthcare Products Association" and "Wyeth Consumer Healthcare," and as published by "Schering-Plough Healthcare Products."

The petition proposes that the dose of phenylephrine hydrochloride be increased to 25 mg. Some information about the effectiveness of the 25 mg dose is available among the various studies. However, the petition concludes that the existing data are insufficient and that regulatory decisions regarding the 25 mg dose would need to be based on the outcome of additional studies.

- Safety

Although effects on blood pressure and heart rate can be anticipated to correlate with level of systemic exposure, based on phenylephrine pharmacology, the limited data available from the published literature about the safety of oral doses of 10 and 25 mg phenylephrine hydrochloride suggest only negligible effects. In addition, adverse event reporting in these trials did not show a significant safety signal. Data from FDA's spontaneous adverse event reporting system (AERS) regarding oral dosing of single ingredient phenylephrine products is very limited, identifies no significant safety concerns, and will be discussed in additional detail at the December 14 meeting.

- Use in Pediatrics

At a joint meeting of NDAC and the Pediatrics Advisory Committee on October 18 and 19, 2007, the use of OTC monograph cough cold ingredients, including phenylephrine, in pediatric patients was extensively discussed. Minutes of this meeting, including the outcome of committee votes, is included in this background package (Tab 3 "Effectiveness and Safety"). Full transcripts of the meeting are also available on the FDA website. The Agency is currently working to determine the actions that will be taken based on the committee's recommendations and additional information may be available at the December 14 meeting. Agency policy regarding the petition request to withdraw recommended dosing for children under the age of 12 will be made based on the previous discussion, so that the December 14 meeting will be focused on considerations for adult dosing.

ONP6929

CITIZEN'S PETITION

February 1, 2007

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

The undersigned submit this petition under 21 CFR Part 10.30 to request the Commissioner of Food and Drugs to amend the dosage of oral phenylephrine listed in the Final Monograph on oral decongestants[1] and in the Final Rule adding phenylephrine bitartrate.[2]

A. Action Requested

We propose that the maximum dose of oral phenylephrine in the labeling for patients ≥12 years should be increased and that approval for use in children <12 years should be withdrawn. Additional studies should be required to validate that a 25-mg dose would be more efficacious than a 10-mg dose of phenylephrine given every 4 hours, and as safe.

1. Exact Wording of Existing Regulation

a. Phenylephrine hydrochloride (attachment #1)

The existing wording of the Federal Register dated August 23, 1994 on page 43410[1] under section (1), Oral, nasal decongestants – (i) For products containing phenylephrine hydrochloride identified in 341.20 (a) (1) is as follows: *"Adults and children 12 years of age and over: 10 mg every 4 hours not to exceed 60 mg in 24 hours. Children 6 to under 12 years of age: 5 mg every 4 hours not to exceed 30 mg in 24 hours. Children 2 to under 6 years of age: 2.5 mg every 4 hours not to exceed 15 mg in 24 hours. Children under 2 years of age: consult a doctor."*

b. Phenylephrine bitartrate (attachment #2)

For dosage listed for phenylephrine bitartrate in the Federal Register, August 1, 2006, page 43362[2], under (iii) For products containing phenylephrine bitartrate identified in 341.20 (a) (4) is as follows: *"Adults and children 12 years of age and over: 15.6 mg every 4 hours not to exceed 62.4 mg in 24 hours. Children 6 to under 12 years of age: 7.8 mg every 4 hours not to exceed 31.2 mg in 24 hours. Children under 6 years of age: Ask a doctor."*

2007P-0047

CP 1

2. *Proposed Changes*

a. Phenylephrine hydrochloride

Adults and children 12 years of age and over: 25 mg every 4 hours not to exceed 100 mg in 24 hours. Children <12 years of age: ask a doctor.

b. Phenylephrine bitartrate

Adults and children 12 years of age and over: 40 mg every 4 hours not to exceed 160 mg in 24 hours. Children under 12 years of age: Ask a doctor.

B. Statement of Grounds

In our peer reviewed Letter to the Editor published in the July, 2006 issue of *The Journal of Allergy and Clinical Immunology*[3], we concluded that phenylephrine is unlikely to relieve nasal stuffiness at the maximum FDA approved dose of 10 mg (attachment #3). This was based upon nasal airway resistance data from 11 studies containing a 10-mg dose arm evaluated by the FDA Review Panel[4-14] and two subsequently published studies not reviewed by the Panel; an efficacy study favoring phenylephrine[15] and a bioavailability study indicating that only 38% of the dose of phenylephrine reached the systemic circulation.[16]

Subsequent to the publication of our letter, we conducted a systematic review of the literature. Fifteen studies were identified;[4-15,17-19] 12 of them included a 10-mg dose.[4-15] Of these 12 studies, only five (42%) demonstrated a difference from placebo in decreasing nasal airway resistance.[5-8,15] In contrast, 8 of 10 (80%) of studies including the 25-mg dose demonstrated a significant difference from placebo.[4-7,15,17-19] In the Cohen study,[15] for example, which apparently was not reviewed by the Panel, there was a statistically significant dose-response for decreasing nasal airway resistance; the 25-mg dose produced a greater reduction than either the 10-mg or 15-mg doses. All of these were randomized, double-blind, crossover studies that measured both symptom scores and improvement in nasal airway resistance, potentially a "gold standard" for the objective measurement of obstructed nasal airflow.[20]

Eight of the studies including a 10-mg dose met the criteria for a meta-analysis.[21] Phenylephrine 10 mg did not affect nasal airway resistance more than placebo; the mean maximal reduction (95% CI) in relative change of nasal airway resistance from baseline between phenylephrine and placebo was 10.1% (-3.8%, 23.9%). (Note that the 95% CI for the difference between phenylephrine and placebo included zero.) In contrast, there was a significant difference between phenylephrine 25 mg and placebo; the mean reduction in maximal nasal airway resistance was 27.6% (17.5%, 37.7%) (attachment #4). Patient-reported decongestion was not consistently better for any phenylephrine dose compared to placebo, and nasal airway resistance was a more sensitive measurement of

efficacy. However, the heterogeneity across studies included in this meta-analysis suggests possible measurement bias. This limits the conclusion about which is the most efficacious dose.

It is noteworthy that all of the studies performed by Elizabeth Biochemical showed that phenylephrine was significantly better than placebo regardless of dose used,[5,6,17-19] whereas studies conducted by other laboratories generally found no difference between the 10-mg dose and placebo. Also, the magnitude of the difference between phenylephrine 10 mg and placebo (e.g. -41%) in the studies conducted by Elizabeth Biochemical[5,6,17-19] were much larger than the difference found at other laboratories who found a difference between 10 mg and placebo. In Clintest #1, for example, the difference was only -16.5%.[7] This raises the question that there may have been some type of bias in the studies conducted by Elizabeth Biochemical or in the reporting of the results.

A recently published literature review[22] and a Cochrane Review[23] similarly concluded that phenylephrine was not effective orally while there was support for the efficacy of this drug when administered as a topical nasal solution.

None of the 15 studies reviewed for this petition demonstrated a significant difference from placebo for heart rate or blood pressure for all doses studied.[21]

The literature search revealed additional reports pertinent to this petition. Oral decongestants that reach the systemic circulation stimulate α_1 receptors in the nasal mucosa and will also stimulate peripheral α_1 receptors in blood vessels, producing vasoconstriction and an increase in blood pressure in a concentration-dependent manner.[24] Chua and Benrimoj evaluated the literature on the effects of non-prescription sympathomimetic agents on blood pressure.[25] They found that a dose of ≥120 mg of oral phenylephrine was required to increase blood pressure in normotensive subjects, i.e., a dose that was at least 12 times the current maximum FDA-approved dose. In contrast, pseudoephedrine produced a significant increase in blood pressure at ≥120 mg, i.e., only twice the maximum recommended dose. The likely explanation for the difference in therapeutic margins between phenylephrine and pseudoephedrine is the high first pass metabolism of oral phenylephrine.[16] It is unlikely that the differences are related to differences in affinity for the α_1 receptor since very small doses of phenylephrine given intravenously produce a marked pressor effect.[24] Also, Chua and Benrimoj cited a few studies indicating that administration of phenylephrine in the form of eye drops, particularly at higher concentrations, was capable of producing an increase in blood pressure in normotensive subjects.[25] The ophthalmic route circumvents the sulfonation of phenylephrine in the gut and the deamination by monoamine oxidase during the first pass through in the liver.

Elis et al[26] reported that 45 mg of phenylephrine given alone did not increase blood pressure, but when taken with a monoamine oxidase inhibitor (MAOI) produced an alarming increase in BP requiring reversal with phentolamine, an α

blocker. They also noted that phenylephrine 10 mg alone did not produce any effect on blood pressure, but when given concurrently with a MAOI, this dose produced an increase in blood pressure. These data suggest that monoamine oxidase plays an important role in the first-pass metabolism of phenylephrine and blocking the inactivation of phenylephrine by monoamine oxidase allows greater concentrations to reach α_1 receptors.

Since an oral dose of 120 mg or higher of phenylephrine is required to increase blood pressure in normotensive patients, we believe that increasing the labeled dose to 25 mg should not increase the risk of systemic adverse effects. It would be prudent, however, to conduct further safety assessment of the 25-mg dose.

During our systematic review of the literature, an abstract in ClinicalTrials.gov was discovered that is relevant to this petition.[27] Schering-Plough has conducted a double-blind, randomized, placebo-controlled trial comparing phenylephrine 12 mg and pseudoephedrine 60 mg in patients with seasonal allergic rhinitis. The congestion score decreased by 7.1% for phenylephrine compared to 2.2% for placebo treatment (p=0.56). Phenylephrine was not significantly different from placebo at any time point. In contrast, pseudoephedrine decreased the congestion score by 21.7% and was significantly more effective than either phenylephrine or placebo (attachment #5).

Wyeth submitted to FDA on November 16, 2006 the results of three unpublished studies that they contend supports the efficacy of phenylephrine (Docket No. 1976N-0052N). We disagree with their contention. In study AHR-GIA, there was no placebo treatment and the change in nasal airway resistance may have decreased as a function of time and not treatment. Also, they used a p value of <0.1 to indicate "marginally significant", whereas a significant p value is <0.05.

In AHR-4010-3 there were no statistical differences in the results of five of the six study sites. Thus, the statistical difference claimed for the pooled data was driven by only one site. Also, in study #7032 phenylephrine alone was not significantly different from placebo.

Lastly, none of the studies reviewed by the OTC Panel or found in the systematic literature search evaluated the effects of phenylephrine in children <12 years. Therefore, there are no data on either the safety or efficacy of this drug in this vulnerable age group. Consequently, we believe that this drug should only be used in children <12 years under the advice of a licensed prescriber and that FDA should withdraw OTC approval for this age group.

C. Environmental Impact Statement

We do not have the resources to conduct an environmental impact analysis. However, FDA has previously determined that amending the final monograph to include phenylephrine bitartrate does not have a significant environmental

impact.[2] Thus, it is unlikely that this petition, if approved, will have an environmental impact.

D. Economic Impact Statement

We do not have the resources to determine the economic impact on small entities.

E. Certification

The undersign certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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2. Department of Health and Human Services. Food and Drug Administration Final Rule. Cold, cough, allergy, bronchodilator, and antiasthmatic drug products for over-the-counter human use; amendment of monograph for OTC nasal decongestant drug products. *Fed Regist.* 2006;71:43358-63. Available online at http://www.epa.gov/fedrgstr/EPA-IMPACT/2006/August/Day-01/i12265.htm. Accessed February 1, 2007.
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List of Attachments

1. Dosage of phenylephrine HCl – Fed Reg 1994;59:43410.
2. Dosage of phenylephrine bitartrate – Fed Reg 2006;71:43362.
3. Hendeles and Hatton – letter to the editor, JACI 2006;118:279.
4. Hatton et al – meta-analysis – published online ahead of print.
5. Abstract of results of Schering-Plough Study #P04579.

Attachment #1

(2) In addition to the information identified in paragraph (b)(1) of this section, the labeling of the product may contain any (one or more) of the following statements:

(i) (Select one of the following: "For the temporary relief of" or "Temporarily relieves") (select one of the following: "stuffy nose," "stopped up nose," "nasal stuffiness," or "clogged up nose.")

(ii) (Select one of the following: "Reduces swelling of," "Decongests," or "Helps clear") "nasal passages; shrinks swollen membranes."

(iii) "Temporarily restores freer breathing through the nose."

(iv) "Helps decongest sinus openings and passages; temporarily relieves sinus congestion and pressure."

(v) "Promotes nasal and/or sinus drainage; temporarily relieves sinus congestion and pressure."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, or pseudoephedrine sulfate identified in § 341.20 (a)(1), (a)(2), and (a)(3) when labeled for adults:* (A) "Do not exceed recommended dosage. [first sentence in boldface type] If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor."

(B) "If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor."

(C) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(D) "*Drug interaction precaution.* Do not use this product if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product."

(ii) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, or pseudoephedrine sulfate identified in § 341.20 (a)(1), (a)(2), and (a)(3) when labeled for children under 12 years of age.* (A) "Do not exceed recommended dosage. [first sentence in boldface type] If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor."

(B) "If symptoms do not improve within 7 days or are accompanied by fever, consult a doctor."

(C) "Do not give this product to a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor."

(D) "*Drug interaction precaution.* Do not give this product to a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your child's prescription drug contains an MAOI, consult a health professional before giving this product."

(iii) *For oral nasal decongestant products labeled for both adults and children under 12 years of age.* The labeling of the product contains the warnings identified in paragraph (c)(1)(i) of this section.

(2) *Topical nasal decongestants*—(i) *For products containing any topical nasal decongestant identified in § 341.20(b) when labeled for adults:* (A) "Do not exceed recommended dosage." [sentence in boldface type]

(B) "This product may cause temporary discomfort such as burning, stinging, sneezing, or an increase in nasal discharge."

(C) "The use of this container by more than one person may spread infection."

(ii) [Reserved]

(iii) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride identified in § 341.20 (b)(2), (b)(3), (b)(4), (b)(6), (b)(7), (b)(8), and (b)(10) when used as nasal sprays, drops, or jellies and when labeled for adults.* (A) "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(B) "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(iv) *For products containing naphazoline hydrochloride identified in § 341.20(b)(6) at a concentration of 0.05 percent.* "Do not use this product in children under 12 years of age because it may cause sedation if swallowed."

(v) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form and when labeled for adults.* "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(vi) *For products containing any topical nasal decongestant identified in § 341.20(b) when labeled for children under 12 years of age.* The labeling of the product contains the warnings identified in paragraph (c)(2)(i) of this section.

(vii) [Reserved]

(viii) *For products containing ephedrine, ephedrine hydrochloride, ephedrine sulfate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, or xylometazoline hydrochloride identified in § 341.20(b)(2), (b)(3), (b)(4), (b)(6), (b)(7), (b)(8), and (b)(10) when used as nasal sprays, drops, or jellies and when labeled for children under 12 years of age.* (A) "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(B) "Do not use this product in a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor."

(ix) *For products containing propylhexedrine identified in § 341.20(b)(9) when used in an inhalant dosage form and when labeled for children under 12 years of age.* "Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor."

(x) *For topical nasal decongestant products labeled for both adults and for children under 12 years of age.* The labeling of the product contains the applicable warnings identified in paragraphs (c)(2)(i), (c)(2)(ii), (c)(2)(iii), and (c)(2)(v) of this section.

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions":

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride identified in § 341.20(a)(1).* Adults and children 12 years of age and over: 10 milligrams every 4 hours not to exceed 60 milligrams in 24 hours. Children 6 to under 12 years of age: 5 milligrams every 4 hours not to exceed 30 milligrams in 24 hours. Children 2 to under 6 years of age: 2.5 milligrams every 4 hours not to exceed 15 milligrams in 24 hours. Children unde 2 years of age: consult a doctor.

(ii) *For products containing pseudoephedrine hydrochloride or*

displaces both State legislative requirements and State common law duties. We also note that even where the express preemption provision is not applicable, implied preemption may arise. See *Geier* v. *American Honda Co.*, 529 US 861 (2000).

FDA believes that the preemptive effect of the final rule would be consistent with Executive Order 13132. Section 4(e) of the Executive order provides that "when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings." FDA provided the States with an opportunity for appropriate participation in this rulemaking when it sought input from all stakeholders through publication of the proposed rule in the **Federal Register** of November 2, 2004 (69 FR 63482). FDA received no comments from any States on the proposed rulemaking.

In addition, on June 19, 2006, FDA's Division of Federal and State Relations provided notice via fax and email transmission to elected officials of State governments and their representatives of national organizations. The notice provided the States with further opportunity for comment on the rule. It advised the States of the publication of the proposed rule and encouraged State and local governments to review the notice and to provide any comments to Docket No. 1976N–0052N, opened in the November 2, 2004, **Federal Register** notice, by a date 30 days from the date of the notice (i.e., by July 19, 2006), or to contact certain named individuals. FDA received no comments in response to this notice. The notice has been filed in Docket No. 1976N–0052N.

In conclusion, FDA believes that it has complied with all of the applicable requirements under the Executive order and has determined that the preemptive effects of this rule are consistent with Executive Order 13132.

X. Effective Date

This final rule becomes effective August 31, 2006.

XI. References

The following references are on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 under Docket No. 1976N–0052N and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site address, but is not responsible for subsequent changes to the Web site after this document publishes in the **Federal Register**.)

1. *The United States Pharmacopeia 29–National Formulary 24*, The United States Pharmacopeial Convention, Inc., Rockville, MD, pp 3005, 2006.

2. *CDER Data Standards Manual* (see sections entitled "Tablet Effervescent" and "Granule Effervescent") at *http://www.fda.gov/cder/dsm/DRG/drg00201.htm*.

3. *The United States Pharmacopeia 28–National Formulary 23, Supplement 2*, The United States Pharmacopeial Convention, Inc., Rockville, MD, pp 3520, 2005.

List of Subjects in 21 CFR Part 341

Labeling, Over-the-counter drugs.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 341 is amended as follows:

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

■ 1. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

■ 2. Section 341.3 is amended by adding paragraph (i) to read as follows:

§ 341.3 Definitions.

* * * * *

(i) *Effervescent dosage form.* A dosage form intended to be dissolved in water before administration. It contains, in addition to the active ingredient(s), mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water.

■ 3. Section 341.20 is amended by adding paragraph (a) (4) to read as follows:

§ 341.20 Nasal decongestant active ingredients.

* * * * *

(a) * * *

(4) Phenylephrine bitartrate in an effervescent dosage form.

* * * * *

■ 4. Section 341.80 is amended by revising the headings in paragraphs (c)(1)(i) and (c)(1)(ii), and by adding paragraph (d)(1)(iii) to read as follows:

§ 341.80 Labeling of nasal decongestant drug products.

* * * * *

(c) * * *

(1) *Oral nasal decongestants*—(i) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate, or phenylephrine bitartrate identified in § 341.20 (a)(1) through (a)(4) when labeled for adults.* * * *

* * * * *

(ii) *For products containing phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate, or phenylephrine bitartrate identified in § 341.20 (a)(1) through (a)(4) when labeled for children under 12 years of age.* * * *

* * * * *

(d) * * *

(1) * * *

(iii) *For products containing phenylephrine bitartrate identified in § 341.20(a)(4).* Include information on the number of dosage units and the quantity of water the dosage units are to be dissolved in prior to administration as shown in the following table:

Age[1]	Dose[1]
Adults and children 12 years of age and over	15.6 milligrams every 4 hours not to exceed 62.4 milligrams in 24 hours
Children 6 to under 12 years of age	7.8 milligrams every 4 hours not to exceed 31.2 milligrams in 24 hours
Children under 6 years of age	Ask a doctor

[1]Headings are not required to appear in the product's labeling

* * * * *

■ 5. Section 341.85 is amended by revising the headings in paragraphs (b)(2) and (b)(3).

§ 341.85 Labeling of permitted combinations of active ingredients.

* * * * *

(b) * * *

(2) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40 (a), (c), (f), (g), (m), (q), and (r) when labeled for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms.****

* * * * *

(3) *For permitted combinations containing an oral analgesic-antipyretic active ingredient identified in § 341.40 (a), (c), (f), (g), (m), (q), and (r) when labeled for relief of general cough-cold symptoms and/or the common cold and for relief of hay fever/allergic rhinitis and/or nasal congestion symptoms.****

* * * * *

Attachment #3

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Attachment #4

Copyrighted Material
can be viewed in the
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5630 Fishers Lane, Room 1061
Rockville, MD

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.

Title of Study:	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).
Studied Period:	09 JAN 2006 to 01 FEB 2006 — **Clinical Phase:** 3

Objective(s): The **primary** 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 **secondary** 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.

Methodology: 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.

Number of Subjects: Thirty-nine subjects received at least one dose of treatment; 38 subjects completed treatment, receiving all three treatment sequences.

Diagnosis and Criteria for Inclusion: 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:

- Skin test positive for the grass pollen allergen used in the chamber at Screening or within the prior 12 months.
- A negative urine pregnancy test at Screening and at monthly intervals for female subjects of childbearing potential.
- The following minimum scores at an evaluation time point during each of the 120-minute screening period challenge sessions:
  1. Nasal Congestion Score of at least 2 (moderate);
  2. Total Nasal Symptoms Score (rhinorrhea, nasal congestion, sneezing, nasal itching) of at least 6;
  3. Total Non-nasal Symptoms Score (eye itching/burning, eye tearing, itching of ears/palate) of at least 2.
- Freedom from any clinically significant disease, other than SAR, that would interfere with the study evaluations.

Subjects meeting any of the following **Key Exclusion Criteria** were not eligible for entry into this study:

- An upper or lower respiratory tract infection within 4 weeks before screening.
- Dependence upon nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal steroids, in the opinion of the investigator.
- A known potential for hypersensitivity, allergy, or idiosyncratic reaction to the study drug or excipients.

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

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: November 15, 2007

From: Oral Nasal Decongestant Cough/Cold Review Team

Through: Office of Nonprescription Products
To: Members of Nonprescription Drug Advisory Committee, Consultants and Guests

Subject: FDA Discussion of Oral Nasal Decongestant Cough/Cold Products

This memo provides information on how FDA evaluates the safety and effectiveness of nonprescription drugs.

How does FDA evaluate nonprescription drug products?
The safety and effectiveness of nonprescription drugs is evaluated by one of two mechanisms, the New Drug Approval (NDA) process or the Over-the-Counter (OTC) Drug Review.

NDA process
The NDA review process evaluates the safety and effectiveness of individual drug products. Drug products that are not generally recognized as safe and effective (not GRASE) by experts qualified by scientific training and experience or that are not eligible for evaluation under the OTC Drug Review are evaluated by this process. NDA products may not be marketed without FDA approval, and once approved must comply with post-marketing reporting requirements that include adverse event reporting and the submission of any information that may have a bearing on the safe and effective use of the drug. The review process is confidential and approval may result in a period of marketing exclusivity.

OTC Drug Review
The OTC Drug Review evaluates the safety and effectiveness of active ingredients for specific nonprescription drug categories, e.g., phenylephrine HCl for oral nasal decongestant use. It is an evaluation of marketed products. Only products meeting specific marketing requirements are eligible for the Review. For a product to be eligible it must have been marketed in the United States prior to the initiation of the review (May 11, 1972). This date was subsequently extended to December 4, 1975. Products that can demonstrate substantial marketing in a foreign country may also be eligible for the Review. Unlike the NDA process, products may continue to be marketed while undergoing evaluation. Such marketing is subject to the risk that some aspect of the product, e.g., active ingredient, dose or labeling may not be found to be generally recognized as safe and effective (GRASE) and could no longer be marketed for these conditions.

In this drug review process, the safety and effectiveness of active ingredients are classified into one of three classes:

Category	Description
Category I	Generally recognized as safe and effective and not misbranded (GRASE)
Category II	Not generally recognized as safe and effective or is misbranded (Not GRASE)
Category III	Insufficient data available to permit classification. Allows a manufacturer an opportunity to show that the ingredients in a product are effective, and, if they are not, to reformulate or appropriately re-label the product

Over the course of the review, the conditions, i.e., specific active ingredients, the safe and effective dose, and labeling necessary for the safe and effective use of the product are established.

Whereas the NDA process is strictly confidential, the OTC Drug Review is accomplished through a multi-step process of public notice and comment as shown below.

OTC Drug Review Step	Process
Expert Advisory Review Panel Evaluation	Evaluation of data submitted in response to FDA's call for data on an OTC drug product category, e.g. cough/cold drug products. Panel deliberations are public.
Advance Notice of Proposed Rulemaking (ANPR)	Publication of the Panel's recommendations along with FDA's proposed regulation based on these recommendations with an opportunity for comment and submission of new data.
Proposed Rule (PR)	FDA's proposed regulation based on the Panel's recommendations and public comment and new data received with an opportunity for comment and submission of new data.
Final Rule (FR)	FDA's regulation.

The end product of the Review is a final regulation that describes active ingredients, their doses, and labeling conditions that are recognized as safe and effective for a specific OTC use. Some final rules also include final formulation testing requirements and protocols to demonstrate the effectiveness of specific product formulations. Products that are compliant with a final regulation may be marketed without prior FDA approval. Manufacturers are not required to comply until the effective date of the final regulation. No marketing exclusivity is conferred under this process.

What are the regulatory standards for drug approval?

In 1985, FDA published standards for adequate and well-controlled studies (50 FR 7493) and these are codified in 21 CFR 314.126. In this section of the CFR, the following characteristics of an adequate and well-controlled study are described:

- There is a clear statement of the objectives and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results
- The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. Generally, the following types of control are recognized:
    (1) Placebo concurrent control
    (2) Dose-comparison concurrent control
    (3) No treatment concurrent control
    (4) Active treatment concurrent control
    (5) Historical control
- The method of selection of subjects provides adequate assurance that they have the disease or condition being studied
- The method of assigning patients to treatment and control groups minimized bias and is intended to assure comparability of the groups with respect to pertinent variable such as age, sex, severity of disease, duration of disease, and use of drugs or therapy other than the test drug
- Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data
- The methods of assessment of subjects' response are well-defined and reliable
- There is an analysis of the results of the study adequate to assess the effects of the drug

In addition, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form. Uncontrolled or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness.

What are the generally recognized safe and effective conditions for the nonprescription use of phenylephrine hydrochloride and phenylephrine bitartrate as oral nasal decongestants?

21 CFR 341 describes the regulatory requirements for the marketing of phenylephrine hydrochloride and phenylephrine bitartrate. The Drug Facts labels for products containing these two ingredients specify required:

- Indications (***Uses***)
- Warnings (***Warnings***)
- Directions for use (***Directions***)

Representative Drug Facts labels for hypothetical products containing either phenylephrine hydrochloride or phenylephrine bitartrate are attached below.

Drug Facts

Active ingredient (in each xxx) ***Purpose***

Phenylephrine HCl 10 mg……Nasal decongestant

Uses • temporarily relieves nasal congestion due to:

- the common cold • hay fever or other upper respiratory allergies

[May also state:]

- temporarily relieves stuffy nose
- reduces swelling of nasal passages; shrinks swollen membranes
- temporarily restores freer breathing through the nose
- promotes nasal and/or sinus drainage
- temporarily relieves sinus congestion and pressure
- helps decongest sinus openings and passages

Warnings

Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains a MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have

- heart disease • high blood pressure
- thyroid disease • diabetes
- trouble urinating due to an enlarged prostate gland

When using this product

- **Do not exceed recommended dosage**

Stop use and ask a doctor if

- you get nervous, dizzy, or sleepless
- symptoms do not get better within 7 days or occur with a fever

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- adults and children 12 years and older: 10 mg every 4 hours; not to exceed 60 mg in 24 hours
- children 6 to under 12 years: 5 mg every 4 hours; not to exceed 30 mg in 24 hours.
- children 2 to under 6 years of age: 2.5 mg every 4 hours; not to exceed 15 mg in 24 hours.
- children under 2 years of age: ask a doctor

Other information

- [optional - tamper evident statement]
- [optional - store at 20-25^{0} C (68-77^{0} F)]

Inactive ingredients [list ingredients in alphabetical order]

Questions or comments? call toll free **1-800-XXX-XXXX** [day and time of day to answer questions]

Drug Facts

Active ingredient (in each xxx) ***Purpose***

Phenylephrine bitartrate 15.6 mg……..Nasal decongestant

Uses • temporarily relieves nasal congestion due to:

- the common cold • hay fever or other upper respiratory allergies

[May also state:]

- temporarily relieves stuffy nose
- reduces swelling of nasal passages; shrinks swollen membranes
- temporarily restores freer breathing through the nose
- promotes nasal and/or sinus drainage
- temporarily relieves sinus congestion and pressure
- helps decongest sinus openings and passages

Warnings

Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains a MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have

- heart disease • high blood pressure
- thyroid disease • diabetes
- trouble urinating due to an enlarged prostate gland

When using this product

- **Do not exceed recommended dosage**

Stop use and ask a doctor if

- you get nervous, dizzy, or sleepless
- symptoms do not get better within 7 days or occur with a fever

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- adults and children 12 years and older: 15.6 mg every 4 hours; not to exceed 62.4 mg in 24 hours
- children 6 to under 12 years: 7.8 mg every 4 hours; not to exceed 31.2 mg in 24 hours.
- children under 6 years of age: ask a doctor

Other information

- [optional - tamper evident statement]
- [optional - store at 20-25^{0} C (68-77^{0} F)]

Inactive ingredients [list ingredients in alphabetical order]

Questions or comments? call toll free **1-800-XXX-XXXX** [day and time of day to answer questions]

Effectiveness and Safety of Phenylephrine Hydrochloride and Phenylephrine Bitartrate as Oral Nasal Decongestants

Office of Nonprescription Products
Center for Drug Evaluation and Research • Food and Drug Administration

REVIEW DATE:	November 14, 2007
FDA DOCKET NOS.:	2007P-0047 and 1976N-0052N
MATERIAL REVIEWED:	● Studies cited in the Advance Notice of Proposed Rulemaking (ANPR) for Over-the Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products ● Relevant studies not cited in the ANPR
PHARMACOLOGICAL CATEGORY:	Nasal Decongestant (Oral)
REVIEWERS:	Michael L. Koenig Michael L. Chasey Mary S. Robinson
TEAM LEADER:	Debbie Lumpkins

TABLE OF CONTENTS

[1] Included in Petitoners' Meta-Analyis (CP1 in Docket No. 2007P-0047)
[2] Included in CHPA Meta-Analysis (C251 in Docket No. 1976N-0052N)

1. EXECUTIVE SUMMARY:

1.1 SUMMARY OF THE ISSUE

FDA currently considers both phenylephrine hydrochloride (PEH) and phenyephrine bitartrate (PEB) to be generally recognized as safe and effective (GRASE) for OTC use for the temporary relief of nasal congestion. PEH was included in the OTC drug review initiated in 1972 and codified in 1994 (59 FR 43386). PEB was added to the monograph in 2006 (71 FR 43358) based on pharmacokinetic data demonstrating that it has similar bioavailability to PEH.

FDA has received a citizen petition (CP1 in Docket No. 2007N-0047) signed by Leslie Hendeles, PharmD, Randy C Hatton, PharmD, FCCP, BCPS, and Almut G. Winterstein, PhD. The petitioners believe that available data do not support the adult and pediatric doses of PEH and PEB that FDA currently recognizes as GRASE and propose an increase in the dose of PEH from 10 to 25 mg and PEB from 15.6 to 40 mg. The petitioners also propose that FDA require additional studies to demonstrate the safety and effectiveness of the requested higher doses. Finally, the petitioners request that FDA limit the use of PEH and PEB as oral nasal decongestants to adults and children 12 years of age and older. Because the issue of limiting the use of cough and cold products (including nasal decongestants) for children was addressed at an October 2007 joint meeting of the Nonprescription Drugs Advisory Committee and Pediatrics Advisory Committee (see Attachment 1), we will not address this request in this review.

The petitioners provide a meta-analysis that concludes that 10 mg PEH does not reduce nasal congestion any more than placebo in eight of ten studies that were part of the original GRASE determination for the ingredient.

On February 1, 2007, FDA received a comment from the Consumer Healthcare Products Association (CHPA) (C251 in Docket No. 1976N-0052N). CHPA disagrees with the petitioners and argues that PEH *is* effective as an oral nasal decongestant. CHPA conducted a separate meta-analysis using seven of the eight studies included in the CP meta-analysis. The CHPA meta-analysis concludes that phenylephrine is "statistically significantly superior to placebo" 30, 60, and 90 minutes post-dose.

In this review, we are including data submitted by Wyeth Consumer Healthcare to support the effectiveness of 10 mg PEH (EMC 140 in Docket No. 1976N-0052N). The data were submitted on November 16, 2006 following the publication, in July 2006, of a letter to the editor of the Journal of Allergy and Clinical Immunology by two of the petitioners (Hendeles and Hatton) (see Attachment #3 in CP1). The letter contended that oral phenylephrine is ineffective as a nasal decongestant.

We have also reviewed data, included in the petition as Attachment #5, and published online at http://clinicaltrials.gov/ct/show/NCT00276016 by the Schering-Plough Corporation.

1.2 CONCLUSIONS ON THE EFFECTIVENESS OF PHENYLEPHRINE HYDROCHLORIDE AND PHENYLEPHRINE BITARTRATE

An evaluation of the studies that FDA relied on for its GRASE determination and more recent studies of the efficacy of PEH as orally-administered nasal decongestant was undertaken. The efficacy of PEB has been extrapolated based on PEH studies using pharmacokinetic bridging data, so conclusions about PEB effectiveness are largely based on determinations regarding PEH.

Of 14 studies evaluating PEH at the 10 mg dose,[1-14] seven studies demonstrated a statistically significant effect on objective measures of nasal patency (reduction in nasal airway resistance, NAR) .[2,3,7,10-13] There were five studies in which PEH was shown to demonstrate statistically significant efficacy based on the subjective endpoint of patient-rated symptom scores.[2,7,10-12] Many of the evaluated studies have known design limitations, such as:

- Lack of placebo arm[12]
- Efficacy demonstrated at one site not replicated by other cites in a multicenter study[13]
- Small number of subjects and limited power to establish significant differences between treatments[2,3,7,10-12]

Other studies were incompletely described as published:

- Summary memoranda only; limited information on study design and conduct[2,3,7,10]
- Inadequate explanation of statistical tests employed[2,3,7]

Of 10 studies in which PEH at the 25 mg dose was evaluated, [1-3,5,7,9,11,15-17]six show that PEH at a dose of 25 mg significantly reduces NAR[2,3,7,11,15,17] and 3 studies demonstrate a statistically significant effect on symptom scores. [3,11,15] These studies also have known design and reporting limitations.

In most of the studies that evaluated both 10 and 25 mg doses of PEH, when the 10 mg dose was shown to be effective, the 25 mg dose was also demonstrated to be effective. However, there is little evidence of a dose-response at the 10 to 25 mg dose level.

NAR is the primary efficacy endpoint in 19 of the 20 studies evaluated. Using rhinomanometry, the patency or openness of the nasal passageway is assessed by measuring air flow through the nose at a fixed pressure. At a constant pressure, air flows more freely (i.e., there is *reduced* resistance) through a more open passageway than through one that is congested. Effective decongestant activity therefore is measured as a *reduction* in NAR relative to baseline values or to treatment with a placebo. Rhinomanometry was widely employed as a means of evaluating decongestant effectiveness during the time studies reviewed by the Panel were conducted (1959 – 1972) and is still, though less commonly, used today.[18-20] Rhinomanometry requires technical expertise in the placement of the device for the measurement of NAR. There are a number of factors that can influence the accuracy of the measurement and introduce variability. These measurement considerations may be a factor in the failure of some studies to demonstrate PEH efficacy. For example, leaks in the apparatus used to make the measurement, the presence of nasal secretions in test subjects, and the pressure

change caused by breathing and swallowing during the test can all impact the accuracy of the measurement.

NAR has been shown to correlate to some extent with symptom score assessments under specific conditions. An evaluation of the available data reveals that where both objective and subjective measures were utilized to evaluate decongestant effectiveness of PEH, the two methods correlate in 7 of 10 studies evaluating the 10 mg dose and 5 of 9 studies evaluating the 25 mg dose.

1.3 CONCLUSIONS ON THE SAFETY OF PHENYLEPHRINE HYDROCHLORIDE AT 10 AND 25 MG DOSES.

Sympathomimetic amines including PEH have been associated with decreases in pulse rate and increases in blood pressure[21]. There were a total of 17 studies that assessed effects of PEH on pulse and blood pressure.[1,3,4,6,8,9,11-14,16,17,21-25] The doses of PEH in these studies ranged from 5 mg[16] to 250 mg.[21] The majority of the studies are single dose studies. Significant decreases in pulse rate and increases in blood pressure were reported for the 100 mg[23] and 250 mg[21] doses of PEH. There were no consistent effects on pulse rate or blood pressure with single doses of either 10 or 25 mg PEH in any of the studies.

The majority of the studies demonstrated no significant changes in pulse rate at the 10 or 25 mg doses of PEH. In the studies where significant effects were seen, the effects were inconsistent. In two studies, 25 mg PEH significantly decreased pulse rates at single time points (and not at others). One of the studies showed a significant decrease in pulse rate at the 30 minute time point,[22] and the other showed a significant decrease in pulse rate at the 60 minute time point.[23] In two other studies,[3,11] pulse rates were significantly *increased* (at 120 minutes for the 10 mg dose and at 60, 90, 120, and 240 minutes for the 25 mg dose[3] and at 30, 60, 90, and 120 minutes for both 10 and 25 mg doses[11]). The increases in pulse rate are described as "minor" in one case[3] and "moderate" in the other.[11]

Similarly, there were no significant effects on blood pressure in the majority of studies evaluated and what was observed was again inconsistent. In only one study[3] did treatment with PEH cause an increase in blood pressure. That study showed significantly increased systolic blood pressure readings at the 60, 90, 120, and 180 minute time points for the 10 mg dose of PEH and at the 60, 90, 120, 180, and 240 minute time points for the 25 mg dose[3]. Two other studies showed significant *decreases* in blood pressure. In one study a statistically significant decrease in systolic blood pressure was noted at a single time point (180 minutes post-administration) for the 10 mg dose[6]. In the other study, treatment with 25 mg PEH resulted in a significant decrease in systolic blood pressure at one time point (60 minutes post-administration) and diastolic blood pressure decreased at two post-administration time points (90 and 120 minutes)[11].

Phenylephrine bitartrate (PEB) and PEH are considered to be pharmacologically identical and interchangeable with regard to efficacy. In 2004, FDA determined that the bioavailability of the effervescent salts of PEB and PEH were similar. No data specific to the safety of PEB was reviewed.

2. BACKGROUND:

PEH was one of eight ingredients classified as a category I (GRASE) ingredient for the temporary relief of nasal congestion by the advisory review panel for OTC Cough-Cold products (Panel) in the advanced notice of proposed rulemaking (ANPR) for Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products (41 FR 38312). The Panel based its determination that 10 mg PEH is generally recognized as *safe* on "clinical experience" and its assessment of 12 clinical studies.[1-4,15-7,21-23,26,27] The studies evaluated changes in pulse rate and blood pressure and, in some cases, patient-reported adverse events (side effects). Based on the studies, the Panel reported that "oral doses of 40 to 60 mg PEH are necessary for consistent clinically meaningful cardiovascular effects" (41 FR 38312 at 38399). In addition, they reported that pulse rate and blood pressure changes resulting from treatment with 10 to 15 mg oral doses of PEH were "equal to or only minimally grater than placebo" and adverse events associated with the 10 mg dose of PEH were described as approximating "the incidence and pattern of a placebo response" (41 FR 38312 at 38399).

The Panel's conclusion that PEH is *effective* at a dose of 10 mg was based on a total of 14 clinical studies[1-3,5-10,15-17,27,28] all of which had reduction in nasal airway resistance as the primary efficacy endpoint. Ten of the studies included patient-reported symptom scores as a secondary means of demonstrating effectiveness.[1-3,7-10,15-17] Five of the 14 studies demonstrated significant nasal decongestant responses to 10 or 25 mg PEH when compared to placebo.[2,3,10,15,17] Average onset time was approximately 15 minutes, with maximum nasal decongestion occurring somewhere between 1 and 2 hours. Even though only 4 of the 14 studies reviewed by the panel demonstrated that 10 mg PEH provided significant nasal decongestion, the Panel determined that the clinical studies, as a whole, sufficiently "documented the effectiveness of phenylephrine hydrochloride as an oral nasal decongestant" (41 FR 38312 at 38399).

The Panel's conclusions and recommendations can be found in the ANPR for Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products (41 FR 38312). The ANPR requested public comment and one comment directly relevant to this review was received. FDA addressed the comment in the subsequent publication of a proposed rule (PR) on January 15, 1985 (50 FR 2220).

The comment questioned the studies used by the Panel to substantiate the effectiveness of phenylephrine hydrochloride as an oral nasal decongestant (Comment 10 on page 2226 of the proposed rule). The comment argued that the panel had based its decision on numerous unpublished studies which "split evenly between mild successes and total failures" and noted that, in one study published in a peer–reviewed journal, no efficacy was seen even with doses greater than 10 mg (50 FR 2220 at 2226). FDA reviewed the information cited by the comment, the Panel's recommendations, and all of the supporting data and concluded that, "based on the studies cited by the Panel, information on clinical use and marketing experience, and the Panel's expertise in evaluating the clinical and marketing experience of this ingredient, there is sufficient basis to determine

the phenylephrine hydrochloride is generally recognized as effective for OTC use as an oral nasal decongestant" (50 FR 2220 at 2226)

No further comments relevant to this issue were received in response to the 1985 PR, and FDA published a final rule (FR) on August 23, 1994 (59 FR 43386). The FR lists PEH as a GRASE oral nasal decongestant ingredient at the following doses (59 FR 43386 at 43410):

- Adults and children 12 years of age and over: 10 mg
- Children 6 to under 12 years: 5 mg
- Children 2 to under 6 years: 2.5 mg

On April 12, 2002, FDA received a citizen petition (CP) requesting the recognition of PEB as a GRASE nasal decongestant active ingredient when delivered via effervescent dosage form. The sponsor submitted information describing an extensive domestic and global marketing history along with an absence of significant safety concerns. They also submitted pharmacokinetic data demonstrating that PEH and PEB have comparable bioavailability profiles. Based on this data and information, FDA proposed adding PEB in effervescent tablet form to the Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products monograph (69 FR 63482). No adverse comments were received and in 2006 FDA published a final rule adding PEB to the Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products monograph (71 FR 43358). PEB is considered a GRASE oral nasal decongestant ingredient at the following doses (71 FR 43358 at 43362):

- Adults and children 12 years of age and over: 15.6 mg
- Children 6 to under 12 years: 7.8 mg
- Children 2 to under 6 years: ask a doctor

3. EVALUATION OF THE DATA

3.1. EFFECTIVENESS

Reviewer's comment: *In this section data relating to the effectiveness of PEH are reviewed. Because many of the studies also included safety assessments, these measurements are also evaluated here.*

3.1.1 Studies cited in the ANPR

3.1.1.1. April 1959 Memo to Lands from F. P. Luduena

Unpublished study "Comparative Study of the Effects of Neo-Synephrine HCl and Propadrine HCl on Nasal Air Resistance (NAR), Blood Pressure and Pulse Rate of Volunteers"

Study objective: Compare the effects of Neo-Synephrine (phenylephrine hydrochloride) with Propadrine (phenylpropanolamine HCl) topically and orally on NAR, blood pressure and pulse rate.

Reviewer's comment: This review addresses the safety and effectiveness of oral decongestants only.

Study design: Double-blind placebo controlled study conducted on two consecutive days.

Doses evaluated: Study evaluated the effectiveness of single doses of two oral nasal decongestant ingredients:

Phenylephrine HCl (Neo-Synephrine or PEH): 10, 25, 50, and 75 mg
Phenylpropanolamine HCl (PPA): 25 and 50 mg

Study population: Healthy adults 20 to 46 years of age. Investigators described the subjects as having "fairly patent nasal passages" and noted that "in some cases, hardly any further shrinkage of the nasal mucosa could be expected." The weights of subjects ranged between 103 and 186 lbs with an average weight of 128.8 lbs.

Number of subjects:

Ingredient	Dose (mg)	No. Subjects
PEH	10	15
	25	15
	50	14
	75	14
PPA	25	15
	50	14

Measurements:

NAR: measured by the method of *Sterntein and Schur (Arch. Otolaryngol. 23:475, 1936)*. Each measurement represented an average of four readings (two with nose piece in the right nostril and two with the nose piece in the left nostril). Readings were taken at baseline and 1, 2, and 5 hours after drug administration.

Pulse rate and blood pressure: Readings were taken at baseline and 1, 2, and 5 hours after drug administration.

Data analysis: Two methods were used to determine the significance of the observed differences: differences between means (mean baseline versus mean reading after drug administration) and differences between the medians (before and after treatment). A nonparametric median test was used for the estimation of significance. Significance was assessed at the $p = 0.05$ level.

Results:

NAR:

PEH: Investigators report an average reduction in NAR for all doses 1 hour after administration. The reduction was not significant at any dose whether the means or medians were compared.

PPA: After the administration of the 50-mg dose NAR decreased at 1 hour and showed a further reduction at 2 hours. The difference was significant only at the 1-hour time point and only when the means were compared.
Investigator's conclusions: The investigators observed a great deal of variation in the readings between individuals and between readings in the same individual. This high degree of variation was attributed by the investigators to occasionally high NAR readings. Most of the NAR readings were low because "in the majority of cases there was no nasal congestion."

Pulse rate: Mean pulse rates decreased in the first two hours after administration of both PEH and PPA at all doses. These decreases were not significant. Mean pulse rates increased significantly above the baseline values 5 hours post-administration.

Blood pressure: Mean systolic blood pressure readings were slightly but not significantly elevated following treatment with the 50 mg and 75 mg doses.of PEH. There were also similar changes to diastolic pressure. Mean systolic blood pressure readings were significantly increased following administration of 50 mg PPA at the 1- and 2-hour time points. Five hours after administration of 50 mg PPA, the mean systolic blood pressure was lower than it was at baseline.

Reviewer's comments: *This study failed to demonstrate that PEH, at doses ranging from 10 to 75 mg, significantly reduces NAR (i.e., relieves nasal congestion). The study's failure to show efficacy may have been partially related to study design factors. A majority of the subjects enrolled in the study were not congested before being treated. To test decongestant efficacy, it would have been better to treat people who were congested. The study also may have been under-powered to detect differences between the NAR readings taken at baseline and at subsequent time points or between drug and placebo effects. There were no more than 15 subjects in any specific trial. The study did not demonstrate that 25 mg PEH has any significant effect on either pulse rate or blood pressure.*

3.1.1.2 June 1967 Memo to Suter from N. A. Hulme

Unpublished study "Nasal Decongestant Study by Elizabeth Biochemical Laboratories – No. 1"

Study objective: This study consisted of two phases. The objective of the first phase was to compare the Sterling-Winthrop Research Institute nasal air flow instrument (used to measure NAR) to a model used by the Vick's Corporation. The objective of the second phase was to evaluate the effectiveness of 25 mg PEH in reducing NAR and relieving patient symptoms of congestion.

Reviewer's comment: *This review concerns only the second phase of this study.*

Study design: Randomized, double-blind, crossover design with placebo and active (ephedrine) controls.

Doses evaluated: This phase of the study evaluated the effectiveness of single doses of two oral nasal decongestant ingredients:

Phenylephrine HCl (Neo-Synephrine or PEH): 25 mg
Ephedrine: 8 mg

Study population: Twenty-five adults with head colds. Demographics of the study subjects were not provided.

Number of subjects: Twelve subjects were treated with PEH and placebo. Six patients received placebo and six patients received PEH on day 1. Administration was reversed on day 2 such that the six who received placebo on day one, received PEH on day 2 and the six who received PEH on day one received placebo on day two. An identical administration scheme was used with the 13 subjects who received ephedrine or placebo.

Measurements:

NAR: Five nasal air flow measurements were taken for each nostril at 30 and 15, minutes before treatment and 0, 15, 30, 45, 60, 90, and 120 minutes after treatment. The five readings from each nostril were combined and the means determined at each time point.

Relief of symptoms: At the time of each nasal air flow measurement, patients were asked to describe their congestion according to a 5-point scale:

Degree of Congestion	Score
Nose feels clear	0
Almost clear	1
Stuffy	2
Very stuffy	3
Completely blocked	4

The symptom scores were reported as the sum of differences (over all time points) between placebo and active medication for each subject.

Turbinate appearance: The appearance of each subject's turbinates was evaluated 30 minutes before medication and at 0, 60, and 120 minutes after medication. Appearance was recorded as being normal, inflamed, or gray and badly swollen.

Data analysis: Analyses of variance were conducted to compare placebo and active medication treatments in both the objective and subjective testing. The investigators did not provide any additional information (e.g., what, if any, type analysis may have been employed).

Results:

NAR:

PEH: Investigators report that 25 mg PEH significantly reduces NAR as early as 30 minutes after oral administration ($p = 0.01$), and this decongestant effect remains significant for at least 90 minutes (i.e., through the 45, 60, 90, and 120 minute time points).

Ephedrine: Significant reduction in air flow was apparent as early as 15 minutes after treatment with 8 mg ephedrine ($p = 0.01$) and remained significant throughout the two hour time course of the study.

Relief of symptoms: Investigators report that the patients' overall symptom scores were significantly lower (i.e., patients had an overall sense of decongestion) following treatment with 25 mg PEH relative to treatment with placebo ($p = 0.01$). The same was true for patients treated with 8 mg ephedrine.

Turbinate appearance: Investigators reported that there were no trends "that could be interpreted in terms of a medication response."

Reviewer's comments: *This study demonstrates that PEH, at a dose of 25 mg, significantly reduces NAR (i.e., relieves nasal congestion) and that patients feel decongested after taking medication containing 25 mg PEH. The effectiveness of 25 mg PEH is reported as both objectively and subjectively comparable to that of ephedrine at an 8 mg dose.*

3.1.1.3. January 1968 Memo to Wessinger from N. A. Hulme

Unpublished study "Neo-Synephrine - Oral Study by Elizabeth Biochemical Laboratories No. 2"

Study objective: Confirmation of the nasal decongestant effectiveness of 25 mg PEH as shown in Elizabeth Biochemical Laboratories No. 1 (ANPR Reference 6 above) and evaluation of the effectiveness of PEH at doses of 10 and 15 mg. Comparison with 50 mg ephedrine sulfate, which investigators predicted to yield the maximum decongestant response under the conditions of the study.

Study Design: Double-blind, randomized, crossover design with placebo and active (ephedrine) controls

Doses evaluated: Study evaluated the effectiveness of single doses of two oral nasal decongestant ingredients:

Phenylephrine HCl (Neo-Synephrine or PEH): 10, 15, and 25 mg
Ephedrine sulfate: 50 mg

Study Population: Thirty-eight subjects having head colds with demonstrable nasal congestion for 2 consecutive days. No additional demographics were provided.

Number of subjects:

Ingredient	Dose (mg)	No. Subjects
PEH	10	16
	15	10
	25	6
Ephedrine	50	6

Measurements:

NAR: Using a modified Butler-Ivy airflow device, five nasal air flow measurements were taken for each nostril at 30, 15, and 0 minutes before treatment and 0, 15, 30, 45, 60, 90, and 120 minutes after treatment. The five readings from each nostril were combined and the means determined at each time point.

Relief of symptoms: At the time of each nasal air flow measurement, patients were asked to describe their congestion according to a 5-point scale:

Degree of Congestion	Score
Nose feels clear	0
Almost clear	1
Stuffy	2
Very stuffy	3
Completely blocked	4

Investigators reported the symptom scores as the sum of differences (over all time points) between placebo and active medication for each subject.

Data analysis:

NAR: Analyses of variance were conducted to compare placebo and active medication treatments. The investigators did not provide any additional information (e.g., what, if any, type of post-hoc analysis was employed).

Relief of symptoms: Investigators state that the significance of differences between placebo and active medication treatments was established using the Wilcoxon Match-Pairs Signed Ranks test.

Results:

NAR:

PEH: Investigators report that "significant decongestion lasted for the full two hour measurement period for all doses." This is true except at 15 minutes post-administration for the 25 mg dose. The investigators attribute a lack of significance at this time point for the 25 mg dose to the low number of subjects participating in that trial (n = 6).

Ephedrine: Significant reduction in air flow was apparent 30 minutes after treatment with 50 mg ephedrine ($p = 0.01$) and remained significant throughout the two hour time course of the study. As was the case with the 25 mg dose of

PEH, investigators attributed a lack of significance at the 15-minute time point to the low number of subjects participating in this trial (n = 6)

Relief of symptoms: Symptom scores significantly correlated with the objective measurements of NAR reduction at the 10 and 15 mg doses (p = 0.01 in both cases), but subjective scores were not significantly different at the 25 mg dose (p > 0.05). The investigators stated that this was most likely due to the low number of subjects evaluated at that dose.

Reviewer's comments: *This study demonstrates that PEH, at doses of 10, 15, amd 25 mg, significantly reduces NAR (i.e., relieves nasal congestion) and that patients feel decongested after taking medication containing PEH at these doses. The objectively measured effectiveness of 25 mg PEH is reported as comparable to that of 50 mg ephedrine (predicted to produce a maximal decongestant response under the conditions of this study). Although there is no apparent dose response, the investigators report that the effect produced by the 10 and 15 mg PEH doses is somewhat less than the maximum effect observed with the 25 mg dose.*

3.1.1.4. June 1969 Memo to Blackmore from N. A. Hulme.

Unpublished study "Oral Neo-Synephrine - Elizabeth Biochemical Laboratories No. 3"

Study objective: Confirmation of the nasal decongestant effectiveness of PEH at doses of 5, 15, and 25 mg. A comparison to the effectiveness of the "known orally active decongestant" phenylpropanolamine (PPA), at its highest accepted dose, and determination of the effects of PEH and PPA on pulse rate and blood pressure.

Study Design: Double-blind, randomized, crossover design with placebo and active (PPA) controls

Doses evaluated: Study evaluated the effectiveness of single doses of two oral nasal decongestant ingredients:

PEH: 5, 15, and 25 mg
PPA: 50 mg

Study Population: Forty-six subjects having head colds with demonstrable nasal congestion for 2 consecutive days. No additional demographics were provided.

Number of subjects:

Ingredient	Dose (mg)	No. Subjects
PEH	5	16
	15	8
	25	9
PPA	50	9

Reviewer's comment: *The study reports that there were 10 subjects in the PPA treatment arm. There results reported were for fewer subjects in each of these arms. The investigator offers no explanation for the discrepancy.*

Measurements:

NAR:

Using a modified Butler-Ivy airflow device, five nasal air flow measurements were taken for each nostril at 30, 15, and 0 minutes before treatment and 15, 30, 45, 60, 90, 120, 180, and 240 minutes after treatment. The five readings from each nostril were combined and the means determined at each time point.

Relief of symptoms: At the time of each nasal air flow measurement, patients were asked to describe their congestion and rate their congestion as shifts from the premedication state. A shift of one degree of congestion was rated as a plus or minus 1; a shift of two degrees was graded plus or minus 2 and so on.

Degree of Congestion
Nose feels clear
Almost clear
Stuffy
Very stuffy
Completely blocked

The sums of the changes at each time point were recorded for each subject. Data were calculated as the sum of the median values of differences (over all time points) between placebo and active treatment for each subject.

Pulse rate and blood pressure: Readings of pulse rate and sitting blood pressure were taken at the time of each nasal airflow measurement. Data were compiled as means at each time point for each medication group.

Data analysis: Analyses of variance were conducted to compare placebo and active medication treatments for measurements of NAR, patient-reported symptom relief, pulse rate, and blood pressure. The investigators did not provide any additional information (e.g., what, if any, type of type of analysis may have been employed).

Results:

NAR:

PEH: Investigators found that the 5 and 15 mg doses of PEH significantly reduced NAR relative to placebo at various time intervals following administration. Significant differences were noted as early as 15 minutes for the 15 mg dose and at 30 minutes for the 5 mg dose. The investigators claim that there is also a significant difference between the 25 mg PEH dose and placebo. However, this claim is not supported by the data submitted in the study. Investigators note the "lack of a strong dose-response relationship" and state that, like Elizabeth Biochemical Laboratories Study (No. 2), the objective changes by all three doses are very nearly the same.

PPA: Significant reduction in air flow was apparent 15 minutes after treatment with 50 mg PPA ($p = 0.01$) and remained significant at this level throughout the four hour time course of the study.

Relief of symptoms: Patient-reported symptom scores correlated with the objective measures for the 15 mg dose of PEH (and 50 mg PPA) but not for the 5 or 25 mg doses of PEH. Investigators pointed out that the first "Elizabeth study" showed a positive correlation between objective and subjective measures at the 25 mg dose of PEH, but that the second Elizabeth study did not.

Pulse rate: Mean pulse rates did not change during the course of the study for 15 mg PEH or 50 mg PPA. Statistically significant *increases* in pulse rate relative to placebo were observed at 30 and 90 minutes post-administration for the 5 mg dose of PEH and at 30 and 240 minutes post-administration for 25 mg PEH. Investigators did not consider these changes to be of any clinical significance.

Blood pressure: Systolic blood pressure data showed statistically significant increases relative to placebo at 120 minutes post-administration for the 5 and 15 mg doses of PEH but not for the 25 mg dose. These increases were equivalent to a "somewhat less than 2 mm" increase and were judged by the investigators to be of no clinical significance. Subjects treated with 50 mg PPA had statistically significant increases in systolic blood pressure at the 30, 60, 90, and 120 minute time periods. These increases were maximal at the 60 minute time point and were equivalent to a 9 mm increase.

Diastolic blood pressure was significantly elevated at the 90 minute time point for 5 mg PEH and the 120 minute time point for 15 mg PEH. No significant changes were reported for the 25 mg dose of PEH. PPA produced significant increases equivalent to about 6 mm at the 60 and 90-minute time points.

Adverse events: No side effects were reported by any subject receiving PEH at any dose.

Reviewer's comments: *In this study, doses of 5 and 15 mg PEH and 50 mg PPA all significantly reduced NAR. At the highest dose (25 mg) of PEH, NAR was not significantly reduced at any time point although, the data trended in that direction, i.e., the NAR measurements for 25 mg PEH were lower than those for placebo at every time point.*

The objective and subjective outcomes in this study do not appear to correlate well. Although 5 mg PEH showed a significant reduction in NAR over all time points, patients failed to notice a significant change in symptom relief. Investigators surmised that a subject's ability to perceive a feeling of decongestant relief may have been at or near a threshold level at the 5 mg dose. Symptom scores and objective measures of decongestion correlated for other doses of PEH and for the 50 mg dose of PPA.

Pulse rate was significantly elevated at only two of the eight time points evaluated for the 5 and 25 mg doses of PEH. Pulse rate was not significantly elevated in any of the time points evaluated in the 15 mg dose of PEH. Increases in pulse rate are unexpected as treatment with sympathomimetics generally results in a decrease in pulse rate. Both systolic and diastolic blood pressure readings were generally unchanged relative to placebo. The significant increases in systolic blood pressure were random, occurring at only one time point (120 minutes) for the 5 and 15 mg doses and returned to baseline values. Similarly, increases in diastolic blood pressure were noted only at 90 minutes (5 mg dose) and 120 minutes (15 mg dose) and returned to baseline values

3.1.1.5. August 1969 Memo to Blackmore from N. A. Hulme.

Unpublished study "Oral Neo-Synephrine - Elizabeth Biochemical Study No. 4"

Study objective: Expand data previously collected by the Elizabeth Biochemical Labs and evaluate decongestant doses of "greater potential interest."

Reviewer's comment: *This is the first Elizabeth Biochemical Labs study to evaluate 20 mg PEH. Previous doses considered were 5, 10, 15, and 25 mg.*

Study Design: Double-blind, randomized, placebo-controlled, crossover design

Doses evaluated: Study evaluated the effectiveness of single doses of Neo-Synephrine (PEH) at three doses: 15, 20, and 25 mg

Study Population: 20 subjects having head colds with demonstrable nasal congestion for 2 consecutive days. No additional demographics were provided.

Number of subjects:

Ingredient	Dose (mg)	No. Subjects
PEH	15	6
	20	5
	25	9

Reviewer's comment: *The study failed to enroll the planned number of subjects. Based on a preliminary analysis of the data the investigators concluded that the differences between placebo and active medication were sufficiently great to justify a full statistical evaluation. This post-hoc determination regarding analysis is not considered to be valid.*

Measurements:

NAR: Using a modified Butler-Ivy airflow device, five nasal air flow measurements were taken for each nostril at 30, 15, and 0 minutes before treatment and 15, 30, 45, 60, 90, 120, 180, and 240 minutes after treatment. The five readings from each nostril were combined and the means determined at each time point. The

mean data were used for subsequent analysis. NAR reductions were reported as means of the percent (fractional units x 100) change from the time 0 reading.

Relief of symptoms: At the time of each nasal air flow measurement, patients were asked to describe their congestion and rate their congestion as shifts from the premedication state. A shift of one degree of congestion was rated as a plus or minus 1; a shift of two degrees was graded plus or minus 2, and so on.

Degree of Congestion
Nose feels clear
Almost clear
Stuffy
Very stuffy
Completely blocked

The sums of the changes at each time point were recorded for each subject. The data were calculated as the sum of the median values of differences (over all time points) between placebo and active medication for each subject.

Pulse rate and blood pressure: Readings of pulse rate and sitting blood pressure were taken at the time of each nasal airflow measurement. The data were compiled as means at each time point for each medication group.

Data analysis: Analyses of variance were conducted to compare placebo and active medication treatments for measurements of NAR, patient-reported symptom relief, pulse rate, and blood pressure. The investigators did not provide any additional information (e.g., what, if any, type of analysis was employed).

Results:

NAR: At the three tested doses, PEH significantly reduced NAR relative to placebo. Significant reductions in NAR were evident 45 minutes after administration of PEH and remained significant throughout the 4 hour time course for the 20 mg dose and for three hours at the 25 mg dose. The 15 mg dose produced variable results with that dose significantly reducing NAR only at the 45, 90, and 120 minute time points

Relief of symptoms: A significant correlation of objective and subjective measures of decongestion occurred only in subjects receiving the 20 mg dose of PEH. Investigators note that subjects receiving the 15 mg dose tended to feel decongestive relief (although the perception was not significant). Investigators suggested that the failure to demonstrate significant effects at doses other than 20 mg may have been due to the "relatively small" number of subjects enrolled in the study.

Pulse rate: Mean pulse rates did not change during the course of the study for 15 mg PEH. Statistically significant *increases* in pulse rate relative to placebo were

observed at 120 and 180 minutes post-administration for the 20 mg dose of PEH and at 180 minutes post-administration for 25 mg PEH. Mean pulse rates were not significantly different from placebo at any dose by the time the study was concluded (4 hours post-medication).

Blood pressure: Systolic blood pressures were not significantly different from placebo values at any of the three tested doses.

Diastolic blood pressure was significantly elevated at only one time point time point (120 minutes) for 25 mg PEH Investigators did not consider any of the changes in diastolic blood pressure to be of clinical significance.

Reviewer's comments: *At the three tested doses (15, 20, and 25 mg), PEH significantly reduced NAR in this study.*

The outcomes of objective and subjective endpoints in this study do not appear to be well correlated. Although 15 and 25 mg PEH showed a significant reduction in NAR over all time points, patients failed to notice a significant change in symptom relief relative to placebo at these doses. Investigators suggest that this lack of correlation is most likely due to very low number of subjects enrolled in the study. That may be the case, but the objective and subjective measures have been shown to correlate in other studies of comparable size.

Pulse rate was significantly elevated at only two time points for the 20 mg dose of PEH (120 and 180 minutes) and at one time point for the 25 mg dose (180 minutes). Increases in pulse rate are unexpected as treatment with sympathomimetics generally results in a decrease in pulse rate (and an increase in blood pressure). Both systolic and diastolic blood pressure readings were generally unchanged relative to placebo. There were no significant changes in systolic blood pressure at any dose, and there was only one significant elevation in diastolic blood pressure (120 minutes at the 25 mg dose).

3.1.1.6. May 1970 Memo to Blackmore from N. A. Hulme.

Unpublished study "Neo-Synephrine - Elizabeth Biochemical Laboratory Study No. 5"

Reviewer's comment: *Pages 2 and 3 of the 4-page memorandum are missing from the publicly available copy of this reference in Docket No. 1976N-0052N. Because the results are reported as in Elizabeth Biochemical Laboratories Studies 3 and 4 (ANPR References 8 and 9), it appears that the protocol used is similar to that in the earlier studies.*

Study objective: Add to data previously collected by the Elizabeth Biochemical Labs demonstrating statistically significant differences between placebo and Neo-Synephrine at various oral doses.

Study Design: Double-blind, randomized, placebo-controlled, crossover design

Doses evaluated: Study evaluated the effectiveness (objectively and subjectively) of single doses of Neo-Synephrine (PEH) at three doses: 10, 15, and 25 mg

Reviewer's comment: *These are the same doses of PEH that were evaluated in Elizabeth Biochemical Laboratories Study No.2 (ANPR Reference 7).*

Study Population: 25 subjects having head colds with demonstrable nasal congestion for 2 consecutive days. No additional demographics were provided.

Number of subjects:

Ingredient	Dose (mg)	No. Subjects
PEH	10	10
	15	6
	25	9

Reviewer's comment: *The study was originally planned to have 48 subjects. Only 25 subjects were tested before the end of the cold season.*

Measurements:

NAR: Using a modified Butler-Ivy airflow device, five nasal air flow measurements were taken for each nostril at 30, 15, and 0 minutes before treatment and 15, 30, 45, 60, 90, 120, 180, and 240 minutes after treatment. The five readings from each nostril were combined and the means determined at each time point. Reductions were reported as means of the percent (fractional units x 100) change from the time 0 reading.

Relief of symptoms: At the time of each nasal air flow measurement, patients were asked to describe their congestion and rate their congestion as shifts from the premedication state. A shift of one degree of congestion was rated as a plus or minus 1; a shift of two degrees was graded plus or minus 2, and so on.

Degree of Congestion
Nose feels clear
Almost clear
Stuffy
Very stuffy
Completely blocked

The sums of the changes at each time point were recorded for each subject. Subjective data were calculated as the sum of the median values of differences (over all time points) between placebo and active medication for each subject. Pulse rate and blood pressure data, were compiled as means at each time point for each medication group.

Pulse rate and blood pressure: Readings of pulse rate and sitting blood pressure were taken at the time of each nasal airflow measurement.

Data analysis: Analyses of variance were conducted to compare placebo and active medication treatments for measurements of NAR, patient-reported symptom relief, pulse rate, and blood pressure. The investigators did not provide any additional information (e.g., what, if any, type of type analysis was employed).

Results:

NAR: PEH significantly reduced NAR at all three tested doses with significant differences from placebo evident as early as 30 minutes post-administration. Treatment with 10 or 15 mg PEH significantly reduced NAR from 30 minutes to 3 hours. Treatment with 25 mg PEH significantly reduced NAR from 30 minutes post-administration through the end of the 4-hour experiment.

Relief of symptoms: The results indicated that a significant correlation of objective and subjective measures of decongestion occurred only in subjects receiving the 25 mg dose of PEH.

Pulse rate: Mean pulse rates were significantly *increased* relative to placebo at 120 minutes post-administration for the 10 mg dose of PEH; at 60 minutes for the 15 mg dose, and at 30, 90, 120, 180, and 240 minutes for 25 mg PEH.

Blood pressure: Systolic blood pressures were significantly elevated relative to placebo values at 60, 90, 120, and 180 minutes for the 10 mg dose of PEH, at 90 minutes for the 15 mg dose, and at 60, 90, 120, and 240 minutes for the 25 mg dose.

Diastolic blood pressure was significantly elevated only the 60 and 90 minute time point for the 10 mg dose of PEH

Reviewer's comments: *At the three tested doses (10, 15, and 25 mg), PEH significantly reduced NAR in this study.*

There again seems to be a disconnect between objective and subjective readings. Although 10and 15 mg PEH showed significant reductions in NAR at a number of post-medication time points, patients failed to notice a significant change in symptom relief relative to placebo. Symptom scores and objective measures of decongestion were significantly correlated only for the 25 mg dose of PEH ($p = 0.05$).

Pulse rate was significantly elevated at one or more time points for all doses of PEH. These changes, however, on only on the order of 3 beats per minute. Increases in pulse rate are unexpected as treatment with sympathomimetics generally results in a decrease in pulse rate. Both systolic and diastolic blood pressure readings were elevated at one or more time points for every PEH dose relative to placebo. With only one exception (systolic blood pressure for the 25 mg dose of PEH), all blood pressure readings were equivalent to placebo at the conclusion of the experiment.

3.1.1.7. McLaurin, J. W., W. F. Shipman, and R. Rosedale, Jr., "A Double Blind Comparison Study of the Effectiveness of Four Sympathomimetic Drugs: Objective and Subjective," *Laryngoscope*, 71:54-67, 1961.

Study objective: Determine:

- How much rhinometric airway improvement occurs from each of four well known sympathomimetic amines as compared to placebo as well as each other
- The subjective response to the therapeutic effects and the correlation between objective and subjective findings
- How much blood pressure change takes place and how the heart rate is affected
- What notable side effects occur subjectively at office time and at bedtime

Study design: Randomized, double-blind, placebo controlled, crossover design

Doses evaluated: Study evaluated the effectiveness of two doses of four oral nasal decongestant ingredients:

Phenylephrine HCl (PEH): 10 mg
Phenylpropanolamine HCl (PPA): 25 mg
Ephedrine sulfate: 25 mg
Pseudoephedrine HCl: 60 mg

Subjects took one dose in the clinic and were instructed to take a second dose 60 minutes (5 to 6 hours after the first dose) before going to bed.

Study population: Subjects with a chief complaint of nasal obstruction and clinical findings that confirmed a soft tissue congestion and edema. Subjects' diagnoses included acute coryza, acute and chronic sinusitis, allergic and vasomotor rhinitis, and hypothyroidism. No subject demographics were provided.

Number of subjects: The study enrolled 130 subjects and finished with 88. For the most part these 42 subjects failed to return for the complete set of comparison tests. Each subject made five separate visits to the clinic taking a different mediation each time (or placebo). Investigators report a total of 440 visits (5 x 88).

Measurements:

NAR: measured by the method of McLaurin (Laryngoscope 70:155-165, 1960). Rhinometry readings expressed as mm H_2O were taken twice: prior to treatment and 60 minutes post-treatment.

Relief of symptoms: Subjects were asked to rate their congestion according to the flowing scale:

- Improvement
  - Slight
  - Moderate
  - Marked
  - Extreme

- No change
- Worse

For the second dose, subjects were asked to record the next day whether or not there was nasal airway improvement before going to bed. Subjects were also asked to report whether or not restlessness or insomnia occurred.

Pulse rate and blood pressure: Readings were taken before and 60 minutes after treatment.

Data analysis:

NAR: Pre-and post-treatment rhinometric measurements were analyzed by "correlation methods" to determine the least squares regression line for each treatment and make comparative analyses of the slopes of these lines. Investigators note that "a large portion of the total variation involved remains unexplained" and attribute this to a failure to adequately control "overwhelming extraneous factors" during the various tests. Means of the pre- and post-treatment values for each of the 5 treatments were calculated and compared by ANOVA. Chi square analysis of pre and post treatment measures for subjects grouped by pretreatment measurements was also performed.

Relief of symptoms: Method of statistical analysis not specified

Pulse rate and blood pressure: Method of statistical analysis not specified

Results:

NAR: The difference in pre-and post-treatment means was significant only for 25 mg ephedrine ($p = 0.05$). The investigators conclude that the effects of PEH, PPA, and pseudoephedrine were "roughly equal" to those of the placebo.

Relief of symptoms: In the clinic PEH was reported to be the least effective of the four test drugs based on a subjective assessment. Forty-eight of the 88 subjects described their congestion as unchanged after treatment with PEH, and two described it as worse post-medication. Investigators report that "when subjected to statistical analysis, the impression is drawn that none of the treatments is more effective than placebo." The investigators drew similar conclusions based on the statistical analysis of bedtime assessments of symptoms.

Pulse rate: Investigators report that PEH had more cases of heart rate increases of 10 beats per minute but that statistical analysis found that none of the test drugs had a significant effect on pulse rate relative to placebo.

Blood pressure: Investigators report that none of the drugs had a significant effect on systolic blood pressure relative to placebo.

Adverse events: Primary complaints were "nervousness" for pseudoephedrine and ephedrine, and headache, nausea, and dizziness/light-headedness for all treatments (highest in the placebo group.). Other complaints "contributed very little" to the adverse event profile.

Reviewer's comments: *This study has a number of limitations:*

- *Only one pre-treatment and one post-treatment time point – Investigators may well have missed important data.*
- *There were large numbers of subjects whose pretreatment measures were low.*
- *The extent of congestion each of the 88 subjects had when they reported for subsequent tests (on different dates) is not clear. The subjects may have had differing degrees of congestion each time they visited.*
- *There was a great degree of variation according to the investigators.*

3.1.1.8. Blanchard, C.L., S.J. Borsanyl, and T.C. Grubb, The Eye, Ear, Nose, and Throat Monthly, 43:76-82, 1964.

Published study "Evaluation of Nasal Decongestant Drugs"

Study objective: Objective evaluation of comparative nasal decongestive action of inhaled, ingested, and topically applied medications

Reviewer's comments: *This study provides no useful information on the effectiveness of PEH. The oral product evaluated in this study is a combination product containing a vasoconstrictor, antihistamine, and analgesic. The specific active ingredients of the combination product are not described.*

3.1.1.9. May 1969 Memo to Blackmore from N. A. Hulme.

Unpublished study "Oral Neo-Synephrine – Huntingdon Research Center Study No. 1"

Reviewer's comment: *This memorandum is dated 1 month earlier than Hulme's memorandum to Blackmore regarding the third Elizabeth Biochemical Laboratories study (ANPR Reference No. 8). The study objectives and design are (intentionally) virtually identical to those conducted by Cintest.*

Study objective: Evaluation of orally active decongestants and confirmation of earlier data obtained by the Elizabeth Biochemical Laboratories

Study Design: Double-blind, randomized, crossover design, with placebo and active controls.

Doses evaluated: Study evaluated the effectiveness (objectively and subjectively) of single doses of Neo-Synephrine (PEH) and phenylpropanolamine (PPA).

PEH: 10 and 25 mg

PPA: 50 mg

Study Population: 48 subjects having head colds with demonstrable nasal congestion for 2 consecutive days. No additional demographics were provided.

Number of subjects:

Ingredient	Dose (mg)	No. Subjects
PEH	10	16
	25	16
PPA	50	16

Measurements:

NAR: Using a Butler-Ivy airflow device, five nasal air flow measurements were taken for each nostril at 30, 15, and 0 minutes before treatment and 15, 30, 45, 60, 90, 120, 180, and 240 minutes after treatment. The five readings from each nostril were combined and the means determined at each time point.

Data analysis: Objective data (NAR reduction) were reported as means of the percent (fractional units x 100) change from the time 0 reading. Analysis of variance was conducted to compare placebo and active medication treatments for measurements of NAR. The investigators did not provide any additional information (e.g., what, if any, type of analysis was employed).

Results:

NAR**:** Neither the 10 not the 25 mg dose of PEH significantly reduced NAR in this study. Fifty mg PPA significantly reduced NAR relative to placebo at only two post-mediation time points (45 and 60 minutes). Investigators found this to be "somewhat surprising in view of the earlier data obtained by the Elizabeth Biochemical labs and recently confirmed by the Cintest Labs study (Study No. 1; ANPR Reference 22). The following possible reasons for the discrepancy were offered:

- several technicians were used and may not have optimally measured air resistance
- different technicians were used to take airflow readings for each half of the two crossover days for 14 subjects
- particular population of subjects not responsive to treatment
- wide variation in NAR values

Reviewer's comments: *It is noteworthy in this study that the active control generally failed to demonstrate effectiveness as an oral nasal decongestant. This same active control was very effective in the third Elizabeth Biochemical Laboratories Study (ANPR Reference 8), significantly reducing NAR relative to placebo (p = 0.01) from 15 minutes throughout the four hour duration of the experiment (n = 9).*

The possible reasons offered by the investigators for this discrepancy seem valid.

3.1.1.10. June 1969 Memo to Blackmore from N. A. Hulme.

Unpublished study "Oral Neo-Synephrine – Huntingdon Research Center No. 2"

Study objective: Accumulation of additional objective and subjective data on subjects having head colds who had been treated with 10 and 20 mg Neo-Synephrine (PEH). Detect possible cardiovascular changes which might be produced at these doses of PEH.

Study Design: Double-blind, randomized, placebo-controlled, crossover design

Doses evaluated: Study evaluated the effectiveness of single doses of PEH at 10 and 20 mg doses.

Study Population: Fifty subjects having head colds with demonstrable nasal congestion for 2 consecutive days. No additional demographics were provided.

Number of subjects

Ingredient	Dose (mg)	No. Subjects
PEH	10	25
	20	24

Reviewer's comment: *The study reports that there were 25 subjects in the 20mg PEH treatment group. Results were reported for only 24 subjects in this arm. No explanation is offered for this discrepancy.*

Measurements:

NAR: Using a modified Butler-Ivy airflow device, five nasal air flow measurements were taken for each nostril at 30, 15, and 0 minutes before treatment and 15, 30, 45, 60, 90, 120, 180, and 240 minutes after treatment. The five readings from each nostril were combined and the means determined at each time point.

Relief of symptoms: The investigators state that subjects rated subjective symptoms using methods previously described and provide no other information. The results reported are consistent with the following technique used in the studies conducted by Elizabeth Biochemical Laboratories:

At the time of each nasal air flow measurement, patients were asked to describe their congestion and rate their congestion as shifts from the premedication state. A shift of one degree of congestion was rated as a plus or minus 1; a shift of two degrees was graded plus or minus 2.

Degree of Congestion
Nose feels clear
Almost clear
Stuffy
Very stuffy
Completely blocked

The sums of the changes at each time point were recoreded for each subject.

Pulse rate and blood pressure: Readings of pulse rate and sitting blood pressure were taken at 30, 15, and 0 minutes before treatment and 30, 60, 90, 120, 180, and 240 minutes after treatment.

Data analysis: Objective data (NAR reduction) were reported as means of the percent (fractional units x 100) change from the time 0 reading. Due to a lack of statistically valid differences in the objective measures for the 10 mg dose and only a single point of significance at the 20 mg dose, the subjective measures were not analyzed. Pulse rate and blood pressure data, were compiled as means at each time point for each medication group. Analyses of variance were conducted to compare placebo and active medication treatments for measurements of NAR, pulse rate, and blood pressure. The investigators did not provide any additional information (e.g., what, if any, type of analysis was employed).

Results

NAR:

PEH: Although "less resistance to airflow was recorded at all time intervals," PEH (10 mg) did not *significantly* reduce NAR at any of nine post-administration time points. At a dose of 20 mg, PEH significantly reduced NAR at only one time point – 45 minutes post-administration. Investigators proposed that the use of several technicians rather than one or two well-trained ones may have contributed to the failure to demonstrate efficacy of PE as a nasal decongestant.

Pulse rate: Mean pulse rates were significantly decreased relative to placebo at only one time point (90 minutes) for the 10 mg dose of PEH. The one significant difference observed was on the order of 2 beats per minute and was not considered to be clinically important.

Blood pressure: Systolic blood pressure data showed statistically significant *decrease* relative to placebo at 180 minutes post-administration for the 10 mg dose of PEH. (Sympathomimetics like PEH generally increase blood pressure). There were no differences between patients treated with placebo and 20 mg PEH.

Diastolic blood pressure was significantly *decreased* at only the 240 minute time point for 20 mg PEH. No significant changes were reported for the 10 mg dose of PEH at any of the nine time points.

Adverse events: No side effects were reported by any subject.

Reviewer's comments *Neither 10 nor 20 mg doses of PEH significantly decreased NAR relative to placebo over the 4 hour course of this study.*

Investigators attribute the lack of effect to the "use of a series of several different technicians to operate the [nasal airflow] instrument." The investigators note that the

responses "appear to follow the pattern seen in the first Huntingdon study" and suggest that the same issues listed in the first Huntingdon study (ANPR Reference 20) may be responsible for the failure to observe significant decongestion in this study.

There were no consistent effects on pulse and blood pressure

3.1.1.11. April 1969 Memo to Blackmore from N. A. Hulme.

Unpublished study "Oral Neo-Synephrine – Cintest Labs Study No. 1"

Study objective: Explore more fully the dosage spectrum of orally administered Neo-Synephrine (PEH) and confirm earlier data (collected by the Elizabeth Biochemical Laboratories) in another laboratory

Study Design: Double-blind, randomized, crossover design, with placebo and active controls.

Doses evaluated: Study evaluated the effectiveness (objectively and subjectively) of single doses of Neo-Synephrine (PEH) and phenylpropanolamine (PPA).

PEH: 10 and 25 mg
PPA: 50 mg

Study Population: 48 subjects "complaining of head colds" with demonstrable nasal congestion for 2 consecutive days. No additional demographics were provided.

Number of subjects:

Ingredient	Dose (mg)	No. Subjects
PEH	10	16
	25	16
PPA	50	15

Reviewer's comment: *The study reports that there were 16 subjects in the 50mg PPA treatment group. Results were reported for only 15 subjects in this arm. No explanation is offered for this discrepancy.*

Measurements:

NAR: Using a Butler-Ivy airflow device, five nasal air flow measurements were taken for each nostril at 30, 15, and 0 minutes before treatment and 15, 30, 45, 60, 90, 120, 180, and 240 minutes after treatment. The five readings from each nostril were combined and the means determined at each time point. Reductions were reported as means of the percent (fractional units x 100) change from the time 0 reading.

Relief of symptoms: At the time of each nasal air flow measurement, patients were asked to describe their congestion and rate their congestion in terms of shifts from the

premedication state. A shift of one degree of congestion was rated as a plus or minus 1; a shift of two degrees was graded plus or minus 2 and so on.

Degree of Congestion
Nose feels clear
Almost clear
Stuffy
Very stuffy
Completely blocked

The sums of the changes at each time point were recorded for each subject. Subjective data were calculated as the sum of the median values of differences (over all time points) between placebo and active medication for each subject.

Data analysis: Analyses of variance were conducted to compare placebo and active medication treatments for measurements of NAR. Differences in patient-reported symptom relief were evaluated by the Wilcoxon Matched-Pairs Signed Rank test. The investigators did not provide any additional information (e.g., what, if any, type of analysis may have been employed).

Results

NAR: Both 10 and 25 mg PEH significantly reduced NAR relative to placebo at three time points. Significant reduction for NAR was seen at 90, 120, and 180 minutes post-administration for the 10 mg dose and at 120, 180, and 240 minutes for the 25 mg dose. PPA, 50 mg, also significantly decreased NAR at three postadministration time points: 60, 90, and 120 minutes.

Investigators note that these results are qualitatively comparable to the results of the Elizabeth Biochemical Labs finding.

Relief of symptoms: Patients treated with 10 mg PEH or 50 mg PPA noticed significant differences in the extent of their congestion ($p = 0.05$ for 10 mg PEH and 0.01 for 50 mg PPA). Those treated with 25 mg also reported less congestion than when they were treated with placebo, but this difference was not significant.

Reviewer's comments: *NAR was significantly reduced in patients treated with 10 or 25 mg PEH, but the onset of effect was longer than that observed in other studies. Treatment with 10 mg PEH did not significantly reduce NAR until 90 minutes post-administration, and 20 mg PEH did not significantly reduce NAR until a full 2 hours after treatment. The active control, PPA, appeared to have a relatively late onset in this study. NAR reduction following treatment with 50 mg PPA was not significant until a full hour after treatment. The absence of data from on the intent to treat subjects is unexplained and introduces questions regarding study validity.*

There appears to be limited correlation between subjective and objective outcomes. Patients reported feeling significantly less congested with both 10 mg PEH and 50 mg PPA but not with 20 mg PEH. Several possible reasons for the lack of correlation

between objective and subjective ratings of nasal decongestant effectiveness will be presented in section XX of this review.

PEH at doses of 10 and 20 mg appeared to have no consistent effect on pulse rate and blood pressure changes.

3.1.1.12. January 1970 Memo to Blackmore from N. A. Hulme.

Unpublished study "Oral Neo-Synephrine – Cintest Study No. 2"

Study objective: Further expand the range of Neo-Synephrine (PEH) dosages tested to include 20 mg and accumulate additional numbers of subjects tested at the 10 and 15 mg levels

Study Design: Double-blind, randomized, placebo-controlled, crossover design

Doses evaluated: Study evaluated the effectiveness (objectively and subjectively) of single doses of Neo-Synephrine (PEH) at doses of 10, 15, and 20 mg

Study Population: 48 subjects with head colds having demonstrable nasal congestion for 2 consecutive days. No additional demographics were provided.

Number of subjects

Ingredient	Dose (mg)	No. Subjects
PEH	10	15
	15	16
	20	15

Reviewer's comment: *The study reports that there were 16 subjects for each treatment group. Results were reported for only 15 subjects in the 10 and 20 mg groups. No explanation is offered for this discrepancy. Also, lack of information on the absence of data on the intent to treat subjects makes this study questionable.*

Measurements

NAR: Using a Butler-Ivy airflow device, five nasal air flow measurements were taken for each nostril at 30, 15, and 0 minutes before treatment and 15, 30, 45, 60, 90, 120, 180, and 240 minutes after treatment. The five readings from each nostril were combined and the means determined at each time point. Reductions were reported as means of the percent (fractional units x 100) change from the time 0 reading.

Relief of symptoms: At the time of each nasal air flow measurement, patients were asked to describe their congestion and rate their congestion in terms of shifts from the premedication state. A shift of one degree of congestion was rated as a plus or minus 1; a shift of two degrees was graded plus or minus 2.

Degree of Congestion
Nose feels clear
Almost clear
Stuffy
Very stuffy
Completely blocked

The sums of the changes at each time point were recorded for each subject. Subjective data were calculated as the sum of the median values of differences (over all time points) between placebo and active medication for each subject.

Pulse rate and blood pressure: Readings of pulse rate and sitting blood pressure were taken at 30, 15, and 0 minutes before treatment and 30, 60, 90, 120, 180, and 240 minutes after treatment. The means of pulse and sitting blood pressure readings were calculated at each post-medication time point for each medication group.

Data analysis Analyses of variance were conducted to compare placebo and active medication treatments for measurements of NAR, patient-reported symptom relief, pulse rate, and blood pressure. The investigators did not provide any additional information (e.g., what, if any, type of analysis may have been employed).

Results

NAR: There were no significant differences between PEH and placebo at any of the three tested doses.

Relief of symptoms: Patient-reported relief from congestion showed no significant differences between any of the three tested doses and placebo.

Pulse rate and blood pressure: There were no significant changes for any of the three tested doses of PEH at any time point.

Investigators determined that "there was no obvious failure in technique," and attributed the lack of significance to one of several possibilities:

- patient failure to fast before receiving medication
- patient failure to take medication
- improper selection of patients
- presence of a viral infection not amendable to drug treatment

Reviewer's comments: *This reviewer concurs with the investigators' ideas as to why they were unable to draw any valid conclusions from this study.*

3.1.1.13. May 1970 Memo to Blackmore from N. A. Hulme.

Unpublished study "Oral Neo-Synephrine – Cintest Study No. 3"

Study objective: Evaluation of the nasal decongestant activity of orally administered Neo-Synephrine (PEH)

Study Design: Double-blind, randomized, placebo-controlled, crossover design.

Doses evaluated: Study evaluated the effectiveness (objectively and subjectively) of single doses of Neo-Synephrine (PEH) at doses of 10, 15, and 25 mg

Study Population: 48 subjects with head colds having confirmed nasal congestion for 2 consecutive days. No additional demographics were provided.

Number of subjects

Ingredient	Dose (mg)	No. Subjects
PEH	10	15
	20	16
	25	16

Reviewer's comment: *The study reports that there were 16 subjects for each treatment group. Results were reported for only 15 subjects in the 10 mg group. No explanation is offered for this discrepancy.*

Measurements

NAR: Using a Butler-Ivy airflow device, five nasal air flow measurements were taken for each nostril at 30, 15, and 0 minutes before treatment and 15, 30, 45, 60, 90, 120, 180, and 240 minutes after treatment. The five readings from each nostril were combined and the means determined at each time point.

Relief of symptoms: At the time of each nasal air flow measurement, patients were asked to describe their congestion and rate their congestion in terms of shifts from the premedication state. A shift of one degree of congestion was rated as a plus or minus 1; a shift of two degrees was graded plus or minus 2.

Degree of Congestion
Nose feels clear
Almost clear
Stuffy
Very stuffy
Completely blocked

The sums of the changes at each time point were recorded for each subject. Subjective data were calculated as the sum of the median values of differences (over all time points) between placebo and active medication for each subject.

Pulse rate and blood pressure: Readings of pulse rate and sitting blood pressure were taken at 30, 15, and 0 minutes before treatment and 30, 60, 90, and 120 minutes after treatment. The means of pulse and sitting blood pressure readings were calculated at each post-medication time point for each medication group**.**

Data analysis: Analyses of variance were conducted to compare placebo and active medication treatments for measurements of NAR, patient-reported symptom relief, pulse rate, and blood pressure. The investigators did not provide any additional information (e.g., what, if any, type of analysis may have been employed).

Results

NAR: Neither 10 mg nor 25 mg PEH significantly reduced NAR at any time point. Treatment with 20 mg PEH resulted in a significant reduction in NAR at only one post-treatment time point (30 minutes, p=0.10).

Relief of symptoms: Patient-reported relief from congestion showed no significant differences between treatment with either 10 or 25 mg PEH. Subjective impression of decongestion was significant only for the 15 mg dose.

Pulse rate: Pulse rate was not significantly altered by treatment with PEH. There was one statistically significant increase in pulse rate 90 minutes post-medication for the 15 mg dose.

Blood pressure: Systolic blood pressure was generally unaffected by treatment with PEH. Systolic blood pressure significantly increased relative to placebo at 60 minutes for the 15 mg dose, and decreased significantly at the same time point for patients treated with 25 mg PEH. The increase in pressure observed with the 25 mg dose was less than 3 mm Hg.

Diastolic blood pressure was significantly decreased relative to placebo only at the 90 and 120 minutes time points for 25 mg PEH. This change is opposite to what would be expected for this class of drugs.

Investigators noted that the objective changes (decrease in NAR) indicate "a very minimal" drug effect and that this is correlates with the subjective results.

Reviewer's comments*: This study failed to show at any of its endpoints statistical differences between the drug and placebo at any timepoint. Information about the intent to treat subjects is lacking and introduces questions about study validity.*

3.1.1.14. Rodgers, J. M., E. B. Reilly, and H. A. Bickerman, Clinical Pharmacology and Therapeutics 14:146, 1973)

Published Abstract: "Physiologic and Pharmacologic Studies on Nasal Airway Resistance."

***Reviewer's comments*:** *This reference is to an abstract. There are insufficient data upon which to draw any conclusions.*

3.1.1.15. OTC Volume 040288B

Unpublished Study: "Evaluation of the effectiveness of phenylephrine HCl tablets (5 mg) in the relief of upper respiratory congestion and symptoms associated with the common cold in a 200 patient study conducted for Whitehall Laboratories"

Study objective: To compare, by objective and subjective means, the decongestant effectiveness of single dose PEH (2 x 5 mg) tablets vs. placebo tablets. To compare by subjective means the effects of multi-dose PEH vs. placebo, with doses to be separated by 4-hour intervals. To evaluate the safety of 10 mg PEH.

Study Design: Randomized, double-blind, placebo-controlled, parallel design

Doses evaluated: objective-Subjective BEI 1025a Study evaluated the effectiveness (objectively and subjectively) of a single 10 mg dose (2 x 5 mg tablets) of PEH. Subjective BEI 1025b evaluated multi-doses of PEH over a 12 hour period.

Study Population: 200 subjects with upper respiratory congestion associated with the common cold and a temperature of 101° F or lower. Subjects were 18 years of age or more and balanced for weight, height, race, sex, and initial "cold presenting symptoms, i.e., stuffynose, runny nose, sneezing, itching (eyes, nose), coughing, and muscle ache. .

Exclusion factors:

- Pre-existing anatomical nasal obstruction
- Females who are menstruating or are within one week of their menstrual period
- Subjects with: cardiovascular disease, cerebrovascular disease, diabetes mellitus, hyperthyroidism, peripheral vascular disease, pulmonary disease

Number of Subjects:

Three Part Study Number of Subject in Each:

Trial	Group	Treatment	No. Subjects
Part I --Objective-Subjective BEI 1025a	1	Placebo	25
	2	PEH (10 mg)	25

Part II --Subjective BEI 1025b	3	Placebo	75
		PEH 10 mg	75
Part III --Objective-Subjective Study BEI 1025a + Subjective Study BEI 1025b	4	PEH	100
		Placebo	100

Measurements:
Part I—Objective-Subjective Study BEI 1025a

NAR: Using electronic posterior rhinometry, nasal air flow measurements were taken at time 0, 15, 30, 60, and 120 minutes after treatment. Investigators determined the differences in NAR between the 0 minute value and each successive time point for each subject in study BEI 1025a, summed the differences for each time point, and computed the absolute and percent changes from baseline values.

Part II---Objective-Subjective BEI 1025a + Subjective Study BEI 1025b
Relief of symptoms: At the time of each nasal air flow measurement, patients were asked to rate their congestion on a 0 – 4 point scale.

Blood pressure: Systolic and diastolic blood pressure readings were taken at each post-medication time point.

Data analysis: Differences in objective data (NAR reduction) were assessed by Student's t-test and by the nonparametric "Sign Test" (Siegel, S., Nonparametric Statistics, McGraw-Hill, pp. 68-75, 1946). Subjective data were pooled and analyzed by the method of Dunn ("Multiple Comparisons Using Rank Sums" in Technometrics, 6:241-252, August 1964). The investigators do not state how the significance of differences in blood pressure was determined.

Results:

The safety and effectiveness of phenylephrine HCl (5 mg x 2 tablets) was evaluated in 200 volunteer subjects. NAR in addition to subjective data was evaluated in 50/200 patients and 150/200 patients were evaluate subjectively.

Part I—Objective-Subjective Study BEI 1025a

NAR (50/200 patients): Investigators noted that 10 mg PEH significantly reduced NAR relative to placebo ($p \leq 0.05$

Time post-medication (minutes)	Change in NAR (%)	
	10 mg PEH (n =25)	Placebo (n = 25)
15	-11.4	+0.2
30	-20.6	-6.4
60	-28.2	-12.7
120	-26.2	+5.5

Part II---Objective-Subjective BEI 1025a + Subjective Study BEI 1025b

Relief of symptoms: Investigators report that PEH, 10 mg, the following symptoms were more effective than placebo: sneezing 115%, runny nose 85%, stuffy nose 58%. The perception of relief was significant for the 30, 60, and 120 minute time points ($p < 0.05$). PEH was no more effective than placebo for coughing and muscle ache. The effect of PEH on itching (eyes, nose) could not be determined because only 3.5% of the patient population had this symptom.
The patients and the investigator find that PEH tablets were more effective than placebo in relieving the symptoms of a cold. Further, the reduction of NAR was correlated with increasing relief of the symptoms of sneezing, runny nose, and stuffy nose.

Blood pressure: There were no significant differences relative to the placebo group. Mean systolic blood pressure was elevated relative to placebo at every time point. Mean elevation was 1.3 mm with a range of 0.2 to 1.4 mm.

Diastolic blood pressure, with one exception was always lower than the placebo group. Mean reduction was 0.56 mm with a range of -0.2 to 0.6 mm)

Adverse Events

There was no significant difference in the kind and number of adverse events in the PEH group and placebo. In the placebo group 11/100 and in the PEH group 8/100 reported side effects. The following adverse events were common to both groups:

.

Adverse Event	PEH	Placebo
Dizzy	1	3
Felt Warm	3	1
Dizzy + Flushing		1
Dry mouth		3
Headache		1
Nausea		2
Extrasystoles	1	
Flush	1	
Nasal Dryness	1	
Slightly shaky	1	

Reviewer's comments: *The objective-subjective study BEI 1025a indicates that a single dose of PEH, 10 mg. effectively reduces NAR, p = 0.05. Objective-subjective study BEI 1025a + Subjective study BEI 1025b, also indicate that PEH taken every 4 hour over a 12.5 hour period is safe and effective in relieving the symptoms of a stuffy nose, runny nose, and sneezing.*

Neither systolic nor diastolic blood pressure appears to have been affected by treatment with multidose 10 mg PEH.

3.1.2 Relevant studies not cited in the ANPR

3.1.2.1. Bickerman, H. A., "Physiologic and Pharmacologic Studies on Nasal Airway Resistance (R_N)," The Proprietary Association. Current Research Methodology in the Evaluation of Proprietary Medicines: *Proceedings of a conference sponsored by the Scientific Development Committee of the Proprietary Association*, 1971

Study objective: This is a review of the advantages and disadvantages of using objective measurements of NAR to assess nasal patency.

Reviewer's comment: *Some data, collected from a total of 104 subjects over a three-year period, is presented to illustrate points in the review. The author favors the use of rhinometry to assess decongestant efficacy and includes one "pharmacologic study" which examines the effectiveness of three oral administered decongestants vs. placebo. The data described below are based on a representative figure (#25) from the publication.*

Study Design: Not provided for each study.

Doses evaluated: Study evaluated the effectiveness of single doses of PEH (10 mg), PPA (40 mg), and pseudoephedrine (60 mg).

Study Population: Patients had chronic nasal congestion. No other information is provided.

Number of subjects: Not provided for each study

Measurements: NAR measurements were made immediately prior to medication ("control values") and 30, 60, 120, 180, and 240 minutes post-medication.

Data analysis: Mean nasal airflow readings were computed for each treatment group (including placebo) at each time point. Means at each time point were compared to controls and expressed as percent change from the control values. Statistical inferences were made but the specific methods used were not provided.

Results: PEH, 10 mg, decreased NAR relative to baseline at only the 2-hour time point. The only significant change in NAR due to treatment with PEH was an *increase* at the 3-hour time point (p = 0.05). Pseudoephedrine, 60 mg, significantly decreased NARat every post-medication time point, and 40 mg PPA significantly decreased NAR at every time point but the last (240 min. post-administration).

Reviewer's comments: *The data considered here is based on one representative figure in a paper primarily intended to be a review. Not enough information is provided to assess the adequacy of the study design, number of subjects, extent of subjects' congestion prior to treatment, or appropriateness of statistical test(s) used. This reviewer cannot draw any meaningful conclusions regarding the efficacy of PEH from this paper.*

3.1.2.2. Cohen, B.M., "Clinical and Physiological 'Significance' of Drug-Induced Changes in Nasal Flow/Resistance," *European Journal of Clinical Pharmacology*, 5:81-86, 1972

Study objective: Comparison of objective and subjective estimates of nasal patency in patients with common colds with simultaneous measurement of changes in pulse rate and blood pressure.

Study Design: Randomized, double blind, placebo-controlled, crossover design.

Doses evaluated: Study evaluated the effectiveness (objectively and subjectively) of single doses of Neo-Synephrine (PEH) at doses of 10, 15, and 25 mg

Study Population: 48 adults with common colds of 24 to 48 hours duration. No additional demographics were provided.

Number of subjects:

Ingredient	Dose (mg)	No. Subjects
PEH	10	16
	15	16
	25	16

Measurements

NAR: Electronic posterior rhinometry was used to determine NAR immediately before treatment and 15, 30, 60, 90, and 120 minutes post-treatment. NAR for each subject was measured three times at each time point and expressed as the mean at each time point.

Reviewer's comment*: It is unclear if the NAR measurements were based on readings for both nostrils or on a single nostril.*

Relief of symptoms: At the time of each nasal air flow measurement, patients were asked to describe their congestion and rate their congestion on a 5-point scale ranging from 0 (clear) to 4 (completely blocked).

Pulse rate and blood pressure: The author reports that these parameters were "monitored clinically."

Data analysis:

NAR: Individual mean NAR readings at each time point were summed and a group mean was determined for each point. Treatment group means at each point were compared to placebo group means and statistical significance was assessed.

***Reviewer's comment**: The author doesn't specify the specific statistical tests were used.*

Relief of symptoms: Mean subjective scores were calculated for each treatment group at each post-medication time interval and compared to placebo means.

Pulse rates and blood pressure: Mean pulse rates and blood pressures were calculated for each treatment group at each post-medication time interval and compared to placebo means.

Results:

NAR: PEH significantly reduced NAR (relative to placebo) at all doses. At the 10 mg dose, PEH significantly reduced NAR at 30 and 60 min post medication ($p = 0.05$). The decrease in NAR remained significant throughout the 2 hour duration of the experiment ($p = 0.01$). At the 15 and 25 mg doses, PEH significantly reduced NAR at the earliest post-medication time point (15 minutes) ($p = 0.05$ in both cases) and NAR remained significantly reduced for the remainder of the study. When serial/nasal airflow resistances of the three PEH doses and the pooled placebo trials were analyzed as percent changes from controls the ranking of improvement was 25 mg >15 mg>10 mg > placebo.

Relief of symptoms: Patient-reported relief from congestion mirrored the objective measurements. Investigators reported significant reductions in symptom scores relative to placebo at PEH doses and post-medication time points identical to those measured objectively. Although the curves of subjective assessments fit closely with NAR, and active treatments could be distinguished from placebo, there was no separation of the three PEH doses.

Pulse rate: Pulse rates following treatment with all three doses of PEH showed "moderate" *increases* that were significant in 8 of the 15 post-medication time points. Significant increases occurred at 30, 90, and 120 minutes for the 10 mg dose. The increase in pulse rate ranged from 5 to 7 beats per minute for this dose. For the 25 mg dose significant increases occurred at 30, 60, 90, and 120 minutes.

The increases ranged from 9 to 13 beats per minute. Interestingly, a significant increase in pulse occurred only at 30 minutes for the 15 mg dose.

Blood pressure: Mean systolic blood pressure readings were generally unaffected by treatment with PEH.

Diastolic blood pressure was significantly *decreased* relative to placebo at 4 of 15 post-medication time points (15 and 25 mg doses).

Patient-reported adverse events: Adverse events rose in frequency with increasing dose of PEH. Investigators described these as "entirely of the nuisance variety."

***Reviewer's comments**: PEH, in this study, shows statistically significant efficacy at doses of 10, 15, and 25 mg. Efficacy is demonstrated both objectively (reduction in NAR) and subjectively (patient-reported symptom relief). A dose response was demonstrated for the NAR endpoint. This study demonstrates a very strong correlation between the objective and subjective measures of decongestant effect.*

Changes in pulse rate and blood pressure occur in directions opposite what is expected for sympathomimetic amines. Pulse rates increased rather than decreased, and both systolic and diastolic blood pressure decreased relative to placebo (rather than increase). This reviewer concurs with the author in his assessment that the changes in cardiovascular measures are not clinically meaningful.

The most commonly reported "side effect" was nervousness. This was reported by 6 patients at the 15 mg dose and by 5 at the 25 mg dose. One subject reported nervousness as a side effect to taking placebo.

3.1.2.3. Unpublished study "Study AHR-G1-A" Submitted to Docket No. 1976N-0052N on November 16, 2006 as part of EMC140 (Wyeth Consumer Healthcare)

Study objective: Compare the decongestant effects of Dimetapp Elixir with those of its components

Study design: Randomized, single-blind, parallel group, single center, single day

***Reviewer's comment**: The Principal Investigator was Dr. Burton Cohen, author of the published study "Clinical and Physiological 'Significance' of Drug-Induced Changes in Nasal Flow/Resistance"*

Doses evaluated: Study evaluated the effectiveness of single doses of four oral nasal decongestants:

Dimetane elixir: Brompheniramine (BR): 8 mg
Neosynephrine elixir: Phenylephrine HCl (PEH): 10 mg

Propadrine elixir: Phenylpropanolamine HCl (PPA): 10 mg
Dimetapp elixir (BR + PEH + PPA at doses above)

Study population: 48 subjects (ages 19 – 74) with nasal congestion due to an upper respiratory infection. Subjects were enrolled within not less than 24 hrs and no more than 72 hours of the onset of symptoms.

Exclusion criteria:

- Less than 48 hours off all drugs with similar pharmacological characteristics
- Chronic pulmonary disease
- Allergic rhinitis
- Pregnant

Number of subjects:

Ingredient	No. Subjects
BR	8
PEH	8
PPA	8
Dimetapp	24

Measurements:

NAR: Investigators measured both inspirational and expirational resistance using a Respiron instrument (electronic posterior rhinometry). NAR was reported in terms of pressure (cm H_2O) at a fixed flow rate of 0.5 L/sec. Measurements were made at baseline and every 30 minutes post-treatment for 4.5 hours.

Relief of symptoms: Subjective assessments of nasal mucosal congestion, nasal mucosal hyperemia, and nasal secretion were assessed on a 0 – 4 point scale as follows.

Score	Symptom
0	Absent; normal
1	Mild; mildly impaired
2	Moderate; moderately impaired
3	Severe; severely impaired
4	Very severe; total obstruction

Ease of nasal breathing was assessed on a separate 0 - 4 point scale as follows:

Score	Symptom
0	Normal
1	Mildly impaired
2	Moderately impaired
3	Severely impaired
4	Total obstruction

Subjective assessments were made at baseline and every 30 minutes post-treatment for 4.5 hours

Pulse rate and blood pressure: Pulse rates (sitting, 3 minutes) and blood pressure readings (sitting, right arm, 3 minutes) were measured at time 0 and 30, 60, 90, 120, 180, 240, and 270 minutes post-treatment.

Data analysis:

NAR: Analyses of covariance were performed on the measurements of NAR at each time point. Pre-drug measurements as well as "control" (time 0) values were used as covariates. Adjusted means of the components were compared with the adjusted means of Dimetapp using Dunnett's t test (one-tailed).

Relief of symptoms: Analyses of variance were performed on ridit-transformed variables. Mean ridits for each component were compared with those of Dimetapp and with "No change" ridits (i.e., the ridit score representing change = 0) using Dunnett's one-tailed t-test.

Pulse rate and blood pressure: Only means at various time points were calculated. The means were not statistically compared.

Results:

NAR: PEH (10 mg) significantly decreased both inspiratory and expiratory NAR relative to the control or baseline value at 60, 90, 120, 150, and 270 min ($p < 0.005$). Significant differences were also seen at the 180 and 210 min time points ($p < 0.10$)

Relief of symptoms: Means of the symptom scores were compared with "no change" ridits (i.e., the ridit score representing a change = 0). For 10 mg PEH, significance was seen at the $p < 0.05$ level for relief of nasal mucosal congestion at the 60, 90, and 270 minutes post-dose time points. Nasal secretion scores were significantly at the 30, 60, 90, 120, 180, and 270 min time points. Nasal mucosal hyperemia scores were significantly at the 60, 90, 120, 150, 180, and 270 min time points. Ease of nasal breathing scores was significantly better at the 60, 90, 120, and 270 minute time points.

Pulse rate: Mean values at all time points were increased relative to the mean value at time 0. The average increase was on the order of 5 beats per minute. No statistical analysis was performed.

Blood pressure: Mean values did not differ substantially from the mean value at time 0. No statistical analysis was performed.

Adverse events: Few were observed. None of these were considered to be significant.

Reviewer's comments: *This study was designed, primarily, to evaluate the decongestant effectiveness of Dimetapp elixir compared to each of its component active ingredients. The effect of PEH, 10 mg, one of the components, is compared to the effect of Dimetapp at time 0, but is not compared to placebo..*

3.1.2.4. Unpublished study "AHR-4010-3" at six sites (0401 – 0406) Submitted to Docket No. 1976N-0052N on November 16, 2006 as part of EMC140 (Wyeth Consumer Healthcare)

Study objective: Determine, by subjective and objective methods, if a combination decongestant formulation containing one half of the proposed OTC monograph dose (each) 12.5 mg phenylpropanolamine (PPA) and 5 mg phenylephrine hydrochloride (PEH) was at least equivalent, in terms of therapeutic effect, to full strength PEH (10 mg) or PPA 25 mg.

Study design: Randomized, double blind, placebo-controlled, parallel group, six center, 3-day study

Reviewer's comment: *The study was originally designed as a multicenter study. The results of one center (site 0401) are reported separately because a significant treatment by investigator interaction was evident when the data from all the centers were pooled. The investigator from this center used a more objective approach and this was the only center to contribute objective data to this study. A complete analysis of the 6 pooled studies, a separate analysis of the data from site 0401, and an analysis of the remaining five studies were provided.*

Doses evaluated: Study evaluated the effectiveness and safety of multiple doses (5 mL grape-flavored elixir every 4 hours for 3 days) of placebo and three oral nasal decongestants:

Placebo: 5 mL
Phenylephrine HCl (PEH): 10 mg/5 mL
Phenylpropanolamine HCl (PPA): 25 mg/5 mL
Combination of PPA (12.5 mg) + PEH (5 mg)/5 mL

Reviewer's comment*: The subjects were able to vary their dosage schedule based on a physician's order. Maximal dosage permissible was 6 doses/24 hours. Minimum dosage permissible was 4 doses/24 hours. No data was provided to show if any of the subjects varied their dosage schedule from the protocol.*

Study population: Adult subjects over 18 years old with acute rhinitis due to upper respiratory infection (URI) of 48 hours duration or less. The four groups were comparable with regard to age, sex, duration of rhinitis, and initial severity of symptoms.

Exclusion criteria:

- Require medication other than nasal decongestants
- Anatomical obstruction of the nasal airways

- Diabetes
- Thyroid disease
- Cardiovascular disease
- Renal disease
- Hepatic disease
- Respiratory disease other than URI
- Pregnant
- Known hypersensitivity to PEH, PPA, or chemically related drugs
- Taking MAO inhibitors, analgesics and related drugs

Number of subjects:

Ingredient	**No. Subjects (All sites)**	**No. Subjects (Site 0401)**
Placebo	65	12
PEH	66	12
PPA	68	12
Combination	63	12

Measurements:

NAR: (**Site 0401 only)** Investigators measured both inspirational and expirational resistance. NAR was reported as the mean of three successive measurements of both inspirational and expirational resistance. Measurements were made at baseline and 15, 30, 45, 60, 120, 180, and 240 minutes post-treatment and were expressed in pressure increments (cm H_2O/L/s at a constant air flow rate of 0.5 L/s).

Relief of symptoms: Subjective assessments of runny nose, stuffy nose, sneezing, headache, and overall therapeutic effect were made by both patients and investigators. Symptom relief was assessed on a 0 – 3 point scale.

Score	**Symptom**
0	Not present
1	Mild
2	Moderate
3	Marked

Subjective assessments by patients were made at baseline and 24, 48, and 72 hours post-treatment. Investigator assessments were made at baseline and 72 hours post-treatment.

Pulse rate and blood pressure: Measurements were made at the enrollment and final (72 hours) visits.

Adverse events: Incidents of adverse events were solicited at the final evaluation

Data analysis:

NAR: (**Site 0401 only)** Analyses of covariance with the baseline measure as the covariate were performed on the decrease from baseline in NAR at each of the post-treatment evaluations and on a summary measure – the area between the NAR curve and the baseline NAR value. P-values were one-tailed.

Relief of symptoms: Two-factor analysis of variance (ANOVA) was used to assess the statistical significance of differences in subjective evaluations. Terms included in the model were investigator, treatment, and treatment by investigator interaction. For the data from the subjective ratings of nasal symptoms, a three-factor ANOVA was utilized. Effects included in this model were baseline symptom severity used as a block effect, investigator, treatment, and treatment by investigator interaction. Investigators stated that "stratifying by baseline severity removes possible effects due to baseline symptom severity from the treatment comparison."

Separate ANOVAs were performed on the data from site 0401 and pooled data from the other five sites.

Pulse rate and blood pressure: Summary statistics for each treatment group taken on the enrollment visit and on the final visit were compared using a paired t-test.

Results:

NAR: (**Site 0401 only)** Following the initial dose, PEH (10 mg) was significantly more effective than placebo in reducing NAR at the 30 ($p < 0.05$), 45 ($p < 0.001$), 60 ($P < 0.001$), 120 ($p < 0.001$), and 180 minute ($p < 0.05$) time points. PEH (10 mg) was not significantly less effective than PPA (25 mg) but was significantly less effective than the combination of PEH and PPA.

Relief of symptoms: (**Site 0401 only**) the combination product was statistically significantly superior to PEH, PPA, and placebo for the nasal symptoms subjective efficacy variables ($p < 0.05$). No formal statistical analysis of the headache data were conducted due to the mild severity of headache at baseline.

Sites 0402 – 0406 (pooled): There were no significant differences among the treatment groups for any of the subjective efficacy variables.

Pulse rate: No significant treatment group change from baseline was detected.

Blood pressure: No significant treatment group change from baseline was detected.

Adverse events: Investigators described these as "minimal with respect to severity and frequency." Fifty-three percent (10/19) of patients who reported adverse events were on placebo and these patients accounted for 12 of the reported 23 adverse events. Only two of the 23 adverse events were associated with PEH use.

Reviewer's comments: *Efficacy of PEH as measured objectively by reduction in NAR was studied at only one of six sites. Investigators at site 0401 determined that NAR was significantly reduced relative to placebo at 30 – 180 minutes after the first dose of PEH was administered. The investigators reported that the effectiveness of PEH as measured objectively was comparable to that of PPA measured by the same method. Furthermore the investigators claimed that the objective and subjective evaluations produced similar results. In fact, the subjective results at this site were not as robust as the objective ones. Both the subjects and the investigators found that PEH reduced the severity of stuffy nose symptoms at 72 hours and of sneezing at 24 and 48 hours (subjects) and 72 hours (investigators). These changes were not significant ($p < 0.1$)*

Only data collected at site 0401 (12 subjects) showed PEH to be significantly superior to placebo as a nasal decongestant. There was no evidence from the pooled studies (68 subjects at five other sites) that PEH produced significant relief of patient- or investigator-reported symptoms of congestion. The investigators note that "there was a statistically significant ($p < 0.01$) treatment by site interaction for both the subject and investigator overall subjective evaluations at 72 hours", but that this "interaction became insignificant when site 0401 was excluded from the analysis."

Investigators offered at least two reasons for the disparity. Subjects at site 0401 tended to:
- *Have more severe nasal congestion and less severe runny nose at baseline*
- *Be older (mean age 47.7) than subjects at other sites (mean age 33.9 years)*

Regardless of the reason, 82 percent (214/262) of the patients who completed this study did not feel that PEH effectively reduced their symptoms of nasal congestion.

There were no issues regarding cardiovascular safety and only an insignificant number and type of adverse events.

3.1.2.5. Unpublished study "Study No. 7032"
Submitted to Docket No. 1976N-0052N on November 16, 2006 as part of EMC140 (Wyeth Consumer Healthcare)

Study objective: Investigate the use of the Respiron (rhinomanometer) under controlled conditions to evaluate and compare the nasal decongestant effects of Dimetapp Elixir and related formulations:

- Dimetane elixir (brompheniramine, BR)
- Propadrine elixir (phenylpropanolamine, PPA)
- Neosynephrine elixir (phenylephrine hydrochloride, PEH)
- Dimetapp vehicle
- Afrin nasal spray (oxymetazole hydrochloride)

Reviewer's comment: *According to the study report Afrin was used to "to obtain a check on the instrument and techniques and to obtain an indication of the possible*

maximum response in a particular subject on a given day." *The study report provides no further mention of the use of Afrin and its use potentially confounds the observed outcomes.*

Study design: Randomized, single-blind, placebo-controlled, single dose, 8-way crossover, full factorial (2 x 2 x 2), single center

Doses evaluated: Study evaluated the effectiveness of single doses of placebo and seven different formulations of oral nasal decongestants:

PEH: 10 mg
PPA: 10 mg
BR: 8 mg
PEH + PPA
PEH + BR
PPA + BR
PEH + PPA + BR

Study population: Eight subjects (5 males and 3 females) with a diagnosis of perennial allergic rhinitis of 2 to 6 years duration. Ages ranged from 8 to 60 years.

Exclusion criteria: Not specified

Number of subjects: The 8 subjects received each of 8 treatments on 8 separate days

Measurements:

NAR: Investigators measured both inspirational and expirational resistance (5 readings at each observation time). Measurements were made at baseline and 30, 60, and 120 minutes post-treatment and were expressed in pressure increments (mm H_2O) at a constant air flow rate of 0.5 L/s). Arithmetic means were determined for 5 replicate determinations of NAR at each observational period.

Pulse rate and blood pressure: No information on how these data were collected.

Adverse events: No information on how these data were collected.

Data analysis

NAR: Analysis of variance was used to evaluate differences between treatment group means.

Pulse rate and blood pressure: Not specified.

Results:

NAR: PEH, 10 mg, reduced NAR relative to placebo at each of three post-treatment time points but not significantly. The reduction in NAR attributable to treatment with PEH was numerically, but not significantly, greater than that due to treatment with PPA at 30 and 60 min. The two treatments were similar at 2 hours post-treatment.

Pulse rate and blood pressure: No clinically significant effect of any treatment on pulse rate or blood pressure in any subject.

Adverse events: None were reported

Reviewer's comments: *Effectiveness of PEH as measured objectively by reduction in NAR was studied at only one of six sites. Investigators at site 0401 determined that NAR was significantly reduced relative to placebo at 30 – 180 minutes after the first dose of PEH was administered. The investigators reported that the effectiveness of PEH as measured objectively was comparable to that of PPA measured by the same method. Furthermore the investigators claimed that the objective and subjective evaluations produced similar results. In fact, the subjective results at this site were not as robust as the objective ones. Both the subjects and the investigators found that PEH reduced the severity of stuffy nose symptoms at 72 hours and of sneezing at 24 and 48 hours (subjects) and 72 hours (investigators). These changes were not significant ($p < 0.1$)*

Only data collected at site 0401 (12 subjects) showed PEH to be significantly superior to placebo as a nasal decongestant. There was no evidence from the pooled studies (66 subjects) that PEH produced significant relief of patient- or investigator-reported symptoms of congestion. The investigators note that "there was a statistically significant ($p < 0.01$) treatment by site interaction for both the subject and investigator overall subjective evaluations at 72 hours", but that this "interaction became insignificant when site 0401 was excluded from the analysis."

According to the investigators, there were no "clinically significant" effects on pulse rate or blood pressure.

3.1.2.6. Unpublished Study: "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" (Schering-Plough)
Submitted to Docket No. 2007P-0047 on February 1, 2007 as an attachment to CP1

Reviewer's comment*: This study is available and was reviewed in abstract form only at Clinical Trials.gov: http://clinicaltrials.gov/ct/show/NCT00276016.*

Study objective:
Primary—
to evaluate the effect of a PEH 12-mg immediate-release capsule on nasal congestion compared with that of placebo in subjects with seasonal allergic rhinitis (SAR) who were exposed to pollen for 6 hours in the Vienna Challenge Chamber (VCC).
Secondary—
1. to estimate the effect of a pseudoephedrine (PSE) 60 mg immediate-release tablet on nasal congestion over a 6-hour period relative to placebo.

2. to evaluate the safety profile of post-dose adverse events and vital signs compared with pre-dose evaluations.

Study design: This was a randomized, investigator-blind, placebo-controlled, three-way crossover study.

Doses evaluated: Phenylephrine (PEH) immediate-release 12 mg capsules, pseudoephrine (PSE) immediate-release tablets 60 mg tablets, and placebo capsules (identity

Study population: subjects 18 to 55 years of age, any race, 2 year history of SAR due to grass pollen

Number of subjects: 39 enrolled: 38 subjects completed the study

Measurements: Data and information is insufficient to determine the exact measurements taken. However, results were given in terms of "nasal congestion score" apparently derived from the subjects' subjective symptom scores.

Data Analysis: Analysis of variance was used to give linear contrast of the treatment means for pairwise comparisons. A 2-sided test at alpha = 0.05 is used to detect a change from baseline of nasal congestion score assuming a standard of 0.05 to compare phenylephrine vs placebo. The study was powered at 80% to detect a difference of at least 0.36 points in change from baseline of nasal congestion score between phenylephrine and place at an alpha =0.05, 2-sided test.

Results: Phenylephrine was compared with PSE to assess relative efficacy. However, phenylephrine was not significantly different from placebo in decreasing nasal congestion scores from baseline. The averaged first 6-hour post baseline mean percent change from baseline in nasal congestion score was --7.1% for PEH treatment compared with --2.2% for placebo treatment (P = 0.56). With a decreasing nasal congestion score of --21.7% PSE was significantly more effective than placebo (P<0.01) and phenylephrine (P = 0.01).

Phenylephrine, 12 mg single taken in a single dose Phenylephrine showed 17% of the decongestant activity demonstrated by PSE over placebo. However, as noted by the investigators, when the results were evaluated by phase, the phase 1 difference between phenylephrine and place (0.31-0.10) was 64% of the difference between PSE and placebo (0.43-0.10). This observation led the investigator to hypothesize that crossover study designs that include PSE may not accurately reflect the treatment sizes that would be seen if the study were conducted as a parallel-group design. Recall biases inherent in the crossver design may have influenced the result for phenylephrine.

***Reviewer's comments**: The study provides insufficient detail to assess the validity of the results.*

3.2. SAFETY

3.2.1. Studies cited in the ANPR

3.2.1.1. Keys, A. and A. Violante, "The Cardio-Circulatory Effects in Man of Neo-Synephrine (1-alpha-hydroxy-beta-methylamino-3-hydroxy-ethylbenzene hydrochloride," *Journal of Clinical Investigation* 21:1-12, 1942.

Study objective: Evaluation of the effects of subcutaneous and intravenous injections and oral administration of Neo-Synephrine (PEH) on pulse rate and blood pressure

Reviewer's comment: *This review focuses on the safety results reported in association with oral administration of PEH only.*

Study design: Subjects were given PEH orally and monitored for changes in pulse rate and blood pressure relative to baseline values.

Doses evaluated: 250 mg PEH

Study population: There were 48 subjects in the study. Thirty-nine were men and nine were women. Subjects ranged in age from 16 to 60 years of age but "the majority were from 18 to 30." No other subject demographics were provided.

Number of subjects: 7

Measurements: Pulse rate and supine blood pressure readings were made for 4 hours at frequent intervals following administration of PEH.

Data Analysis: Individual measurements were pooled and the means determined at each post-medication time interval. There is no discussion of any statistical analysis performed on the data.

Results: Investigators report the following mean changes, (n = 7):

- Pulse rate – decline from 67 to 46
- Systolic blood pressure – increase from 112 to 143
- Diastolic blood pressure – increase from 71 to 96

Maximal effects for the above occurred about 40 minutes after administration.

Reviewer's comments: *The investigators chose an oral dose of 250 mg of PEH, because this was considered "roughly the equivalent of 5 mg given subcutaneously." This dose is 2.5 times greater than the largest oral dose used in other studies reviewed by the panel and is ten times greater than the dose proposed by the petitioner in CP1. It is interesting to note that the authors conclude that the threshold dose for Neo-Synephrine (50 mg) is 6 times lower than the upper limit for a safe and comfortable dose (300 mg) The article*

goes on to say that with rare exceptions, no sensations or symptoms other than pilomotor excitation are elicited by dosages below300 mg.

3.2.1.2. June 1968 Memo to Bird, J.G. from H. Stander.

Unpublished study "Analysis of Blood Pressure and Pulse Results From Subjects Given Placebo, Neo-Synephrine®, and Phenylpropanolamine, Orally"

Study objective: Test three doses of Neo-Synephrine (PEH), an active control, and a placebo for their effects on pulse rate and blood pressure

Study design: Randomized, double-blind, latin square design, with placebo and active controls

Doses evaluated: Study evaluated the effectiveness of single doses of two oral nasal decongestant ingredients:

Phenylephrine HCl (Neo-Synephrine (PEH): 15, 20, and 25 mg
Phenylpropanolamine HCl (PPA): 50 mg

Study population: Twenty subjects. Demographics were not provided

Number of subjects: Twenty subjects received each of four medications and placebo over five test periods

Measurements: Three pre-medication (40, 20, and 0 min) and four post-medication (15, 30, 60, and 120 min) pulse rate and blood pressure readings were taken

Data analysis: Mean fractional changes (relative to baseline) were calculated at each post-medication time point and compared to the corresponding placebo values by analysis of variance.

Results:

Pulse rate: All treatments including placebo resulted in decreased pulse rates at every post-medication time point. PEH significantly decreased mean pulse rates at the 30 min post-medication time point for the 15 mg dose ($p = 0.01$) and for the 25 mg dose ($p = 0.05$). No significant decreases in pulse rate were noted for either 20 mg PEH or 50 mg PPA. Maximal effect on pulse rate for all doses was seen at approximately 60 minutes.

Blood pressure: Mean diastolic blood pressure readings were elevated at every time point for all treatments including placebo, but significantly only at the 120 minute time point for 15 mg PEH ($p = 0.05$). Mean systolic blood pressure readings were significantly elevated following treatment only with PPA at the 60 and 120 min time points ($p = 0.01$ in both cases). The trend of the systolic and diastolic blood pressure readings were still increasing at the final time point (120 min).

Reviewer's comments: *In this study no consistent effect of PEH on either pulse or blood pressure was demonstrated. The minimal changes that were observed were not dose-related.*

3.2.1.3. January 1967 Memo to Luduena form H. Stander.

Unpublished study "EP 14. Analysis of Blood Pressure and Pulse Results from Subjects Given Placebo and Neo-Synephrine®, Orally"

Study objective: Test four doses of Neo-Synephrine (PEH) and a placebo for their effects on pulse rate and blood pressure

Study design: Randomized, double-blind, latin square design, with placebo and active controls

Doses evaluated: Study evaluated the effectiveness of single doses of oral PEH at 3 doses: 10, 25, 50, and 100 mg

Study population: Twenty subjects. Demographics were not provided

Number of subjects: Twenty subjects received each of the four doses of PEH and placebo over five test periods

Measurements: Three pre-medication (40, 20, and 0 min.) and four post-medication (15, 30, 60, and 120 min) pulse rate and blood pressure readings were taken

Data analysis: Mean fractional changes (relative to baseline) were calculated at each post-medication time point and compared to the corresponding placebo values by analysis of variance. An analysis of the three pre-medication readings for pulse and blood pressure showed no significant differences between the 20 and 0 minute readings. There was, however, a significant difference between these means and the 40 minute means. Consequently, the 40 minute means were not used in the calculation of post-medication results.

Results:

Pulse rate: All treatments including placebo resulted in decreased pulse rates at every post-medication time point. PEH significantly decreased mean pulse rates at the 30 min post-medication time point for the 100 mg dose ($p = 0.05$) and at the 60 min time point for the 25 ($p = 0.05$), 50 ($p = 0.01$), and 100 mg ($p = 0.01$) doses. Maximal effect on pulse rate for all doses was seen at approximately 60 minutes.

Blood pressure: Mean systolic blood pressure readings were significantly elevated following treatment only with the highest dose of PEH (100 mg) at the 30 and 60 min time points ($p = 0.05$ in both cases). Mean diastolic blood pressure readings were not significantly elevated at any time point for any dose. The trend of the

systolic blood pressure readings were still increasing at the final time point (120 min).

Reviewer's comments: *In this study 100 mg clearly produced effects on pulse and systolic blood pressure. The effects of lower doses are less clear with no apparent dose response.*

3.2.1.4. June 1968 Memo to Hulme from J.G. Bird.

Unpublished study Neo-Synephrine Oral – In-House Pulse and Blood Pressure Study

Reviewer's comments: *This reference is a further discussion of the clinical significance of the findings in ANPR Ref. 2 above. This reviewer concurs with Dr. Bird (principal investigator) in his assessment that "no effects have, within the limits of this experiment, been reliably demonstrated following single oral doses of Neo-Synephrine Hydrochloride, as regards pulse rates and blood pressure."*

3.2.2. Relevant studies not cited in the ANPR

3.2.2.1 Thomas, S. H. L., K. L. Clark, R. Allen, and S. E. Smith, "A comparison of the cardiovascular effects of phenylpropanolamine and phenylephrine containing proprietary cold remedies," *British Journal of Clinical Pharmacology*, 32:705-711, 1991

Study objective: Evaluate the cardiovascular effects of two OTC proprietary cold remedies, one containing phenylpropanolamine, and the other (R)-phenylephrine hydrochloride.

Study Design: Randomized, double blind, 3-way crossover design.

Doses evaluated: Study evaluated the safety of two OTC combination cold products:
Mu-cron (2 tablets/dose)
Phenylpropanolamine (PPA), 50 mg
Paracetamol (acetaminophen), 1 g
Boots Cold Relief (2 tablets/dose)
Phenylephrine (PEH), 10 mg
Paracetamol (acetaminophen), 0.8 g
Ascorbic acid, 100 mg
Caffeine, 60 mg
Boots Pain Relief (2 tablets/dose)
Paracetamol (acetaminophen), 1 g
Caffeine, 60 mg

Reviewer's comments*: The Boots Pain Relief product was included as a placebo.*

Study Population: 16 healthy subjects:

Ages: 20 – 23 years; mean 21
Weights: 47 – 86 kg; mean 69 kg
Heights: 1.56 – 1.88 m; mean 1.70 m
Exclusion: prior history of cardiovascular or respiratory disease

Number of subjects: 16 subjects

Measurements:

Pharmacokinetics: Area under the effect-time curve between 0 and 4 hours..

Pulse rate and blood pressure: Quintuplicate measurements were taken on supine patients 30 minutes and immediately before treatment as well as 30, 60, 90, 120, 180, and 240 minutes after dosing.

Stroke volume, cardiac output and peripheral resistance: Measured non-invasively using a NCCOM3 (BoMed) Impedance Cardiograph. Ten separate impedance measurements were made at each time point (see pulse rate and blood pressure time points).

Forearm bloodflow and forearm vascular resistance: Measured using a conventional strain gauge plethysmography technique taking quintuplicate measurements at each time point. (n = for these measurements).

Data analysis The hemodynamic effects of each treatment were analyzed using a two-way repeated measures analysis of variance (ANOVA) comparing measures made at each time point with those taken immediately prior to drug administration (time 0). In addition, the changes induced by each of the drugs (post-drug value minus time 0 value) were compared at each time point using a repeated measures ANOVA with Duncan's multiple range test. A similar analysis of variance method was used to compare areas under the pharmacodynamic effect-time curves between 0 and 4 hours.

Results:

Pulse rate and blood pressure: Treatment with Boots Cold relief containing 10 mg PEH did not result in significant changes in pulse rate or blood pressure relative to baseline (t = 0). Treatment with the product containing PPA did not significantly affect pulse rate relative to baseline but significantly increased both systolic and diastolic blood pressure ($p < 0.05$ in both cases).

Stroke volume, cardiac output and peripheral resistance: Stoke volume, and cardiac output was not significantly affected by treatment with the PEH-containing product relative to baseline. There was a "small but significant" increase in total peripheral resistance relative to the product not containing PEH ($p < 0.05$). This effect was maximal 30 to 60 minutes after administration and was associated with a small but significant increase in AUC. Stroke volume and peripheral resistance

were significantly increased by treatment with the PPA-containing product relative to baseline ($p < 0.05$). Cardiac output was not significantly affected by treatment with the PPA-containing product.

Forearm bloodflow and forearm vascular resistance: These parameters were not significantly affected by treatment with the PEH-containing product but were significantly affected, relative to baseline values, by treatment with the PPA-containing product.

***Reviewer's comments**: This study finds that a PEH-containing product (10 mg PEH) has minimal cardiovascular effects. The PEH-containing product caused a small and short-lived, but significant, increase in total peripheral resistance measured over 4 hours. There were no other significant or consistent effects attributable to PEH on the other cardiovascular parameters that were measured.*

4. PHARMACOKINETICS

4.1. PHENYEPHRINE HYDROCHLORIDE (PEH)

What we know about the pharmacokinetics of orally-administered phenylephrine (PE) is based on single dose studies conducted more than 20 years ago. A review by Kanfer et al.[29] cites three studies conducted between 1963 and 1981. All three of these studies evaluated the pharmacokinetics of tritiated PE and could not readily distinguish parent PE from its conjugated metabolites. None of the studies meet current FDA standards for determining pharmacokinetic parameters.

Absorption
PE taken orally is completely absorbed and extensively metabolized pre-systemically with most metabolism occurring within enterocytes in the gut wall. Kanfer et al. note that only about 38% of PE reaches the systemic circulation as a result of "extensive first-pass metabolism" (see below). Furthermore, there can be a great deal of interindividual and even intraindividual variability in bioavailability.[30,31] Maximum concentrations of PE, in the studies cited by Kanfer et al., ranged from 0.9 to 298 ng/ml (1mg and 7.8 mg doses of PE base respectively) and occurred between 1.0 to 1.3 hours post-administration.

Distribution
Following oral administration, serum levels of ^{3}H-PE decline monoexponentially. This is in contrast to the biexponential decline observed following intravenous (IV) administration.[29] Kanfer et al. note that there are no data on the extent of protein binding, and that "penetration into the brain appears to be minimal.[29]"

Metabolism
As noted above, orally-administered PE is extensively metabolized in the gut wall. Kanfer et al. note that metabolism also takes place in the liver. Metabolites are primarily sulfate conjugates formed in the gut wall. Some glucuronidation of PE also occurs.

Noteworthy too is deamination by monoamine oxidase (MAO). The Advisory Review Panel evaluating OTC nasal decongestant ingredients noted that oral PE should **not** be taken by patients taking MAO inhibitors, because concurrent use of PE and MAO inhibitors can induce "clinically significant cardiovascular responses."[32]

Elimination
Both parent PE and its metabolites are excreted almost entirely in the urine. Kanfer et al. note that the elimination half-life of PE after both IV and oral administration varies between 2.1 and 3.4 hours. Hengstmann and Gorozny report the $t_{1/2}$ to be 2.5 hours following oral administration and 2.6 hours following IV administration (1 mg doses in both cases).[33]

Special Populations
Kanfer et al. note that there are no pharmacokinetic data in the pediatric population and there is only minimal data in geriatric patients.[31] One study examining the pharmacokinetics of PE in combination with acrivastine is noted in the review by Kanfer et al.[31] Elimination half-life was reported to be about 45% longer in elderly patients and the apparent volume of distribution was estimated to be about 25% higher in elderly vs. younger patients.

4.2 PHENYLEPHRINE BITARTRATE (PEB)

Reviewer's comment: *As noted above, PEB and PEH have comparable bioavailability profiles from pharmacokinetic studies. An evaluation of that data is provided here.*

An Open-Label, Randomized, Multiple Dose, Four-Way Crossover Study Evaluating the Pharmacokinetics of Effervescent Phenylephrine Hydrochloride, Effervescent Phenylephrine Bitartrate, Encapsulated Phenylephrine Hydrochloride, and Encapsulated Phenylephrine Bitartrate in Normal Healthy Volunteers

Study objective: The objective of this study was to evaluate the pharmacokinetic profiles of an effervescent phenylephrine HCl, an effervescent phenylephrine bitartrate, an encapsulated phenylephrine HCI 10 mg dose, and an encapsulated phenylephrine bitartrate in normal healthy volunteers.

Study design: Open-label, randomized, four-way crossover, multiple dose study. This was a Phase I, single-center study in healthy volunteers.

Doses evaluated:
- 10 mg effervescent phenylephrine HCl (5 mg x 2)
- 15.6 mg effervescent phenylephrine bitartrate (7.8 mg x 2)
- 10 mg encapsulated phenylephrine HCl
- 15.6 mg encapsulated phenylephrine bitartrate

Each treatment was administered at 0, 4, 8 and 12 hours of each period for a total of 4 doses.

Study population: All subjects, male and female, were in general good health as evidenced by medical history, physical examination, 12-lead electrocardiogram, and clinical laboratory results including hematology, chemistry, urinalysis, Hepatitis B/C, HIV, alcohol and drug screening. Female subjects had a negative pregnancy screen and were either post-menopausal or used and agreed to continue to use an acceptable form of birth control. No other subject demographics were provided.

Number of subjects: 25

Measurements: Blood samples (5 mL) for the determination of phenylephrine in human plasma were collected at the following time points from the initial dose: 0 hour (pre-dose 10-15 minutes), and 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 8.0, 12.0, 12.25, 12.5, 13.0, 14.0, 15.0, 16.0, 20.0 and 28.0 hours. At 1.5, 4, 8 and 12 hours an additional 2 mL sample was obtained for creatinine clearance analysis.

From the initial dose administered until the end of each treatment period, all urine voided was collected and pooled (time intervals: 0-3, 3-5, 5-7, 7-9, 9-l 1, 11-13, 13-17, 17-21, 21-25, 25-28 hours). From each interval a 10 mL sample was obtained for determination of phenylephrine in human urine. In addition, a 5 mL sample was obtained from the 0-3, 3-5, 7-9 and 11-13 hour intervals for creatinine clearance analysis.

Data Analysis: This trial followed a 4 x 4 Latin Square (William's) design, which was balanced for treatment and sequence effects. An analysis of variance (ANOVA) model with sequence, subject (sequence), period and treatment as factors was utilized. For statistical comparisons, the log-transformed variables C_{min}, C_{max}, and AUC were used. The interval for 0-4 hours was defined as t_0. The standard error and mean difference between log-transformed variables were calculated, and 90% confidence intervals constructed. In addition, analysis of the untransformed variables C_{min}, C_{max}, %, fluctuation, K_e, CL_R, CL/F, AUC, and $t_{1/2}$ were tabulated.

Results: A review of the pharmacokinetic data for total phenylephrine in plasma for each subject and treatment plus the means for each treatment along with selected pharmacokinetic parameters showed that all 4 treatments were essentially identical. This indicates there is no effect by the salt form used and that the hydrochloride is equivalent to the bitartrate when dosed in the same dosage form.

	PEH effervescent	PEB effervescent	PEH encapsulated	PEB encapsulated
C_{max}	206.79	206.89	222.15	201.54
T_{max}	1.1	1.0	1.4	1.4

There are however differences between the solution and the capsule dosage forms. This is consistent with more rapid gastric emptying and therefore earlier and faster absorption

from the solution than the capsule. For the first dose of solution, the phenylephrine appears in the plasma earlier and rises to its C_{max} at an earlier time. The capsule doses start later, but rise at about the same rate as the solution. Over the 4 hours the area (AUC) is about the same for both solutions and capsules.

Reviewer's comments: *This study demonstrated the bio-equivalence of phenylephrine hydrochloride and phenylephrine bitartrate. It was the primary data source used to add phenylephrine bitartrate to the Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic monograph.*

5. OVERALL ASSESSMENT

5.1. EFFECTIVENESS

Half the studies of PEH at the 10 mg dose (seven studies) did not demonstrate a statistically significant effect on nasal airway resistance or symptom scores. The data for the 25 mg dose are similar. In 6 of 10 studies that evaluated a 25 mg dose there was a statistically significant effect. There were, however, positive trends in the remaining four studies.

Under the regulations data from two adequate and well-controlled studies would be sufficient to support the effectiveness of PEH. Unfortunately, these studies have known design and reporting limitations. These deficiencies are described in detail in this review, but, in general, the studies are small and lacking many details necessary to provide a convincing demonstration of effectiveness. Given the similar bioavailability of PEB conclusions about the effectiveness of this salt can be drawn.

5.2. SAFETY

The data suggest that doses significantly higher than 25 mg are necessary to cause the cardiovascular effects that are characteristic of sympathomimetic drugs, e.g., increases in blood pressure. In the studies evaluated there were no consistent cardiovascular effects for PEH at the 10 or 25 mg doses. There were also no significant adverse events reported for any dose of PEH in the studies evaluated. Based on the available data and the the similar bioavailability of the bitartrate salt, there does not appear to be any oblivious safety concerns for the petitioners' requested increase in doses for PEH and PEB.

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7. ATTACHMENT

Final Report of the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee, October 18-19, 2007.

Statistical Review

(Citizen Petition/Phenylephrine)

Date: 10/31/07

From: Stan Lin, PhD, Division of Biometrics IV, Office of Biostatistics

Through: M. Huque, PhD, Director, Division of Biometrics IV, Office of Biostatistics

Subject: Review of Citizen's Petition on the effectiveness of Phenylephrine on nasal decongestion and CHPA analysis of the single dose 10 mg and other accompanying documents

To: Susan Johnson PhD, Associate Director, Office of Nonprescription Products

Executive Summary

The current citizen petition (CP) was based on a meta-analysis of some of the studies previously reviewed by an advisory panel in 1976, However, the clinical endpoint used for the meta-analysis is the maximal reduction in nasal airway resistance measured periodically during the first two hours after administration of a single dose of 10 mg phenylephrine hydrochloride (PEH). It is not clear whether the maximal reduction in nasal airway resistance is a validated clinical endpoint for separation of drug effect. Because this endpoint was not mentioned in the original studies, it is doubtful it was the basis for the original design and analysis of the studies included in the meta-analysis. Therefore, it is not clear whether this endpoint should form the basis for a re-evaluation of the efficacy of the 10 mg PEH. This is because a meta-analysis is always a post-hoc re-assembly or re-analysis of already existing data. Especially when a new endpoint is used for the re-analysis, it can help to formulate new hypothesis, but it rarely can be relied upon as new confirmatory evidence for efficacy or the lack of it, without new data.

Of the original studies included in both the CP meta-analysis and the Consumer Healthcare Products Association (CHPA) meta-analysis in response to the CP, there is evidence of treatment by study interaction at the different time points where NAR was measured. This indicates certain heterogeneity in the studies and their outcomes, and the heterogeneity potentially limits the poolability of data across the studies. Of the individual studies, they were of similar (small) sizes. Some show efficacy and some show lack of efficacy. Of the studies which showed efficacy for the 10 mg PEH, two were conducted at the same site, the Elizabeth Biochemical Laboratory. The same laboratory also conducted efficacy of other dose of PEH. All of the Elizabeth studies showed relatively strong efficacy whatever dose was studied. With limited replication of positive finding from other sites, the lack of multicenter representation of the generally small studies at Elizabeth Biochemical Laboratory can limit the generalizability of their

results. If this is deemed to be relevant to the re-evaluation of efficacy of PEH 10 mg, then the CP might have merit generating new hypothesis with the endpoint used in its meta-analysis, and new studies will need to be conducted accordingly.

Study AHR-4010-3, submitted as part of the EC140 submission to the docket, does not add very much to the determination of efficacy of PEH 10 mg. This is because only one center, as a substudy, randomized 12 subjects to the PEH 10 mg, and collected NAR data for up to 3 hours. However, the endpoint used for the study, total NAR, is different from the CP mentioned studies.

Introduction

The FDA currently recognizes phenylephrine hydrochloride (PEH) and phenylephrine bitartrate (PEB) as generally recognized as safe and effective (GRASE) nonprescription oral nasal decongestants. Current maximal does of PEH and PEB were established through FDA'S Over-the-Counter Drug Review. In 1976, the FDA published an advance notice of proposed rule making in which the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products proposed PEH to be GRASE. The Panel reviewed a total of 13 studies and concluded that seven of the studies demonstrated PEH to be effective in clearing the nasal airway (i.e., reducing nasal airway resistance, NAR). The other six studies did not show PEH to be effective at reducing nasal airway resistance. The FDA issued a proposed rule and 1985 and final rule (FR) in 1994 adding PEH to the monograph as a GRASE active ingredient.

ONP received a citizen petition (CP) from Drs. Leslie Hendeles and Randy Hatton earlier this year. The CP authors contend that oral phenylephrine (PE) is ineffective as a nasal decongestant at maximum allowable monograph doses based on the following:

- Poor oral bioavailability
- Lack of effectiveness of 10 mg phenylephrine hydrochloride (PEH) in a randomized, double-blind, placebo-controlled, crossover study
- Meta-analysis of eight studies previously reviewed by an FDA advisory review panel
- Clinical study conducted by Schering-Plough in early 2006
- Literature reviews

The CP requests that the FDA do two things:

- Increase the maximum allowable doses of PEH from 10 to 25 mg
- Limit use of PEH and PEB to adults and children 12 and over.

Two relevant documents contending that PEH is an effective oral nasal decongestant have been posted in the public docket. Both of these documents were added to the

docket since the July 2006 publication of an article by Hendeles and Hatton[1] which reported that 10 mg PEH is not an effective nasal decongestant:

- EMC140 from Wyeth Consumer Healthcare, containing three previously unpublished studies conducted between 1967 and 1983.
- C251 from the Consumer Healthcare Products Association (CHPA), containing a meta-analysis of seven of the eight studies included in the CP meta-analysis. (C253 is essentially C251 published in Clinical Therapeutics, Vol 29; June, 2007.)

The issue of PE (phenylephrine) effectiveness as an oral nasal decongestant has raised congressional interest. Representative Henry Waxman has written four letters to the FDA asking, among other things, that we bring this matter before an advisory committee. In response to both the CP and the planning of an advisory committee meeting, the ONP has assembled a review team including members from ONP, DPAP, and Biostatistics. This document presents findings from the statistical review.

Review Comments

For ease of cross-reference, the studies referred to in this review, and thus the studies referred to in the meta-analyses (CP and CHPA), are attached in a table at the back of this review.

Comment: None of the studies presented in this review was accompanied by its original study protocol. The original protocol-specified primary efficacy endpoint(s) is therefore unknown to this reviewer. As a result, it's not clear that using the maximal reduction of NAR as an endpoint to re-analyze the same set of data for an efficacy determination, as in the meta-analysis of Hatton etc., would be wholly appropriate (for confirmatory evidence).

Comment: The Hatton etc. meta-analysis focused on measurements between 0 and 120 minutes from the data measured in the studies. Furthermore, the maximal reduction of NAR from baseline during that time period can be at different time points for each subject and also among the treatments, including the placebo treatment. Example of this can be seen from the time course of the average NAR measurements, as depicted in Figure1 in the appendix. It appears several of the PE group showed maximal reduction occurred on or before 60 minutes, whereas for the placebo group, most of the curves continued to decline. Therefore, a between-treatment comparison of the average maximum reductions could be for at different time points (this was not clearly described in the meta-analysis.) Furthermore, it is more likely that the comparison of average maximum reductions would result in a treatment difference that is less statistically significant, merely because it is a maximum compared to a maximum, so that it may be a comparison of a later placebo response to an earlier treatment response and that difference is likely smaller than if the responses at a fixed time point were compared. In

[1] J Allerg Clin Immunol 118:279-280 (2006)

addition, it is possible that individual maximum of a set of measurements has larger variance than for the measurements themselves, which would also make a treatment comparison less statistically significant.

Comment: The CHPA meta-analysis included only the "cross-over" studies (a type of clinical study where the intent is to have each subject serves as his/her own control). There were 7 such studies. The pool from which the studies were selected is the same set of studies as that included in the meta-analysis of Hatton etc., and which is the same set of studies reviewed by the 1976 FDA panel. This meta-analysis included a maximum of 113 subjects from the 7 studies. Compared to the Hatton etc. meta-analysis, the CHPA meta-analysis did not include the one parallel group study (the 1975 Cohen, B.M. and Kuebler W.F. study which was a parallel comparison study.)

The CHPA meta-analysis included different analysis of variance models for the meta-analysis. One was a fixed effects model in which study was assumed a fixed effect, with patient a random factor with unequal within-subject and between subject variance components across studies. Another model used was a random effects model, with baseline, patient, treatment, study, and treatment by study interaction in the model, but with patient, study, and treatment by study interaction considered random. The primary efficacy time point was selected to be 30 and 60 minutes after dosing, (i.e., specified for the meta-analysis,) although if data was available for other time points, analyses for these other time points were also made.

Along with the meta-analysis, the individual studies were also re-analyzed with an ANCOVA model incorporating baseline NAR. CHPA results for both this individual study re-analysis and the meta-analysis are summarized in tables (I & II) in the back. The reanalysis show four of the crossover studies showed significant difference in NAR reductions compared to placebo, and the other three did not, at the chosen primary time points and some others. Table I also includes summary results for a parallel group study, which was not included in the meta-analysis because of its study design difference, and also a different NAR measurement method.

Comment: From an examination of the Table I, it is not surprising that the 7 crossover studies show a significant treatment by study interaction. The Elizabeth Biochemical studies generally show a much larger difference from placebo than the other studies of comparable or larger studies. It is not clear from the information available on the studies, what causes the heterogeneity in effect. However, this heterogeneity poses a question to the validity of the meta-analyses, which combine the heterogeneous individual study results. The comparatively large treatment effects from the Elizabeth Biochemical studies likely overwhelm the results from the other studies to give positive results for the meta-analysis, which hides the much smaller or non-positive individual study results.

Without exception, meta-analysis is always performed when a group of prior studies is already available, usually diverse in enrollment, study design, conduct and efficacy endpoints. It is easy to see how meta-analysis is useful in safety evaluation of a

treatment, or to discover potential new efficacy hypothesis about a treatment. However, because the studies included in a meta-analysis are usually already in the public domain, having been known to the meta-analytic investigator, it is hard to imagine that hypotheses evaluated against the data of the studies in the meta-analysis are not driven by the knowledge of the data. In this sense, result of a meta-analysis is not confirmatory evidence in nature.

As for the Schering-Plough study mentioned in the CP, it was a randomized, investigator-blind, placebo-controlled, three-way crossover, single center study of phenylephrine, PSE, and placebo in subject with seasonal allergic rhinitis who have been exposed to pollen fro 6 hours in the Vienna Challenge Chamber. Thirty nine subjects received at least one dose of treatment, 38 completed treatments, receiving all three treatment sequences. Results showed no significant difference from placebo in subjectively evaluated nasal decongestant effect at 6 hours, which was the primary efficacy variable.

Comment: EMC140 of Wyeth Consumer Healthcare provides a review of three previously unpublished studies containing PE 10 mg, conducted between 1967 and 1983.

Study AHR-GIA, was a randomized, single dose, double-blind, partial factorial, parallel group, single-center study conducted in 48 subjects altogether (age 19-74) with nasal congestion due to an upper respiratory infection. The study was conducted in 1973. Subjects were enrolled within 24-72 hours of the onset of symptoms. There was no placebo control and there were 8 subjects randomized to the PE 10 mg group.

Study AHR-4010-3 was a randomized, six-center, multiple-dose, double-blind, and parallel group study conducted in subjects with nasal congestion due to an upper respiratory infection conducted in 1983. Subjects were enrolled within 48 hours of the onset of symptoms. Subjects were required to take study medication every 4 hours over a 72-hour period. The study evaluated PE 10 mg, PPA 25 mg, PE 5 mg+PPA12.5 mg, and placebo. Using a four-point categorical scale (0=not present, 1=mild, 2=moderate, 3=marked), subjective evaluations of runny nose, stuffy nose, sneezing and headache were provided by the subject at baseline, and at 24, 48 and 72 hours after taking the first dose of study medication, and by the Investigator at baseline and at 72 hours. Also using 4 and 5-point categorical scales (1=marked benefit, 2=moderate benefit, 3=minimal benefit, 4=no benefit, or 5=worse), both the subject and the investigator provided an overall evaluation of therapeutic effect at the end of the evaluation period. In addition to the patient and investigator subjective assessments, only subjects enrolled at one study site (site 0401) underwent objective assessments of nasal inspiratory and expiratory resistance at 15, 30, and 45 minutes, and 1-4 hours after the first dose of medication. The study enrolled a total of 274 subjects (ages 18-77 years) at 6 sites, including 48 at site 0401, where 12 subject were randomized to each of the four treatment groups. PE 10 mg was found to be statistically significantly better than placebo for total nasal airway resistance at 30-180 minutes after the first dose was

administered. (Note, no details provided and *total* nasal airway resistance was not clearly defined.)

Study #7032 was conducted in 1967. This was a randomized, single-dose, single-blind, placebo controlled, full-factorial, 8-way crossover, single-center study conducted in 8 subjects (ages 8-60) with stable or chronic nasal congestion due to allergy. During each treatment period, NAR was measured at baseline and at 30, 60, and 120 minutes after dosing using a Respiron instrument. Subjects were required to have a NAR reading of at least 10 mm at baseline. Results show no significant between treatment differences in NAR was found.

Thus, of the three unpublished studies mentioned in EMC140, one potentially showed significant difference from placebo in *total* NAR, at the one site that measured NAR. However, the overall study only showed at best a marginal effect of PE on subjective measurements of nasal decongestion.

Summary:

The CP is based on a meta-analysis of some of the studies previously reviewed by an advisory panel. The clinical/laboratory endpoint used in the CP meta-analysis is the maximal reduction over time in NAR. More than likely this was not the endpoint used in the planning or analysis of the original studies. Because difference in maximal reduction might need larger sample size to show statistical significance, and because the heterogeneity in NAR reduction among the studies, it is not surprising the meta-analysis mentioned in the CP did not show a statistically significant difference in maxiaml NAR reduction after a single dose of phenylephrine 10 mg. The same heterogeneity might also call into question the pooling together of the studies for either of the meta-analyses, the CP one or the CHPA one. Without the meta-analyses, then one is left with the examination of the individual studies. The majority of the studies were of very small size, and about equal numbers showing a significant reduction in NAR as not, at time points 15, 30, 45, 60, 90 and 120 minutes, where the majority of the studies had recordation of data.

Even though the two meta-analyses were about the efficacy of the PE 10 mg, it is not clear that its onset and duration of decongestant effect were ever clearly characterized. Both of which can affect the effective dosing regimen. On the other hand, it was mentioned in the meta-analyses that not all of the studies in the pool that were evaluated by the 1976 panel were included in the current analyses because of lacking of their data or details and which might have more information that could help to define these endpoints, (or efficacy).

It is worth noting that the meta-analysis effectively included no new data than those already examined by the 1976 panel. Most of the studies were single center, of sizes 15 or 16 with one which included 25 subjects per treatment. Among the studies conducted at the different laboratories, several also included the PE 25 mg. While some of the

studies did not demonstrate the efficacy for either dose, the five studies performed at the Elizabeth Biochemical Laboratory were all able to demonstrate a significant difference whenever either 10, 25 mg or both of the PE doses were studied. It may be simply that good laboratory procedures were followed more at this laboratory than others, but these were single-center studies and the results would be deemed more robust and more generalizable if they were multi-center studies.

11/4/07

Stan Lin, PhD,
Mathematical Statistician

Concurrence: 11/5/07
Mohammad Huque, Ph.D.
Director, Division of Biometrics,
Office of Biostatistics, OTS, CDER

cc: Debbie Lumpkins, Team Leader, ONP
Michael Koenig, ONP
Scott Furness, ONP
Walter Ellenberg, ONP

Table 1. Results of the reanalyses of the individual studies.

Study No. (Design)/ Statistic	Time After Dosing, min							
	15	30	45	60	90	120	180	240
1 (Crossover)[10]								
Treatment difference (95% CI)	-1.26 (-1.87 to -0.65)*	-3.11 (-3.97 to -2.26)*	-5.74 (-6.60 to -4.87)*	-5.44 (-6.64 to -4.25)*	-4.70 (-6.03 to -3.38)*	-3.44 (-4.91 to -1.96)*	NA	NA
2 (Crossover)[11]								
Treatment difference (95% CI)	-0.05 (-0.44 to 0.35)	-1.68 (-2.33 to -1.03)*	-3.51 (-4.38 to -2.65)*	-3.82 (-4.64 to -3.01)*	-2.90 (-3.65 to -2.15)*	-2.09 (-2.80 to -1.38)*	-1.17 (-1.71 to -0.63)*	-0.38 (-1.05 to 0.30)
3 (Crossover)[12]								
Treatment difference (95% CI)	-0.17 (-1.70 to 1.36)	-2.24 (-4.36 to -0.12)*	-1.90 (-4.53 to 0.73)	-3.14 (-7.01 to 0.74)	-4.75 (-8.90 to -0.59)*	-4.88 (-8.80 to -0.95)*	-6.81 (-11.09 to -2.52)*	-6.66 (-12.38 to -0.94)*
4 (Crossover)[13]								
Treatment difference (95% CI)	-0.13 (-1.85 to 1.60)	0.31 (-1.40 to 2.02)	0.13 (-2.47 to 2.74)	-1.81 (-4.90 to 1.29)	0.39 (-2.92 to 3.70)	1.05 (-3.22 to 5.31)	0.63 (-4.62 to 5.87)	0.68 (-5.75 to 7.12)
5 (Crossover)[14]								
Treatment difference (95% CI)	-0.58 (-1.93 to 0.77)	-0.21 (-2.44 to 2.03)	-0.07 (-2.46 to 2.31)	-0.13 (-2.75 to 2.48)	0.15 (-2.93 to 3.23)	0.93 (-2.19 to 4.05)	NA	NA
6 (Crossover)[15]								
Treatment difference (95% CI)	-0.57 (-2.82 to 1.68)	-0.06 (-3.29 to 3.17)	1.11 (-1.22 to 3.43)	1.53 (-2.37 to 5.43)	0.17 (-3.62 to 3.96)	2.70 (-2.45 to 7.84)	0.83 (-4.25 to 5.91)	-1.65 (-9.22 to 5.92)
7 (Crossover)[16]								
Treatment difference (95% CI)	0.99 (-0.98 to 2.95)	-0.36 (-3.61 to 2.89)	2.09 (-0.88 to 5.05)	1.44 (-2.81 to 5.70)	-0.18 (-4.00 to 3.63)	2.89 (-0.69 to 6.48)	1.49 (-1.05 to 4.02)	1.61 (-2.82 to 6.03)
8 (Parallel group)[17]								
Treatment difference (95% CI)	-0.60 (-1.14 to -0.07)*	-0.67 (-1.23 to -0.11)*	NA	-0.68 (-1.28 to -0.09)*	NA	-0.96 (-1.48 to -0.44)*	NA	NA

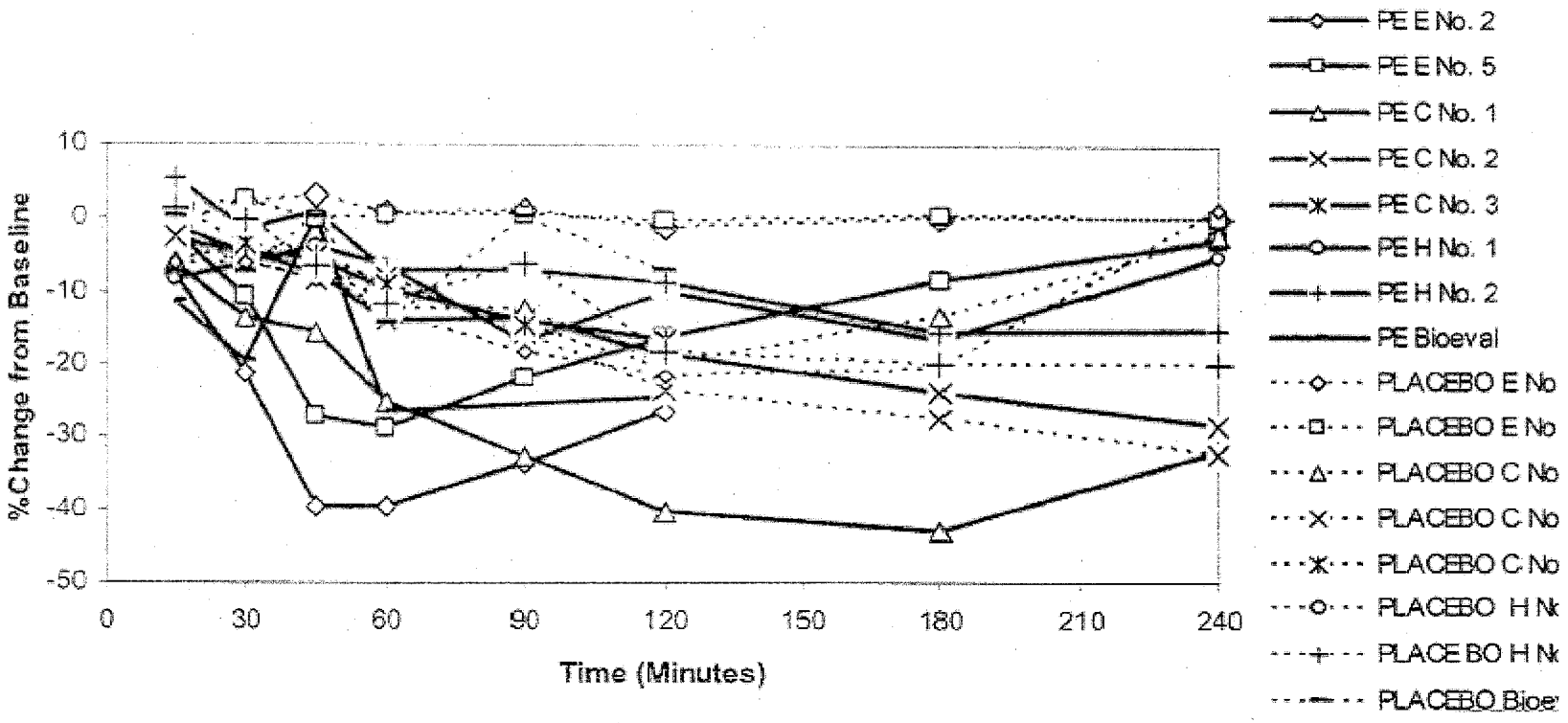
NA = not applicable (study design did not include this time point); 95% CI = lower and upper limits of the 95% CI for the treatment difference (phenylephrine – placebo).
*$P \leq 0.05$.

Table II: Results of the meta-analyses.

Model/Statistic	Time After Dosing, min							
	15	30	45	60	90	120	180	240
2b								
Treatment difference (95% CI)	-0.27 (-0.61 to 0.08)	-1.68 (-2.23 to -1.14)*	-2.71 (-3.57 to -1.85)*	-3.68 (-4.39 to -2.97)*	-2.80 (-3.54 to -2.06)*	-2.02 (-2.67 to -1.37)*	-1.09 (-1.61 to -0.58)*	-0.33 (-1.21 to 0.55)
3								
Treatment difference (95% CI)	-0.41 (-1.18 to 0.36)	-1.32 (-2.56 to -0.09)*	-1.38 (-3.51 to 0.74)	-2.30 (-4.34 to -0.26)*	-2.24 (-4.17 to -0.31)*	-1.01 (-3.42 to 1.40)	-0.95 (-4.85 to 2.96)	-0.32 (-1.21 to 0.57)

Model 2b = fixed-effects model, assuming patient as a random factor with unequal within-subject and between-subject variance components across studies; 95% CI = lower and upper limits of the 95% CI for the treatment difference (phenylephrine - placebo); model 3 = random-effects model with terms for baseline, patient, treatment, study, and treatment-by-study interaction, but with patient, study, and treatment-by-study interaction considered random.
*$P \leq 0.05$.

Figure 1 % Change from Baseline by Study and Time (minutes)



Cross-references of studies

Panel Rev'd	10mg (12 Studies, 5 Sig/pbo, (Sys Rev)	25mg (10 Studies, 8 Sig/pbo, (Sys Rev)	CP Ref	Study	Hatton Ref	10mg (8 of 12 Studies, MA)	25mg (8 Studies, MA)	CHPA Ref (10mg MA)
√		S	4	1 Memo to Lands from F. P. Luduena. Comparative study of the effects of Neo-Synephrine HCL and Propadrine HCL on nasal air resistance (NAR), blood pressure and pulse rate of volunteers. In: FDA OTC Volume 040298. April 23, 1959.	17		×	9
√	S	S	5	2 Memo to Wessinger from N. A. Hulme. Nasal decongestant study by **Elizabeth Biochemical No 2.** In: FDA OTC Volume 040298. January 1968.	20			Study 1
√	S	S	6	3 Memo to Blackmore from N. A. Hulme. Neo-Synephrine – **Elizabeth Biochemical Laboratory Study No 5.** In: FDA OTC Volume 040298. May 1970.	28			2 (10)
√	S	S	7	4 Memo to Blackmore from N. A. Hulme. Oral Neo-Synephrine – Cintest Labs Study No 1. In: FDA OTC Volume 040298. April 1969.	22			3 (16)
√	S		8	5 Cohen BM. Objective and subjective evaluation of phenylephrine HCl versus placebo tablets. In: FDA OTC Volume 04088B. June 1975. This is parallel group study	13			8 (25/trt)
√			9	6 Memo to Blackmore from N. A. Hulme. Oral Neo-Synephrine-Huntington Research Center Study No 1. In: FDA OTC Volume 040298. May 1969.	23			6 (16)
√			10	7 Memo to Blackmore from N. A. Hulme. Oral Neo-Synephrine-Huntington Research Center Study No 2. In: FDA OTC Volume 040298. June 1969.	24		No 25 mg	7 (25)
√			11	8 Memo to Blackmore from N. A. Hulme. Oral Neo-Synephrine – Cintest Study No 2. In: FDA OTC Volume 040298. January 1970.	26		No 25 mg	4 (15)
√			12	9 Memo to Blackmore from N. A. Hulme. Oral Neo-Synephrine – Cintest Study No 3. In: FDA OTC Volume 040298. May 1970.	27			5 (15)
√			13	10 Bickerman HA. Physiologic and pharmacologic studies on nasal airway resistance (RN). Presented at a conference sponsored by the Scientific Development Committee of the Proprietary Association. Washington, DC. December 8, 1971. (Available in the Online Repository at www.jacionline.orq.)	29			14
√			14	11 McLaurin JW, Shipman WF, Rosedale R. Oral decongestants. A double-blind comparison study of the effectiveness of four sympathomimetic drugs: objective and subjective. Laryngoscope. 1961 ;71:54-67.	18			13
Not Rev'd			15	12 **Cohen BM.** Clinical and physiologic "significance" of drug-induced changes in nasal flow/resistance. *Eur* J Clin Pharmacol. 1972;5:81-86.	30		×	15
		S	17	13 Memo to Suter from N. A. Hulme. Nasal decongestant study by **Elizabeth Biochemical No 1.** In: FDA OTC Volume 040298. June 1967.	19			10
		S	18	14 Memo to Blackmore from N. A. Hulme. Oral Neo-Synephrine – **Elizabeth Biochemical Study No 3.** In: FDA OTC Volume 040298. June 1969.	21			11
		S	19	15 Memo to Blackmore from N. A. Hulme. Oral Neo-Synephrine – **Elizabeth Biochemical Study No 4.** In: FDA OTC Volume 04.0298. August 1969.	25			12
				16 Memo to Hulme, NA from H Stander, "Neo-Synephrine Oral Study – Elizabeth Biochemical Laboratories No. 2" 1968 (included in FDA OTC Volume 040298)				1 (16)
				17 Cohen, B M , Kuebler W.F. "Conduct of a 200 patient double-blind placebo controlled study to evaluate the effectiveness qf phenylephrine hydrochloride (5 mg) tablets in relieving upper respiratory congestion and symptoms associated with the common cold': Whitehall Laboratories / Bio-Evaluation Inc., 1975 (included in FDA OTC Volume 040288B) This is parallel group study				8 (25/trt)

MA = Meta-analysis; S = Sig; × = Included in CP systematic review, not in CP meta-analysis, presumably they have no 10 mg.
Elizabeth studies show sig diff from pbo regardless dose
Study n where PE was significantly different from Pbo in the CHPA MA (Number in parentheses in column is number of subjects)
Study 17 (CHPA #8), and Study #5 (CP #8, Hatton #13) are the same study (10 mg. NAR meas'd only after the first dose, for 50 subjects)
Study 16 (CHPA #1) is an addendum to Study #2, to justify the use of 0 time meas prior to medication for analysis

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

Memorandum

Date:	10/30/07
To:	Debbie Lumpkins, IDS Team Leader OND/Office of Nonprescription Products
From:	Xu Wang, M.D., Ph.D., Medical Officer Division of Pulmonary and Allergy Products, HFD-570
Through:	Charles E. Lee, M.D., Medical Team Leader Division of Pulmonary and Allergy Products, HFD-570
Through:	Badrul A. Chowdhury, M.D., Ph.D., Director Division of Pulmonary and Allergy Products, HFD-570
Subject:	Clinical endpoints and general study design for evaluation of the efficacy of an oral nasal decongestant

1. BACKGROUND

The Office of Nonprescription Products received a citizen petition (CP) regarding the effectiveness of oral phenylephrine as a nasal decongestant at maximum allowable monograph doses. Current maximal doses of phenylephrine hydrochloride (PEH) and phenylephrine bitartrate (PEB) were established through FDA's Over-the-Counter Drug Review. FDA issued a proposed rule in 1985 and final rule in 1994 adding PEH to the monograph as a generally recognized as safe and effective (GRASE) active ingredient for relief of nasal congestion. Based on bioequivalence with PEH, PEB was added to the monograph in 2006.

The OTC monograph dose of PEH is:

- Adults and children 12 years of age and over: 10 milligrams every 4 hours not to exceed 60 milligrams in 24 hours.
- Children 6 to under 12 years of age: 5 milligrams every 4 hours not to exceed 30 milligrams in 24 hours.
- Children 2 to under 6 years of age: 2.5 milligrams every 4 hours not to exceed 15 milligrams in 24 hours.
- Children under 2 years of age: consult a doctor.

The OTC monograph dose of PEB is:

- Adults and children 12 years of age and over: 15.6 milligrams every 4 hours not to exceed 62.4 milligrams in 24 hours.
- Children 6 to under 12 years of age: 7.8 milligrams every 4 hours not to exceed 31.2 milligrams in 24 hours.
- Children under 6 years of age: ask a doctor.

The issue of phenylephrine effectiveness as an oral nasal decongestant has raised congressional interest, and will be presented by ONP at a meeting of the Nonprescription Drug Advisory Committee (NDAC). ONP asked for input from DPAP regarding currently preferred clinical endpoints and the general study design of clinical trials to evaluate the effectiveness of an oral nasal decongestant.

This recommendation provides current DPAP thinking on the design of such trials and in no way addresses OTC monograph language, deliberations, or conclusions of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products, or the efficacy or safety of PEH or PEB.

2. DPAP RECOMENDATION

Nasal congestion is one of the characteristic symptoms of rhinitis. It is a subjective complaint, which is also reported by patients as nasal blockage, nasal obstruction, blocked nose, and stuffy nose. The primary goal of treating rhinitis patients with decongestants is to relieve their nasal congestion symptom. Thus, an objective measurement, such as nasal air resistance (NAR), actually represents a surrogate endpoint in assessing the effect of a drug on a patient's symptoms. The patient self-assessed nasal

congestion symptom score is DPAP's preferred primary efficacy endpoint for evaluating the effectiveness of an oral nasal decongestant because it represents the patient's assessment of their symptoms. It should be noted that the most of the indications for decongestants that are specified by the OTC monograph address symptoms experienced by consumers: nasal congestion, stuffy nose, stopped up nose, nasal stuffiness, and clogged up nose.

NAR is an assessment of nasal air flow by rhinomanometry. A number of factors may lead to the poor correlation between NAR measurements and symptoms of nasal congestion. Nasal cycling, a centrally mediated pattern of alternating nasal congestion and decongestion, causes physiological variations in NAR and results in large "noise artifacts." Other common reasons for NAR measurement inaccuracy include air leak between the nosepiece, the presence of nasal secretions that are common in rhinitis patients, and the pressure change caused by breathing and swallowing during the test. [1,2,3] Although it is less useful than symptom scores in evaluating nasal congestion in rhinitis patients, NAR is more helpful in differentiating a mucosal from a structural cause of the nasal congestion and assessing the severity of anatomical abnormalities that are causing airway obstruction in nose, including nasal valve abnormality, septal deviation, and polyposis. [4]

The preferred primary clinical endpoints to evaluate the effectiveness of an oral nasal decongestant in allergic rhinitis trials are patient self-rated instantaneous and reflective composite symptom scores. The instantaneous scores measure the symptom severity immediately preceding the time of scoring, giving an assessment of efficacy at the end of dosing interval. The reflective scores measure the symptom severity over a predefined time period, giving an assessment of consistency of efficacy throughout the dosing interval. These summed scores generally include the following four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing, rated on a 0-3 scale of severity. Addition of non-nasal symptoms to the composite score might be pertinent for certain drug products such as systemically active antihistamines, and should be considered on a case-by-case basis. While both patient self-rated symptom scores and physician-rated scores can be measured, the patient-rated scores are preferred as the primary measure of effectiveness.

DPAP currently recommends multicenter, double-blind, placebo-controlled, parallel-group efficacy and safety studies to evaluate the effectiveness of nasal decongestants. An active control, such as pseudoephrine hydrochloride or pseudoephedrine sulfate, is recommended to provide a measure of assay sensitivity. Such a study may be performed in patients with seasonal allergic rhinitis, naturally acquired colds, or induced colds. We would recommend that the study include an assessment of patient compliance, including both a daily patient diary record of medication use and pill counts performed by study staff. As noted above, the preferred measure of effectiveness would be reflective and instantaneous nasal congestion symptom scores. Scores should be recorded by patients in a diary at least as often as the daily dosing interval. Measures of air flow may be included as secondary or exploratory endpoints, but noted above, they are not considered

to be appropriate assessments of patient symptoms. Adverse events should also be recorded in the daily patient diary record.

Additional information may be found in the Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Program for Drug Products, which represents DPAP's current thinking on general study design and clinical endpoints in trials to evaluate the effectiveness of products intended to treat symptoms associated with allergic rhinitis.

References

1. Eccles R. Anatomiy and physiology of the nose and control of nasal airflow. In Adkinson NF, Jr. Yunginger JW, Busse AA, et al. editors. Middleton's Allergy, Principles & Practice. 6th ed. Philadelphia, 2003, Mosby, p775.
2. Uzzaman A, Metcalfe DD, Komarow HD. Acoustic rhinometry in the practice of allergy. Ann Allergy Asthma Immunol 2006; 97:745-52.
3. Huang ZL, Ong KL, Goh SY, et al. Assessment of nasal cycle by acoustic rhinomwtry and rhinomanometry. Otolaryngol Head Neck Surg 2003;128:510-6.
4. Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: Complete guidelines of the joint task force on practice parameters in allergy, asthma and immunology. Ann Allergy Asthma Immonul 1998;81:478-518.

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February 1, 2007

Dockets Management Branch
Food and Drug Administration (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: OTC Monograph for Nasal Decongestant Drug Products; Docket 76N-052N

Dear Sir or Madam:

Reference is made to a recent series of communications between Representative Waxman and the FDA on the efficacy of 10 mg phenylephrine. As a result of these communications, a task group of the Consumer Healthcare Products Association (CHPA) obtained copies of all studies cited in the bibliography of the phenylephrine section of the 1976 OTC Review panel report on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products. In addition, a literature search for additional studies investigating phenylephrine's efficacy was conducted. A review of all data obtained led to the conclusion that a meta-analysis of a set of studies would be feasible and would make a meaningful contribution to the discussion regarding the efficacy of phenylephrine. The CHPA Phenylephrine Task Group carried out this meta-analysis and CHPA is herewith submitting the report to the Docket 76N-052N, OTC Monograph for Nasal Decongestant Drug Products. Two expert biostatisticians, Michael Stoto, Ph.D., of Georgetown University, and Dallas Johnson, Ph.D., of Kansas State University, reviewed the meta-analysis. Their reports are also herewith submitted to the docket.[1]

The results of the meta-analysis support the Agency's opinion that phenylephrine at a dose of 10 mg is an effective oral nasal decongestant.

Sincerely,

Heinrich Schneider, Dr. Med.
Vice President, Regulatory and Scientific Affairs

cc: Dr. Charles Ganley, Office of Nonprescription Products

[1] All attachments are releasable.

1976N-0052N

C251

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Enclosures:

(1) Consumer Healthcare Products Association (CHPA) Phenylephrine Task Group, "Efficacy Meta-Analysis of Single-Dose 10 mg Phenylephrine vs. Placebo in Adults With Acute Nasal Congestion Due to Common Cold", Final Report; January 30, 2007

(2) Memorandum to Heinz Schneider from Michael Stoto, "Phenylephrine meta-analysis", January 27, 2007

(3) Letter to Heinz Schneider from Dallas E. Johnson; January 18, 2007

HS/mm

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Consumer Healthcare Products Association (CHPA) PHENYLEPHRINE TASK GROUP

Efficacy Meta-Analysis of Single-Dose 10 mg Phenylephrine vs. Placebo in Adults With Acute Nasal Congestion Due to Common Cold

Final Report (January 30, 2007)

CHPA Phenylephrine Task Group

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Report Date: January 30, 2007

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REPORT

Efficacy Meta-Analysis of Single-Dose 10 mg Phenylephrine vs. Placebo in Adults With Acute Nasal Congestion Due to Common Cold

1. BACKGROUND AND OBJECTIVES

Phenylephrine is a sympathomimetic drug which has been used as a nasal decongestant in the United States and globally since the 1940s. At that time, to be marketed in the US a drug had to be proven to be safe whereas proof of effectiveness was not required. Beginning in 1972, as a result of amendments to the US drug law, the FDA initiated the OTC Drug Review and determined on the basis of all available data which medicines could be deemed "generally recognized as safe and effective". To accomplish this task, OTC companies and others submitted thousands of volumes of safety and efficacy information and the FDA assembled outside expert advisory panels which reviewed all available data and established OTC drug monographs for specific OTC drug categories. Similar to other active ingredients used in cough and cold medicines, phenylephrine was evaluated by the Advisory Review Panel on Over-the-Counter (OTC) Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products. This panel conducted a review of the information available and deemed phenylephrine as generally recognized as safe and effective as a nasal decongestant at oral doses of 10 mg. The panel's conclusions were published by the FDA in 1976 *(Ref. 1)*. In 1994, the FDA issued the Final Monograph for OTC Nasal Decongestant Drug Products recognizing 10 mg phenylephrine as a safe and effective nasal decongestant *(Ref. 2)*.

The issues associated with the illicit conversion of pseudoephedrine to methamphetamine caused OTC companies to replace pseudoephedrine with phenylephrine in many of their products, which in turn drew new attention to phenylephrine's efficacy. In a recent publication, the authors questioned whether the FDA panel reached a correct conclusion on the basis of the available data at the time of the review in the 1970s *(Ref. 3)*.

These developments prompted a task group of the Consumer Healthcare Products Association (CHPA) to obtain copies of all studies that were cited in the bibliography of the phenylephrine section of the 1976 OTC Review panel report on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products. In

addition, a literature search for additional studies investigating phenylephrine's efficacy was conducted. A review of the data led to the conclusion that a meta-analysis would be both feasible for a set of studies and a meaningful contribution to the discussion regarding the efficacy of phenylephrine.

The objectives of the analyses of the CHPA Phenylephrine Task Group were:

- to compare single-dose 10 mg phenylephrine and placebo separately for each crossover and parallel group study of adult patients with acute nasal congestion due to head cold/common cold.
- to perform a pooled (individual-level) meta-analysis comparing 10 mg phenylephrine and placebo using all available raw data from placebo-controlled, single-dose crossover studies in adult patients with acute nasal congestion due to a common cold.

2. STUDIES AVAILABLE FOR THE ANALYSES

Three sources were used for identification and collection of placebo-controlled efficacy studies with orally administered phenylephrine used as single active ingredient.

A. The bibliography of the phenylephrine section of the 1976 OTC Review on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products *(Ref. 1).*

Within this set of data, 14 reports were identified as efficacy trials with single-active phenylephrine:

1) *Memo to Hulme, N.A from H. Stander, "Neo-Synephrine Oral Study – Elizabeth Biochemical Laboratories No. 2", 1968 (included in FDA OTC Volume 040298)*

2) *Memo to Blackmore from N.A. Hulme, "Neo-Synephrine – Elizabeth Biochemical Laboratoriy Study No. 5", 1970 (included in FDA OTC Volume 040298)*

3) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 1", 1969 (included in FDA OTC Volume 040298)*

4) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 2", 1970 (included in FDA OTC Volume 040298)*

5) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 3", 1970 (included in FDA OTC Volume 040298)*

6) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Huntingdon Research Center Study No. 1", 1969 (included in FDA OTC Volume 040298)*

7) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Huntingdon Research Center Study No. 2", 1969 (included in FDA OTC Volume 040298)*

8) *Cohen, B.M., Kuebler W.F., "Conduct of a 200 patient doubleblind placebo controlled study to evaluate the effectiveness of phenylephrine hydrochloride (5 mg) tablets in relieving upper respiratory congestion and symptoms associated with the common cold", Whitehall Laboratories / Bio-Evaluation Inc., 1975 (included in FDA OTC Volume 040288B)*

9) *Memo to Lands from F.P. Luduena, "Comparative Study of the Effects of Neo-Synephrine HCl and Propadrine HCl on Nasal Air Resistance (NAR), Blood Pressure and Pulse Rate of Volunteers", 1959 (included in FDA OTC Volume 040298)*

10) *Memo to Suter from N.A. Hulme, "Nasal Decongestant Study by Elizabeth Biochemicals Laboratories No. 1", 1967 (included in FDA OTC Volume 040298)*

11) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Elizabeth Biochemical Study No. 3", 1969 (included in FDA OTC Volume 040298)*

12) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Elizabeth Biochemical Study No.4", 1969 (included in FDA OTC Volume 040298)*

13) *McLaurin, J.W., Shipman, W.F,. Rosedale, R.. "Oral Decongestants. A Double-Blind Comparison Study of the Effectiveness of Four Sympathomimetic Drugs: Objective and Subjective." Laryngoscope, 71: 54-67, 1961*

14) *Rodgers, J.M., Reilly, E.B., and Bickerman, H.A., "Physiologic and Pharmacologic Studies on Nasal Airway Resistance," Clinical Pharmacology and Therapeutics, 14:146, 1973. Data presented at a conference sponsored by the Scientific Development Committee of the Proprietary Association, Washington DC, December 8, 1971*

B. A recently published review on nasal decongestants for the common cold conducted by the Cochrane Collaboration *(Ref. 4)*.
In performing this comprehensive review, the Cochrane Collaboration searched for randomized, placebo-controlled trials with nasal decongestants (including phenylephrine) in adults and children suffering from the common cold. Databases that were searched for this review included MEDLINE, EMBASE, CENTRAL (the Cochrane Central Register of Controlled Trials), and Current Contents.

Only one placebo-controlled trial with oral single-active phenylephrine was identified. This was the publication of *McLaurin et al.* cited under 13 in Section A above.

C. A literature search conducted by CHPA via PubMed (a free service provided by the U.S. National Library of Medicine which provides access to MEDLINE and to articles in selected journals not included in MEDLINE).

In addition to studies already cited under Sections A and B above, this search yielded one placebo-controlled trial with oral phenylephrine:

15) Cohen, B.M., "Clinical and Physiological 'Significance' in Drug-Induced Changes in Nasal Flow/Resistance". European Journal of Clinical Pharmacology, 5:81-86, 1972

In total, 15 studies were identified as placebo-controlled trials of oral phenylephrine used as single-active nasal decongestant.

3. STUDIES INCLUDED IN THE ANALYSES

For inclusion in the analyses, a study had to meet the following criteria:

1. Randomized single-dose, placebo-controlled trial
2. Orally administered, single-active phenylephrine at a dose of 10 mg
3. Adult patients with acute nasal congestion due to a common cold
4. Nasal airway resistance (NAR) was an efficacy endpoint
6. Study report contains sufficient individual subject data to allow reanalysis and/or meta-analysis for the comparison of the 10 mg dose level of phenylephrine and placebo

On the basis of these criteria, 8 studies were considered for the analyses.

1) *Memo to Hulme, N.A from H. Stander, "Neo-Synephrine Oral Study – Elizabeth Biochemical Laboratories No. 2", 1968 (included in FDA OTC Volume 040298)*

2) *Memo to Blackmore from N.A. Hulme, "Neo-Synephrine – Elizabeth Biochemical Laboratoriy Study No. 5", 1970 (included in FDA OTC Volume 040298)*

3) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 1", 1969 (included in FDA OTC Volume 040298)*

4) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 2", 1970 (included in FDA OTC Volume 040298)*

5) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 3", 1970 (included in FDA OTC Volume 040298)*

6) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Huntingdon Research Center Study No. 1", 1969 (included in FDA OTC Volume 040298)*

7) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Huntingdon Research Center Study No. 2", 1969 (included in FDA OTC Volume 040298)*

8) *Cohen, B.M., Kuebler W.F., "Conduct of a 200 patient doubleblind placebo controlled study to evaluate the effectiveness of phenylephrine hydrochloride (5 mg) tablets in relieving upper respiratory congestion and symptoms associated with the common cold", Whitehall Laboratories / Bio-Evaluation Inc., 1975 (included in FDA OTC Volume 040288B)*

The studies are identified in Table 1 (Studies 1 – 8). Of these 8 studies, 7 were of a similar design (i.e., randomized, double-blind, two-treatment, two-period, two-sequence crossover trials, NAR as efficacy endpoint) and were combined for meta-analysis (Studies 1 - 7). The eighth study was a double-blind, parallel group study and was not included in the meta-analysis of the crossover trials. This study (Study 8) was reanalyzed separately as were each of the 7 studies included in the meta-analysis.

There were a total of 163 patients available for analysis as follows:

TABLE 1: STUDIES INCLUDED IN THE ANALYSES

Study No. (design)	Study ID	Baseline Nasal Airway Resistance (NAR) (Phenylephrine/Placebo)	Number of Subjects with Data
1 (crossover)	Elizabeth No. 2	13.43 / 13.08*	16
2 (crossover)	Elizabeth No. 5	12.98 / 12.72*	10
3 (crossover)	Cintest No. 1	22.3 / 20.61*	16
4 (crossover)	Cintest No. 2	28.05 / 26.73*	15
5 (crossover)	Cintest No. 3	21.15 / 21.39*	15
6 (crossover)	Huntingdon No. 1	24.61 / 23.85*	16
7 (crossover)	Huntingdon No. 2	25.11 / 28.36*	25
8 (parallel group)	Bio-evaluation	5.29 / 4.99**	50 (25 per treatment)

* units

**cm H_2O/l/min @ 0.5 l/sec flow

There were 113 subjects included in the crossover trials comprising the meta-analysis. All subjects had data and were included in the analysis.

4. STUDIES EXCLUDED FROM THE ANALYSES

The following 7 studies were excluded from the analyses. Table 2 below provides characteristics of these studies and reasons for their exclusion.

9) *Memo to Lands from F.P. Luduena, "Comparative Study of the Effects of Neo-Synephrine HCl and Propadrine HCl on Nasal Air Resistance (NAR), Blood Pressure and Pulse Rate of Volunteers", 1959 (included in FDA OTC Volume 040298)*

10) *Memo to Suter from N.A. Hulme, "Nasal Decongestant Study by Elizabeth Biochemicals Laboratories No. 1", 1967 (included in FDA OTC Volume 040298)*

11) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Elizabeth Biochemical Study No. 3", 1969 (included in FDA OTC Volume 040298)*

12) *Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Elizabeth Biochemical Study No.4", 1969 (included in FDA OTC Volume 040298)*

13) *McLaurin, J.W., Shipman, W.F., Rosedale, R.. "Oral Decongestants. A Double-Blind Comparison Study of the Effectiveness of Four Sympathomimetic Drugs: Objective and Subjective." Laryngoscope, 71: 54-67, 1961*

14) *Rodgers, J.M., Reilly, E.B., and Bickerman, H.A., "Physiologic and Pharmacologic Studies on Nasal Airway Resistance," Clinical Pharmacology and Therapeutics, 14:146, 1973. Data presented at a conference sponsored by the Scientific Development Committee of the Proprietary Association, Washington DC, December 8, 1971*

15) *Cohen, B.M., "Clinical and Physiological 'Significance' in Drug-Induced Changes in Nasal Flow/Resistance". European Journal of Clinical Pharmacology, 5:81-86, 1972*

TABLE 2: STUDIES EXCLUDED FROM THE ANALYSES

Study No.	Study ID	Reason for Exclusion
9	Lands from Luduena	Subjects were healthy volunteers
10	Elizabeth No. 1	Study investigated phenylephrine at dose levels other than 10 mg
11	Elizabeth No. 3	Study investigated phenylephrine at dose levels other than 10 mg

12	Elizabeth No. 4	Study investigated phenylephrine at dose levels other than 10 mg
13	McLaurin et al.	Participants enrolled were patients with nasal obstruction from a variety of disorders, including coryza, acute and chronic sinusitis, allergic or vasomotor rhinitis and hypothyroidism. No analysis of subgroups was performed.
14	Rodgers et al.	Participants had chronic rhinitis
15	Cohen	Lack of individual–level data (only mean treatment estimates by time point available)

5. METHODS

Efficacy Parameters:

In all studies included in the meta-analysis, NAR was the efficacy endpoint. NAR was determined by an identical procedure (using a modified Butler-Ivy airflow device). According to the original study reports, five NAR measurements were taken at pre-dose and at all post-baseline time points for each study subject. However, these five measurements were not provided in these reports. The average of the five measurements was provided. These average values may have been rounded for listing in these reports.

Subjective impressions of changes in nasal congestion were scored in the studies, but there were insufficient data for analysis.

Two parameters were analyzed for the meta-analysis and for the analysis of each study:

1. Change from baseline (pre-dose) NAR at each post-baseline time point (15, 30, 45, 60, 90, 120, 180, and 240 minutes post-dose), defined as post-baseline NAR - baseline NAR.

2. LN-ratio NAR [defined as LN (NAR at a post-baseline time point) – LN (baseline NAR)] at each post-baseline time point (15, 30, 45, 60, 90, 120,

180, and 240 minutes post-dose). At each time point, this is mathematically identical to the natural logarithm of the ratio of the post-baseline to baseline values, LN (post-baseline NAR at a time point / baseline NAR).

Note that the 45, 90, 180, and 240 minute post-baseline time points were not included in the design of Study 8; the 180 and 240 minute time points were also not included in the designs of Studies 1 and 5.

Criteria for Evaluation:

On the basis of medical considerations and consumer expectations the following criteria were chosen:

- Statistical significance at the 30 minute and 60 minute post-dosing time points (primary time points).
- 20% reduction from baseline NAR for phenylephrine. A 20% reduction from baseline is a reduction noticeable by patients (*Ref. 5*).

Statistical Methods:

Analyses by Study:

In the original study reports, the investigators used analysis of variance (without a covariate adjustment for baseline) to analyze the NAR measurements. However, for this report, the individual data values for each crossover study were analyzed using analysis of covariance (adjusting for pre-dose baseline average measurement, a covariate). For these crossover studies, the statistical model included 'patient' as a random factor. Information on which treatment sequence a patient was randomized to was not available in the original study reports; therefore, treatment sequence and period could not be included in the statistical model and a test for first-order carryover could not be done. Patient was a random factor for the analysis of Study 8 also, but was not included in the statistical model as this was a parallel group study.

Pooled Meta-Analyses:

Since Study 8 was a parallel group study and not a crossover study, it was not included in the meta-analysis.

For all meta-analyses performed for each efficacy parameter, the individual data values for each crossover study were included. Analysis of covariance

(ANCOVA), adjusting for pre-dose baseline average measurement (a covariate) was performed for all analyses.

First, prior to the use of statistical models to compare treatments, an analysis was performed to test "heterogeneity" at each post-dose time point, that is, to determine if the treatment difference between phenylephrine and placebo varied in direction or magnitude from study to study at a post-dose time point. This would further determine if phenylephrine differed from placebo in some studies and not others or if the treatment difference between phenylephrine or placebo was larger for some studies than for others at a post-dose time point. This test for "heterogeneity" is a test of the "treatment-by-study interaction" term from the following statistical models:

- **Model 1:** a fixed effects meta-analysis model using parametric ANCOVA, adjusting for baseline (a covariate), with terms for patient, study (a fixed factor), treatment (a fixed factor), and the treatment-by-study interaction. This model was used twice:
  - Model 1.a: assuming patient as a fixed factor with unequal within-subject variance components across studies
  - Model 1.b: assuming patient as a random factor with unequal within-subject and between-subject variance components across studies.

For the meta-analyses, two statistical models were used to perform analysis of covariance comparing the efficacy of phenylephrine and placebo at each post-dose time point:

- **Model 2:** a fixed effects meta-analysis model which is Model 1 above, but without the treatment-by-study interaction term. Study is again assumed to be fixed. This model was used twice:
  - Model 2.a: assuming patient as a fixed factor with unequal within-subject variance components across studies
  - Model 2.b: assuming patient as a random factor with unequal within-subject and between subject variance components across studies.

- **Model 3:** a random effects meta-analysis model, with baseline, patient, treatment, study, and treatment-by-study interaction in the model, but with patient, study, and treatment-by-study interaction considered random.

The SAS System Version 8.2 PROC MIXED code to generate results from all models analyzed is given in Appendix 1.

The assumptions of the parametric statistical models noted above, normality and equality of variance, were checked by inspection of plots of residuals vs. predicted values and boxplots of residuals for each treatment group (seen in Appendix 2 for by-study analyses and in Appendix 3 for the meta-analysis). Although variances of the two treatments appear to be equal, there appears to be a departure from normality for some analyses, although sometimes the distributions of residuals appear symmetrical. There appears to be comparability between the two efficacy parameters with regard to how well the normality and equality of variance assumptions fit the data for the treatment factor in the model. Differences between studies in term of patient variability were noted in the original reporting of these studies; therefore, within and between-subject variances components were allowed to vary for analyses using Models 1, 2, and 3 (as described above).

All p-values for treatment effect terms in Models 2 and 3 were considered statistically significant if $p \leq 0.05$.

The results of Model 2.a were generally comparable to those for Model 2.b. Determinations concerning the efficacy of phenylephrine are primarily based on the results from Model 2.b and Model 3 for the change from baseline parameter, a more commonly used parameter. A sensitivity analysis was performed using the LN-ratio parameter. Results of analyses of the change from baseline parameter and the LN-ratio parameter were generally comparable. **Therefore, the results of the Model 2.b and 3 change from baseline analyses are presented in the Results section of this report.** A summary table of results of the analyses of the change from baseline and LN-ratio parameters is provided in Appendix 4 (Appendix 4.1 for by-study analyses and Appendix 4.2 for meta-analyses).

Appendix 5 contains a listing of the standard errors of treatments for Models 2.a, 2.b, and 3 for both efficacy parameters for all analyses performed. The 95% confidence intervals on the difference between treatments (generated from PROC MIXED) are also provided; the difference between treatments provided is based on adjusted (least squares) treatment means. Forest plots are provided in Figures 1 to 8 to show the confidence intervals on the treatment difference by post-dose time point for each study (assuming patient is random) and for the meta-analyses (based on Models 2.b and 3).

Treatments means are plotted by post-dose time point for each parameter by study (assuming patient is a random factor) and for the meta-analyses (using all models) in Figures 9 to 16. For figures representing the results of analyses of the change from baseline parameter, percent change from baseline for a treatment is plotted against time. Percent change for a treatment is calculated as: (least squares adjusted treatment mean x 100) / (baseline mean for a treatment). The lower and upper 95% confidence interval limits plotted for a treatment in these figures are the lower and upper confidence limits for the adjusted treatment mean converted to percent change from baseline.

6. RESULTS

RESULTS BY STUDY:

Figures 1 to 8 show an estimate of the treatment difference between phenylephrine and placebo with corresponding 95% confidence interval for each post-dose time point. Estimates and confidence intervals are provided for each study (assuming patient is random) and for the meta-analyses (based on Models 2.b and 3). Confidence intervals that do not contain 0 are statistically significantly in favor of phenylephrine over placebo.

Statistically significant differences in favor of phenylephrine over placebo were found in Studies 1, 2, 3 and 8. The results are indicated in Table 3.

Statistically significance differences were not found between phenylephrine and placebo for Studies 4, 5, 6, and 7, but directional differences were found as shown in Table 4. The maximum percent changes from baseline achieved for phenylephrine in these studies were 29%, 17%, 17%, and 16%, for Studies 4, 5, 6, and 7, respectively. However, for placebo, the maximum percent changes from baseline were 32%, 21%, 22%, and 20%, respectively.

TABLE 3: RESULTS OF STUDIES WITH STATISTICALLY SIGNIFICANT DIFFERENCES

Study No. (design)	Study ID	Statistic	Post-dose time points statistically significant ($p \leq 0.05$) in favor of phenylephrine over placebo							
			15 mins	30 mins	45 mins	60 mins	90 mins	120 mins	180 mins	240 mins
1 (crossover)	Elizabeth No. 2	Significant?	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	#	#
		Treatment Difference (Confidence Interval)	-1.26 (-1.87, -0.65)	-3.11 (-3.97, -2.26)	-5.74 (-6.60, -4.87)	-5.44 (-6.64, -4.25)	-4.70 (-6.03, -3.38)	-3.44 (-4.91, -1.96)		
2 (crossover)	Elizabeth No. 5	Significant?	NS	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	NS
		Treatment Difference (Confidence Interval)	-0.05 (-0.44, 0.35)	-1.68 (-2.33, -1.03)	-3.51 (-4.38, -2.65)	-3.82 (-4.64, -3.01)	-2.90 (-3.65, -2.15)	-2.09 (-2.80, -1.38)	-1.17 (-1.71, -0.63)	-0.38 (-1.05, 0.30)
3 (crossover)	Cintest No. 1	Significant?	NS	$p \leq 0.05$	NS	NS	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$
		Treatment Difference (Confidence Interval)	-0.17 (-1.70, 1.36)	-2.24 (-4.36, -0.12)	-1.90 (-4.53, 0.73)	-3.14 (-7.01, 0.74)	-4.75 (-8.90, -0.59)	-4.88 (-8.80, -0.95)	-6.81 (-11.09, -2.52)	-6.66 (-12.38, -0.94)
8 (parallel group)	Bio-evaluation	Significant?	$p \leq 0.05$	$p \leq 0.05$	##	$p \leq 0.05$	##	$p \leq 0.05$	##	##
		Treatment Difference (Confidence Interval)	-0.60 (-1.14, -0.07)	-0.67 (-1.23, -0.11)		-0.68 (-1.28, -0.09)		-0.96 (-1.48, -0.44)		

Source: Appendix 4.1 and Appendix 5

Confidence Interval = Lower and Upper Limits of a 95% Confidence Interval on the treatment difference (phenylephrine minus placebo)

The design of Study 1 did not include the 180 and 240 min. time points

The design of Study 8 did not include the 45, 90, 180, and 240 min. time points

NS = not statistically significant

TABLE 4: DIRECTIONAL DIFFERENCES IN STUDIES 4, 5, 6, AND 7

Study No. (design)	Study ID	Statistic	Post-dose time points with directional differences (D) in favor of phenylephrine over placebo							
			15 mins	30 mins	45 mins	60 mins	90 mins	120 mins	180 mins	240 mins
4 (crossover)	Cintest No. 2	Directional?	D	-	-	D	-	-	-	-
		Treatment Difference (Confidence Interval)	-0.13 (-1.85, 1.60)	0.31 (-1.40, 2.02)	0.13 (-2.47, 2.74)	-1.81 (-4.90, 1.29)	0.39 (-2.92, 3.70)	1.05 (-3.22, 5.31)	0.63 (-4.62, 5.87)	0.68 (-5.75, 7.12)
5 (crossover)	Cintest No. 3	Directional?	D	D	D	D	-	-	#	#
		Treatment Difference (Confidence Interval)	-0.58 (-1.93, 0.77)	-0.21 (-2.44, 2.03)	-0.07 (-2.46, 2.31)	-0.13 (-2.75, 2.48)	0.15 (-2.93, 3.23)	0.93 (-2.19, 4.05)		
6 (crossover)	Huntingdon No. 1	Directional?	D	D	-	-	-	-	-	D
		Treatment Difference (Confidence Interval)	-0.57 (-2.82, 1.68)	-0.06 (-3.29, 3.17)	1.11 (-1.22, 3.43)	1.53 (-2.37, 5.43)	0.17 (-3.62, 3.96)	2.70 (-2.45, 7.84)	0.83 (-4.25, 5.91)	-1.65 (-9.22, 5.92)
7 (crossover)	Huntingdon No. 2	Directional?	-	D	-	-	D	-	-	-
		Treatment Difference (Confidence Interval)	0.99 (-0.98, 2.95)	-0.36 (-3.61, 2.89)	2.09 (-0.88, 5.05)	1.44 (-2.81, 5.70)	-0.18 (-4.00, 3.63)	2.89 (-0.69, 6.48)	1.49 (-1.05, 4.02)	1.61 (-2.82, 6.03)

Source: Appendix 4.1 and Appendix 5

Confidence Interval = Lower and Upper Limits of a 95% Confidence Interval on the treatment difference (phenylephrine minus placebo)

The design of Study 5 did not include the 180 and 240 min. time points.

RESULTS OF META-ANALYSES:

Using Model 1 results, statistically significant treatment-by-study interactions (all p-values $\leq$0.217) occurred for all time points (15 through 240 minutes) as expected given results of by-study analyses shown above (interaction p-values not provided in any table, but available in Appendix 3). Directional differences in favor of phenylephrine over placebo were seen in all studies, but not at all time points post-dose (Table 4 and Appendix 4.1). Directional treatment differences in favor of phenylephrine over placebo were seen for at least 2 and up to 6 time points in the 8 studies available for analysis.

For meta-analyses, statistical significance in favor of phenylephrine over placebo was achieved at the primary time points (30 and 60 minutes post-dose) and also for the 90 minute post-dose time point for both Models 2.b and 3. Statistical significance in favor of phenylephrine over placebo was also seen for the 45, 120, and 180 minute post-dose time points using Model 2.b (Table 5).

Note that there was a reduced sample size for the 180 and 240 minute time points as compared to earlier time points since only five studies were available for analysis at the 180 and 240 minute time points. Lack of statistical significance seen at the 120 and 180 minute post-dose time points (for Model 3) and at the 240 minute post-dose time point (for Models 2.b and 3) may be due to reduced power given increased variance and/or reduced sample size seen at these time points (Appendix 5).

Using estimates taken from both Models 2.b and 3, the percent changes from baseline for phenylephrine were at most 4%, 9%, 15%, 21%, 21%, 23%, 25%, and 20% for the 15, 30, 45, 60, 90, 120, 180, and 240 minute time points, respectively. Percent changes from baseline were at least 6 percentage points higher and at most 16.6 percentage points higher for phenylephrine as compared to placebo between 30 and 90 minutes post-dose (6 percentage points at 30 and 45 minutes and as high as 16.6 percentage points at 60 minutes).

The average change from baseline NAR for phenylephrine was approximately two-thirds to 2 times greater than that for placebo between 15 and 90 minutes post-dose.

TABLE 5: RESULTS OF META-ANALYSIS

Model	Statistic	Post-dose time points statistically significant ($p \leq 0.05$) in favor of phenylephrine over placebo							
		15 mins	30 mins	45 mins	60 mins	90 mins	120 mins	180 mins	240 mins
2.b	Significant?	NS	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	$p \leq 0.05$	NS
	Treatment Difference (Confidence Interval)	-0.27 (-0.61, 0.08)	-1.68 (-2.23, -1.14)	-2.71 (-3.57, -1.85)	-3.68 (-4.39, -2.97)	-2.80 (-3.54, -2.06)	-2.02 (-2.67, -1.37)	-1.09 (-1.61, -0.58	-0.33 (-1.21, 0.55)
3	Significant?	NS	$p \leq 0.05$	NS	$p \leq 0.05$	$p \leq 0.05$	NS	NS	NS
	Treatment Difference (Confidence Interval)	-0.41 (-1.18, 0.36)	-1.32 (-2.56, -0.09)	-1.38 (-3.51, 0.74)	-2.30 (-4.34, -0.26)	-2.24 (-4.17, -0.31)	-1.01 (-3.42, 1.40)	-0.95 (-4.85, 2.96)	-0.32 (-1.21, 0.57)

Source: Appendix 4.2 and Appendix 5

Confidence Interval = Lower and Upper Limits of a 95% Confidence Interval on the treatment difference (phenylephrine minus placebo)

NS = not statistically significant

7. SUMMARY AND CONCLUSIONS

Eligible studies:

- Eight out of 14 reviewed studies fulfilled the criteria for inclusion in the analyses (Studies No.1 – 8). One other trial, the study conducted by Cohen (Study No. 15), met all selection criteria except for providing individual patient data. It is important to note that this study demonstrated that 10 mg phenylephrine significantly improved NAR compared to placebo. So it is justifiable to assume that the results of the meta-analysis would still be positive had Study No.15 been included.

Analyses of individual studies:

- Statistically significant differences in favor of 10 mg phenylephrine over placebo were seen in 4 of 8 individual studies analyzed.
- Although the direction and the size of the treatment difference was not consistent for all studies at all post-dose time points (Model 1), directional treatment differences in favor of 10 mg phenylephrine over placebo were seen for at least 2 and up to 6 time points in the 8 studies available for analysis.

Meta-analysis:

- For the meta-analysis including 7 crossover studies (Studies No.1 – 7), phenylephrine was statistically significantly superior to placebo at the primary time points, 30 and 60 minutes post-dose, and at 90 minutes post-dose (using the results of both Models 2.b and 3). Also, phenylephrine was statistically significantly favored over placebo at the 45, 120, and 180 minute post-dose time points (Model 2.b).
- Reductions from baseline were on the order of 20%, a reduction considered to be noticeable by the patient. In one model (Model 2.b), reductions from baseline for phenylephrine were at least 21% from 60 to 180 minutes post-dose. In the second model (Model 3), reductions were 18% at 60 minutes post-dose, and at least 20% from 90 to 180 minutes post-dose.
- Study No. 8 was a parallel group study and was not included in the meta-analysis. In this study, phenylephrine was shown to be statistically significantly superior to placebo at the four time points assessed (15, 30, 60, and 120 minutes post-dose). Therefore, it can be assumed that the results of the meta-analysis would have remained positive had Study No.8 been included.

In conclusion, both the meta-analysis of seven crossover studies and the results of a parallel group study demonstrated that phenylephrine at a dose of 10 mg is an effective decongestant.

References:

Ref.1 FDA, Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products. Federal Register, Vol. 41, No.176, p.38399-38400, 1976

Ref.2 FDA, Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Nasal Decongestant Drug Products. Federal Register, Vol. 59, No.162, p.43386-43412, 1994

Ref.3 Hendeles, L., Hatton, R.C., "Oral phenylephrine: An ineffective replacement for pseudoephedrine?". Journal of Allergy and Clinical Immunology, 118: 279-280, 2006

Ref.4 Taverner, D., Latte, J., Draper, M., "Nasal decongestants for the common cold (Review)." Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD001953. DOI: 10.1002/14651858.CD001953.pub2.; published in the Cochrane Library 2006, Issue 4

Ref.5 Cohen, B.M., "Clinical and Physiological "Significance" in Drug-Induced Changes in Nasal Flow/Resistance. European Journal of Clinical Pharmacology, 5:81-86, 1972

Figure 1
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
15 Minutes Post-Dose

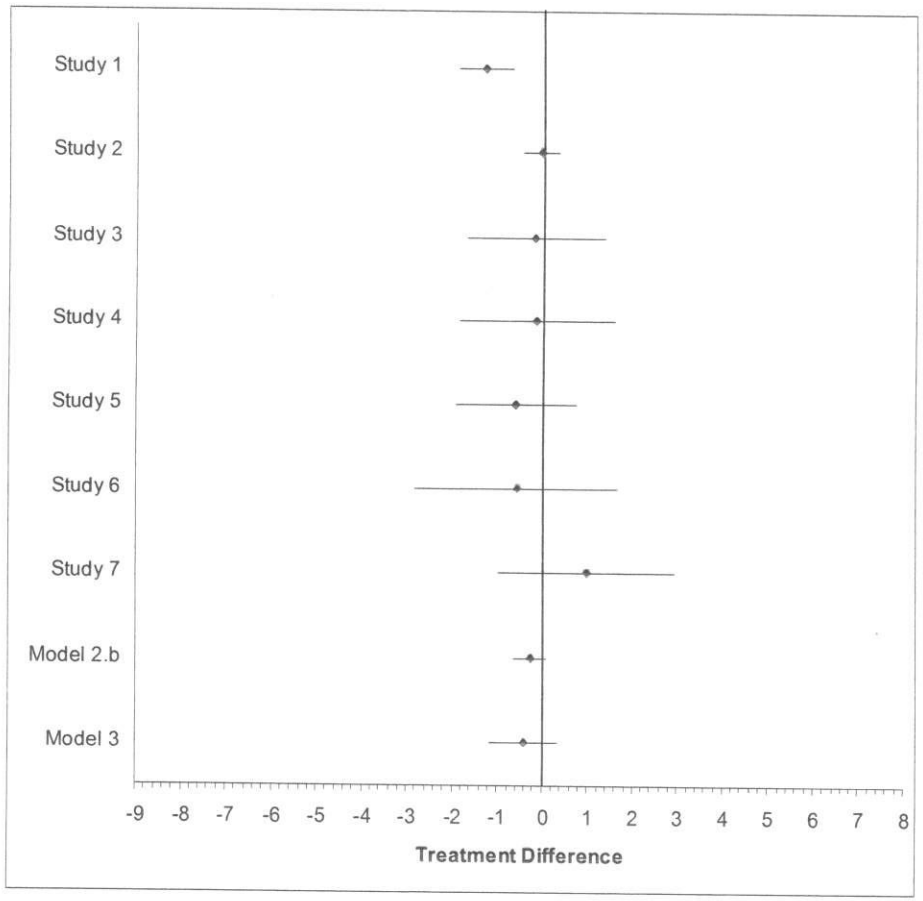


Figure 2
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
30 Minutes Post-Dose

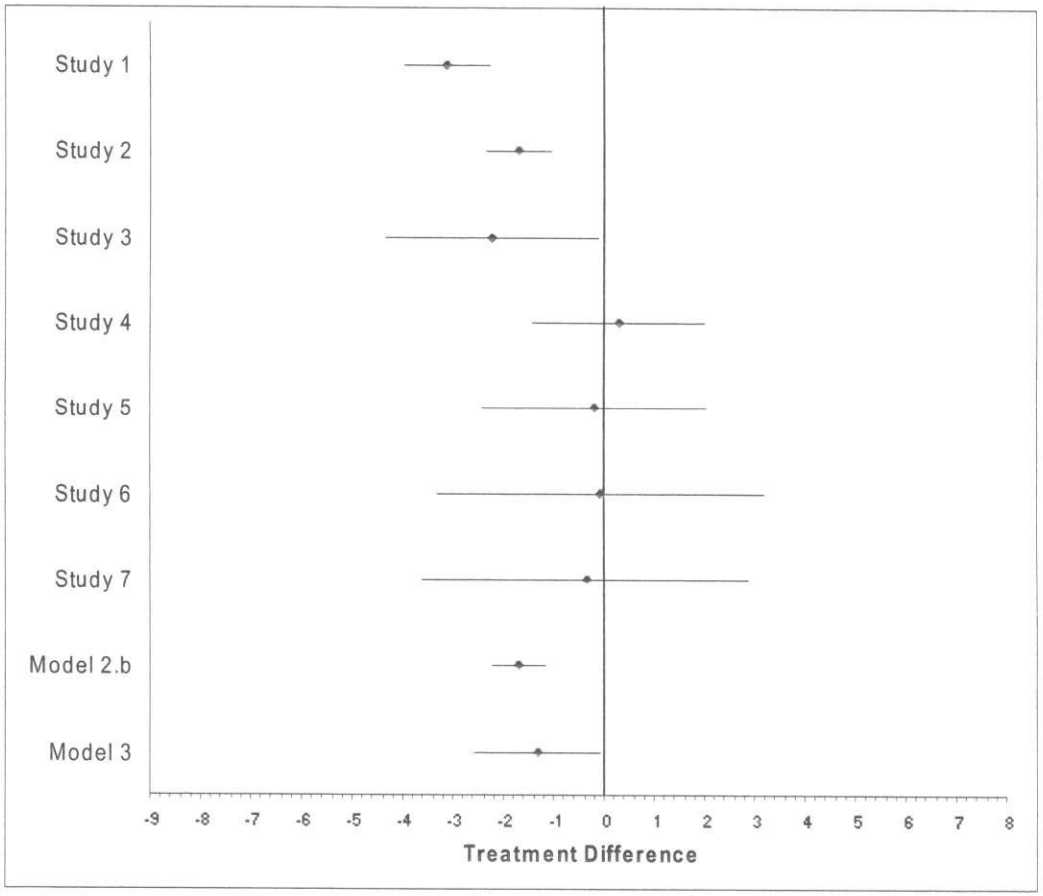


Figure 3
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
45 Minutes Post-Dose

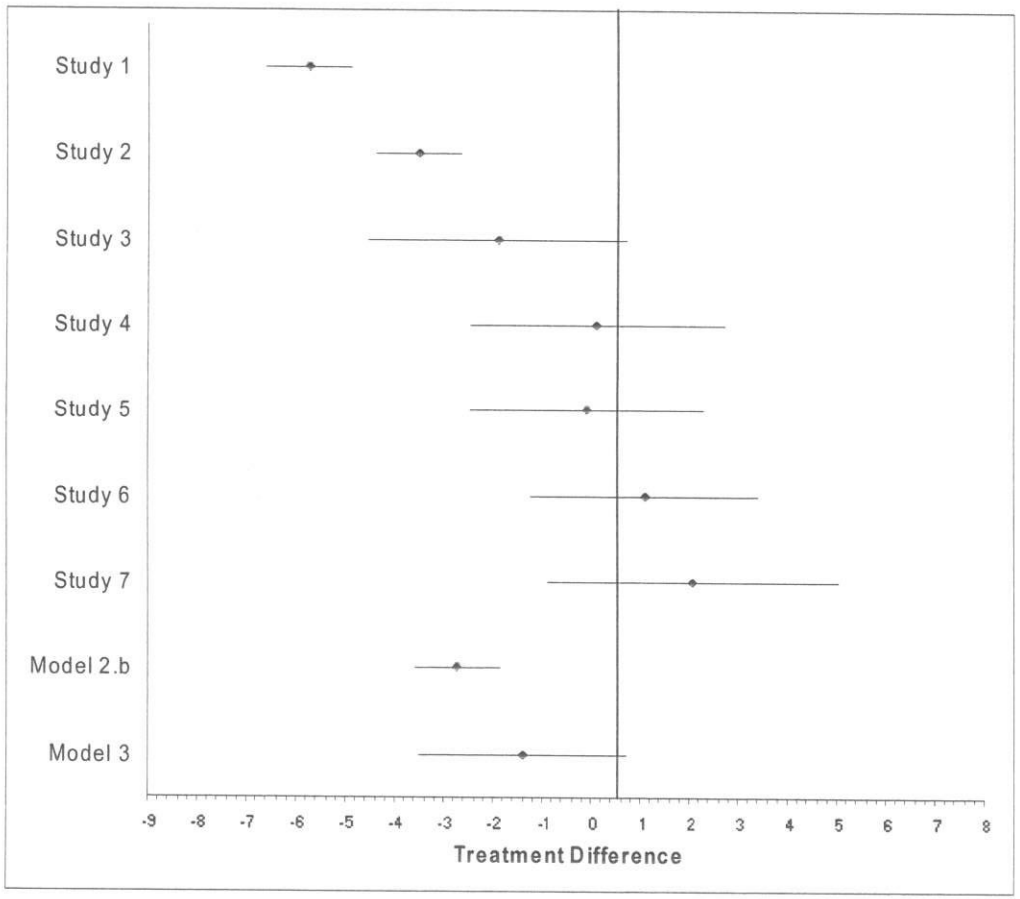


Figure 4
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
60 Minutes Post-Dose

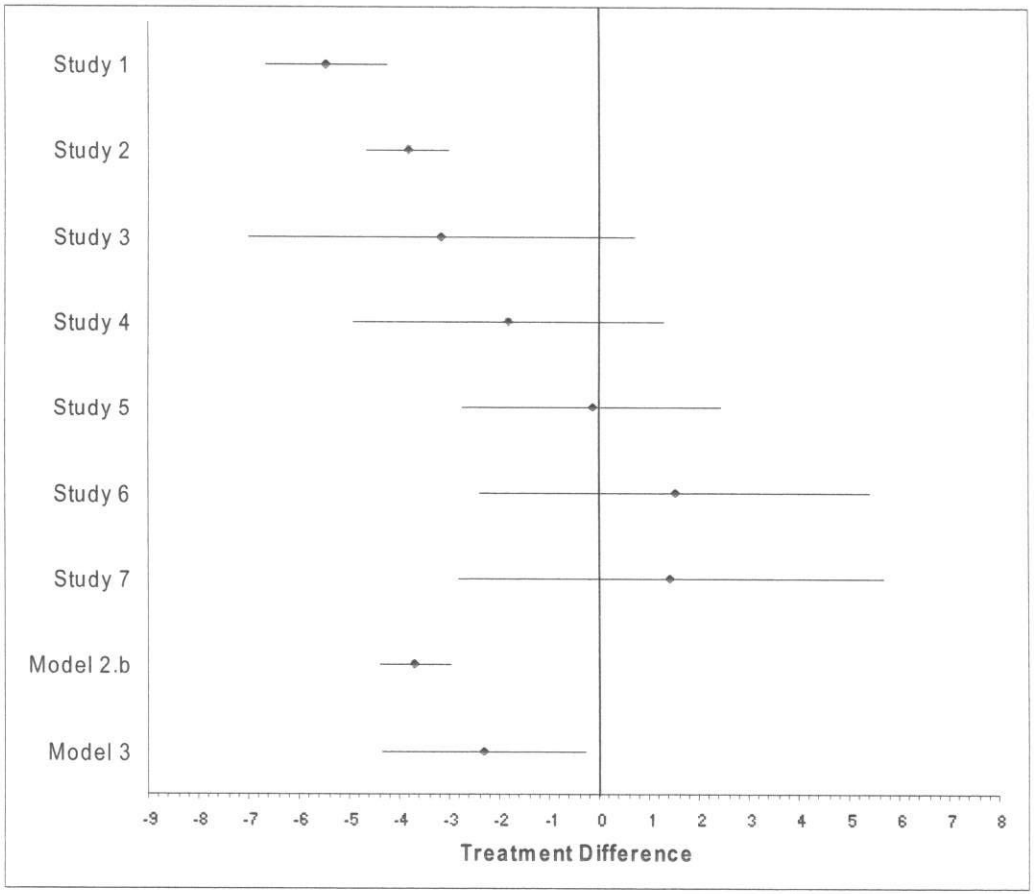


Figure 5
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
90 Minutes Post-Dose

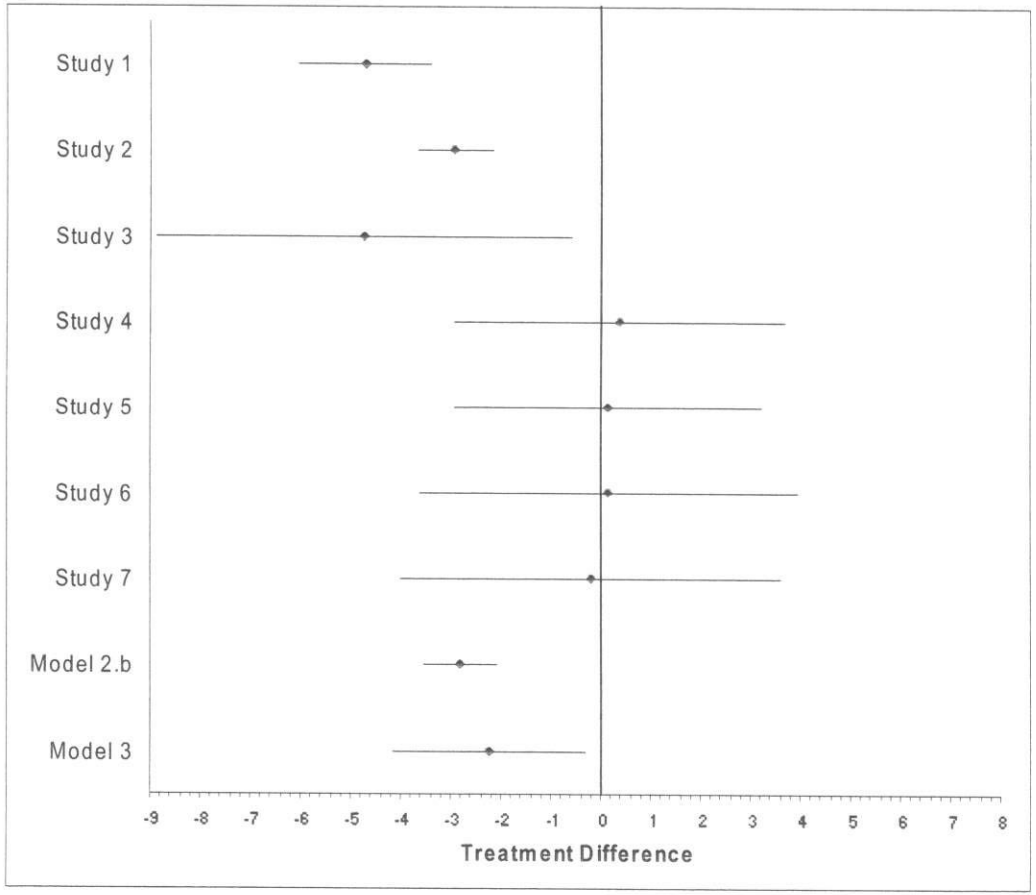


Figure 6
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
120 Minutes Post-Dose

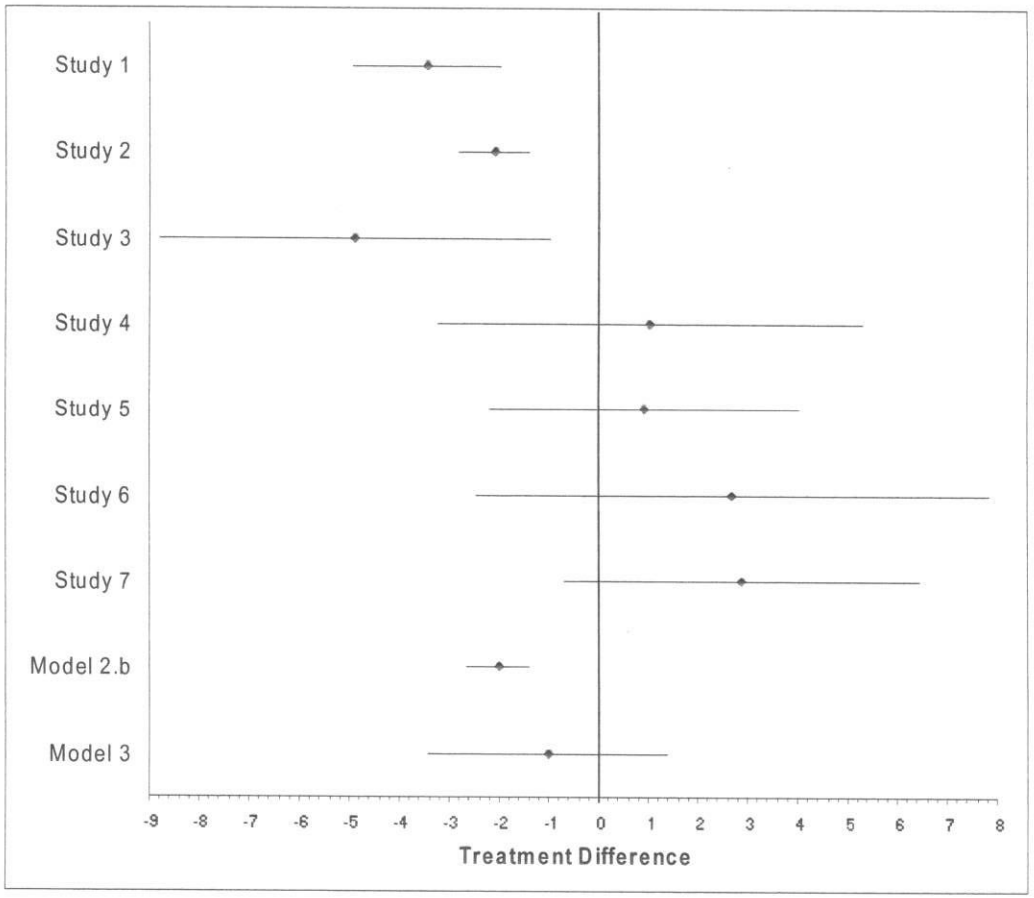


Figure 7
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
180 Minutes Post-Dose

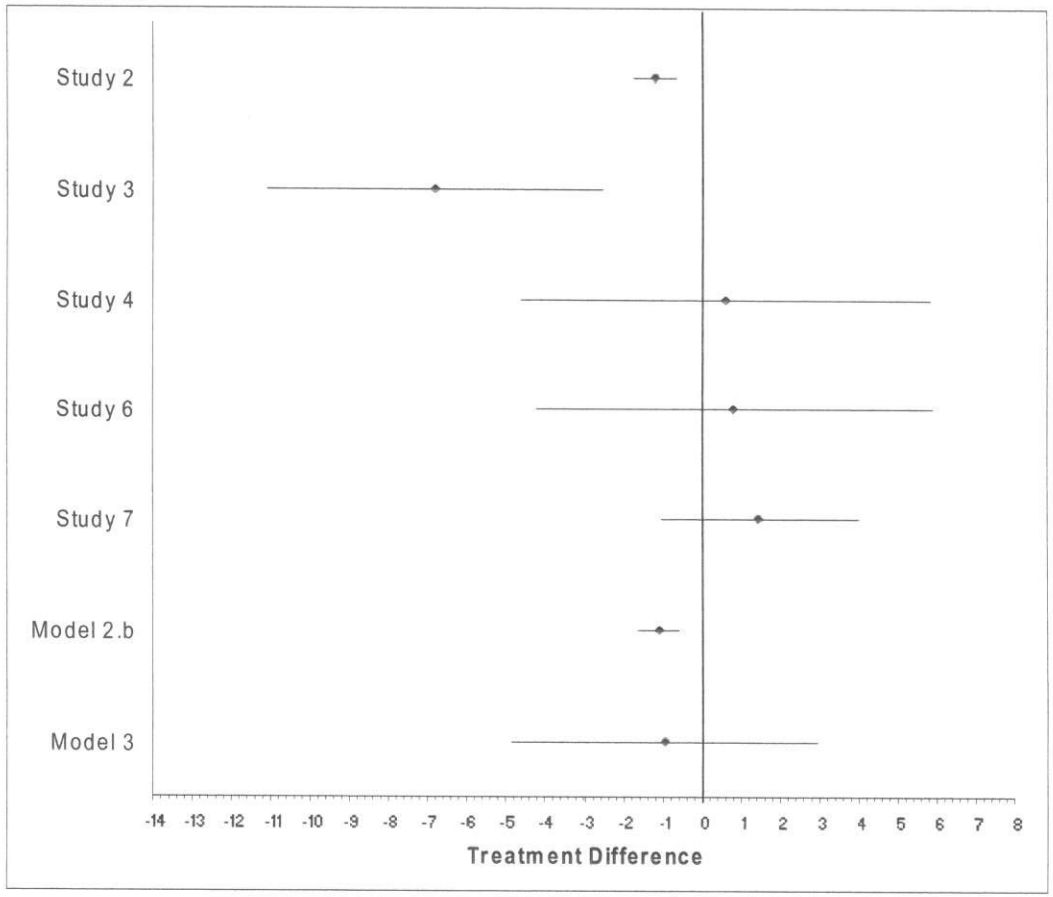


Figure 8
Change from Baseline NAR: Treatment Difference (Phenylephrine minus Placebo) with 95% Confidence Limits By Study Assuming Patient is Random and for the Meta-Analysis Using Models 2.b and 3
240 Minutes Post-Dose

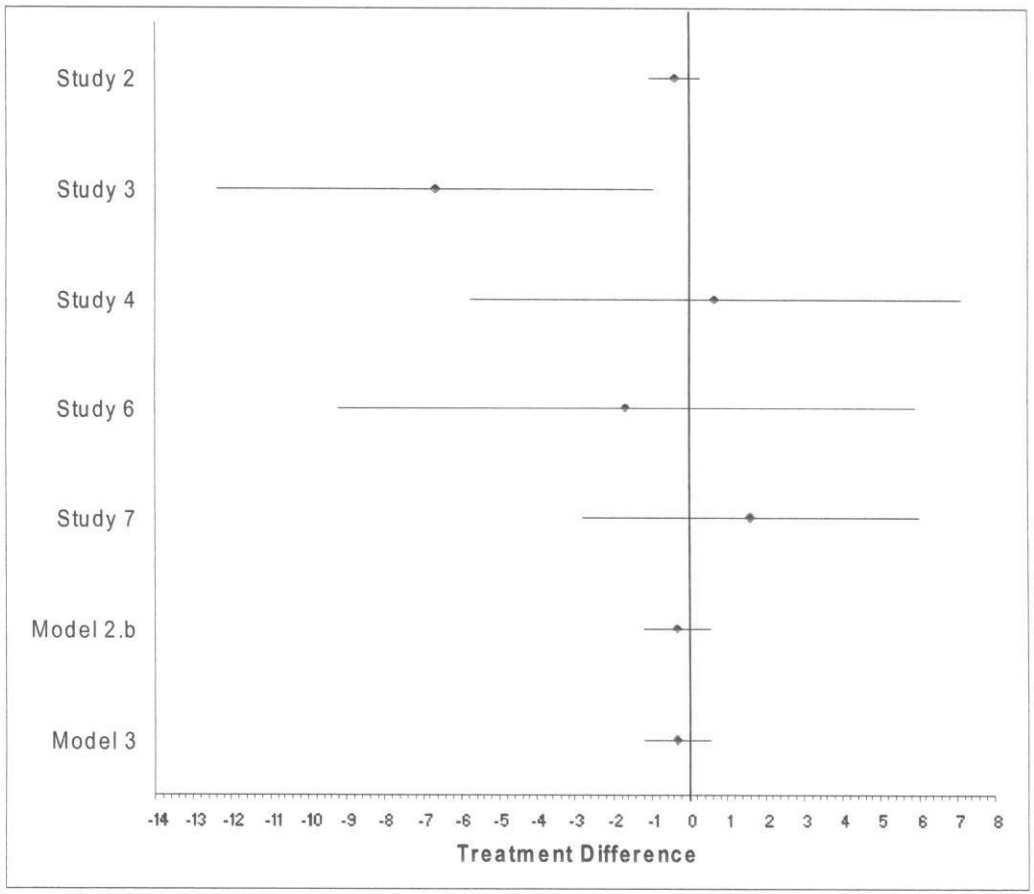


Figure 9
% Change from Baseline by Study and Time (minutes) with 95% Confidence Limits for Each Treatment
Patient is Random

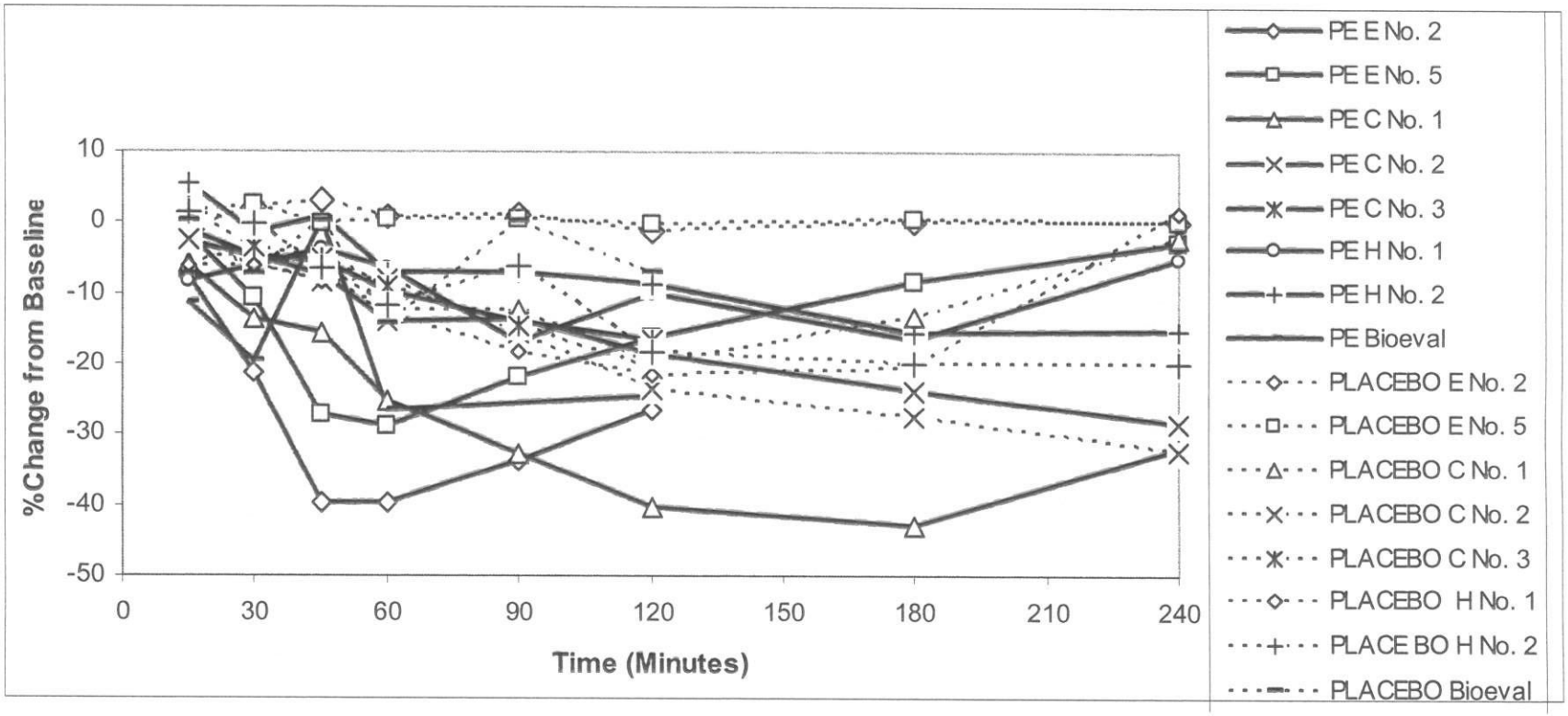


Figure 10
% Change from Baseline by Time (minutes) with 95% Confidence Limits for Each Treatment
Model 2.a – Patient is Fixed

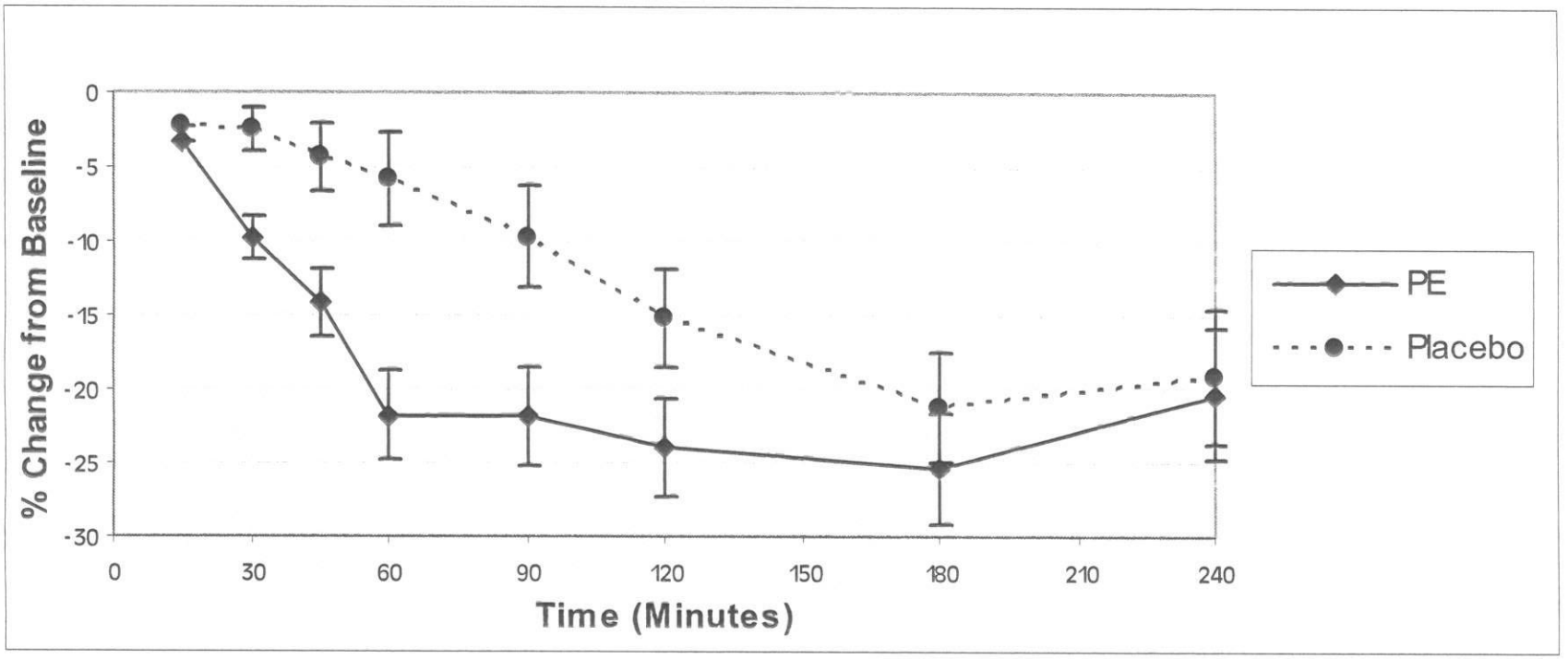


Figure 11
% Change from Baseline by Time (minutes) with 95% Confidence Limits for Each Treatment
Model 2.b – Patient is Random

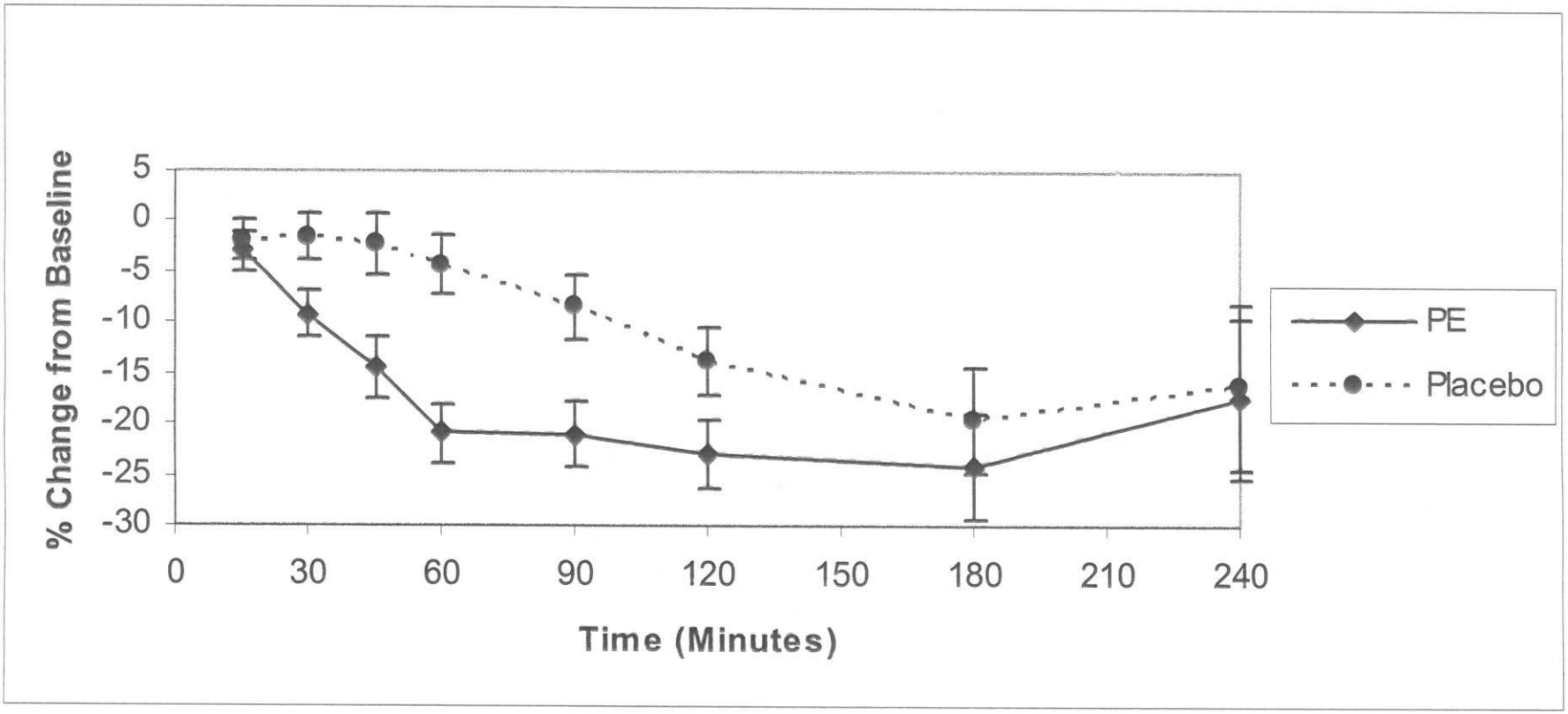


Figure 12
% Change from Baseline by Time (minutes) with 95% Confidence Limits for Each Treatment
Model 3 – Patient, Study, and Treatment-by-study Interaction are Random

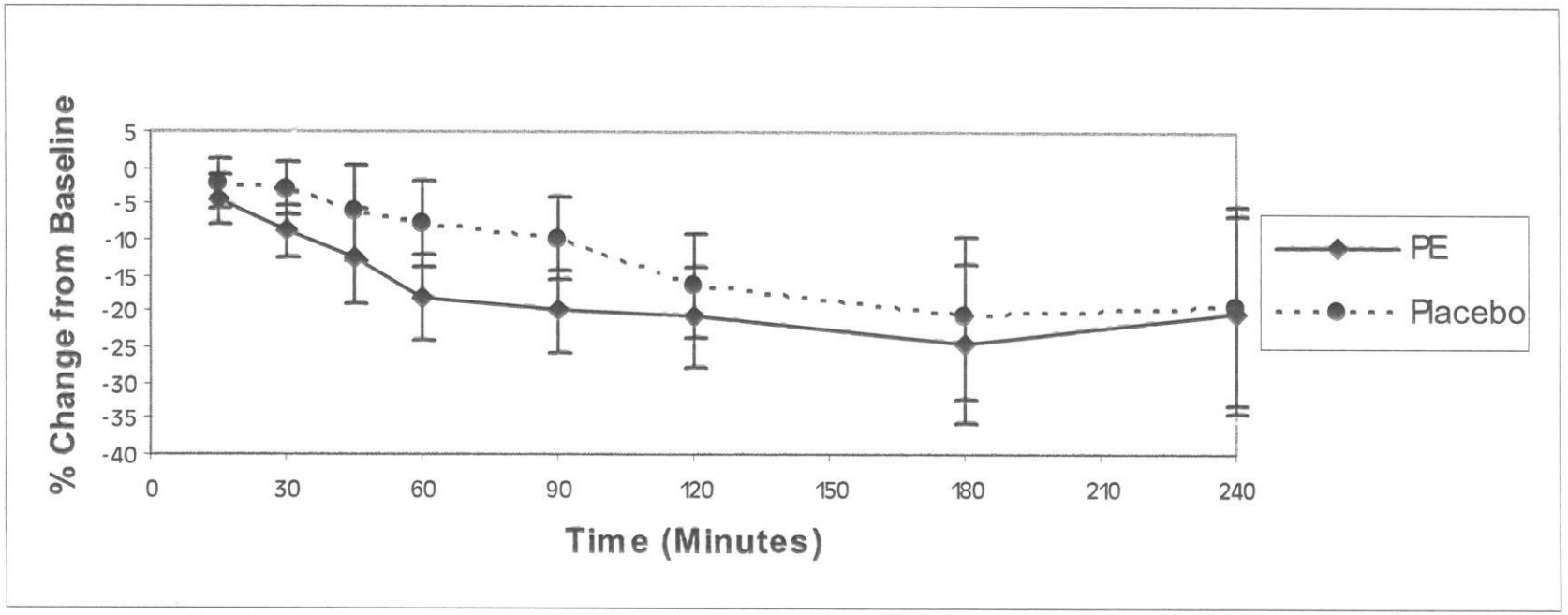


Figure 13
LN-Ratio By Study and Time (minutes) with 95% Confidence Limits for Each Treatment
Patient is Random
LN-Ratio Has Been Back-transformed from the ln Scale to Base10 Scale

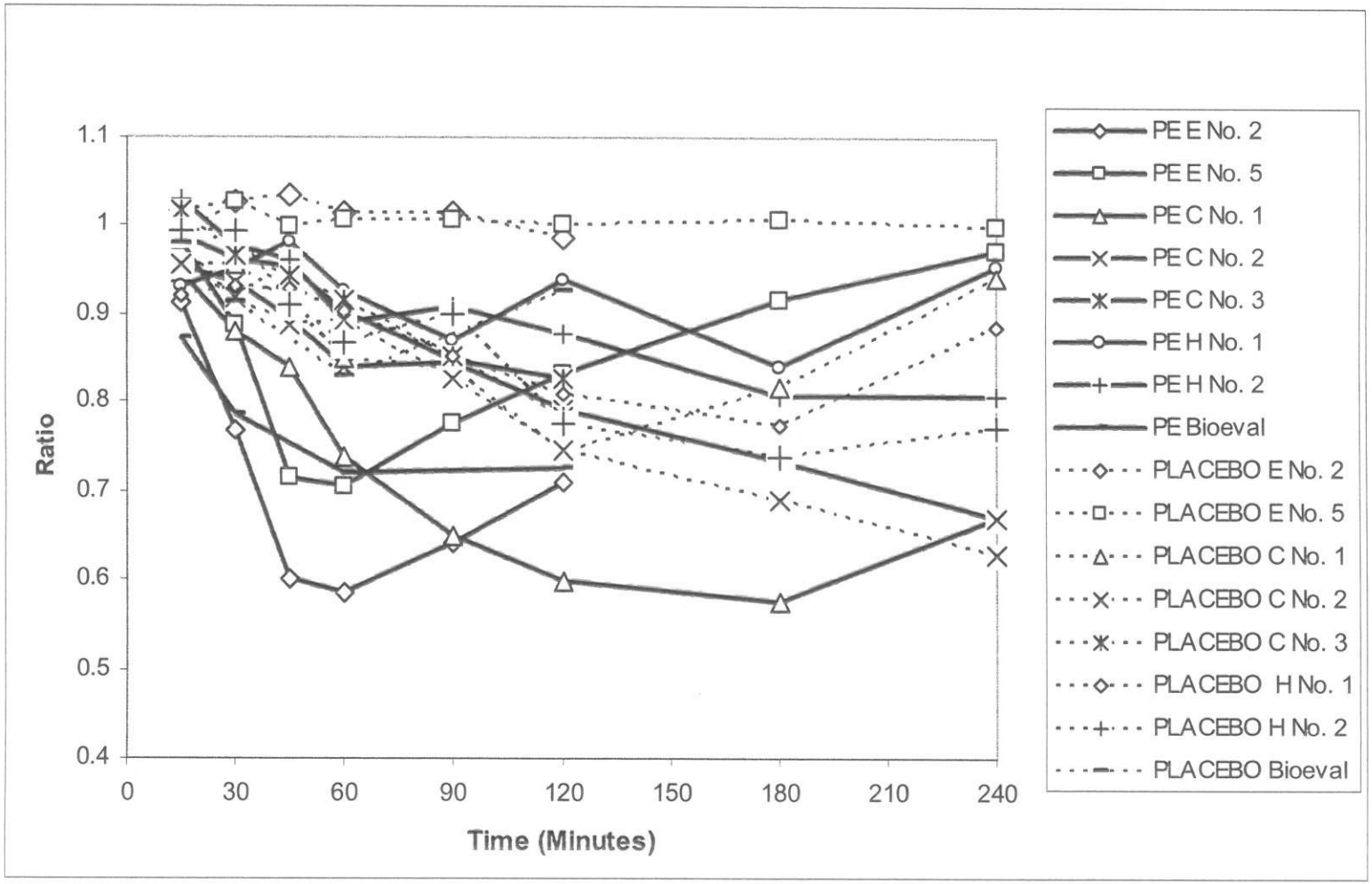


Figure 14
LN-Ratio by Time (minutes) with 95% Confidence Limits for Each Treatment
Model 2.a – Patient is Fixed
LN-Ratio Has Been Back-transformed from the ln Scale to the Base10 Scale

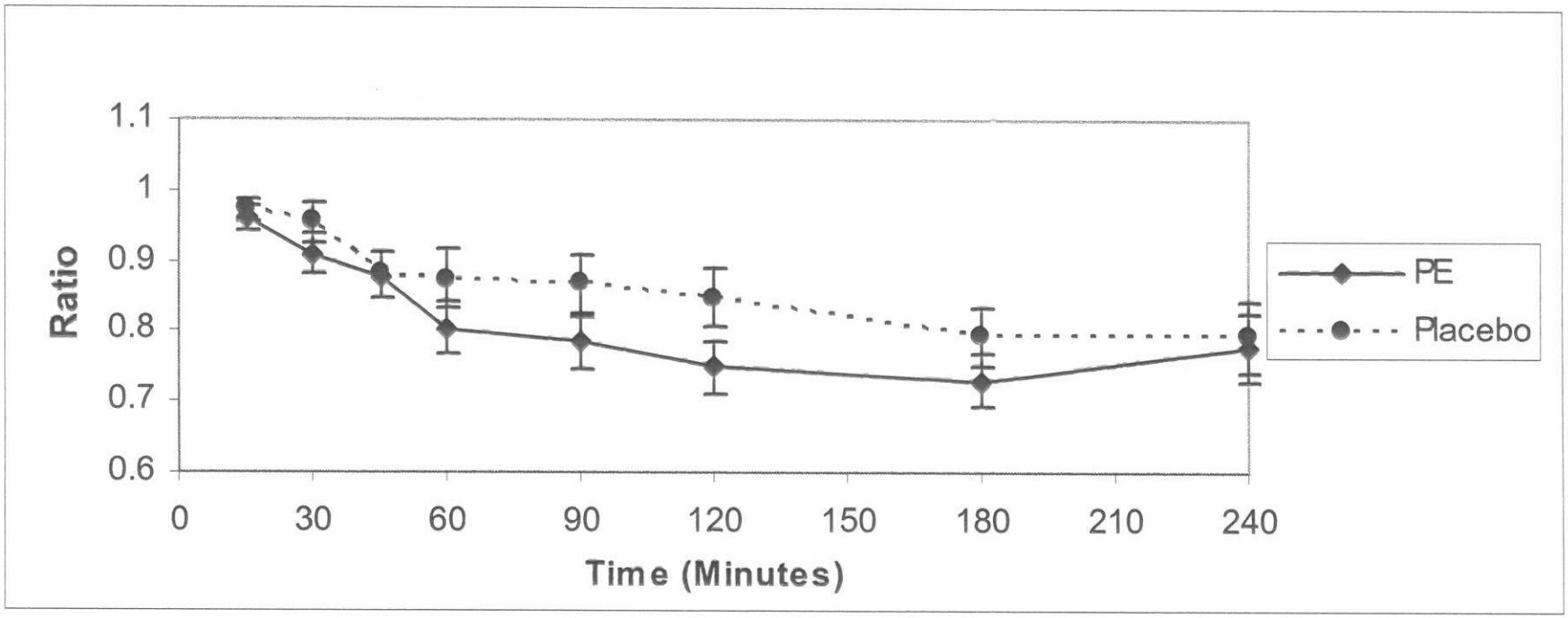


Figure 15
LN-Ratio by Time (minutes) with 95% Confidence Limits for Each Treatment
Model 2.b – Patient is Random
LN-Ratio Has Been Back-transformed from ln Scale to Base10 Scale

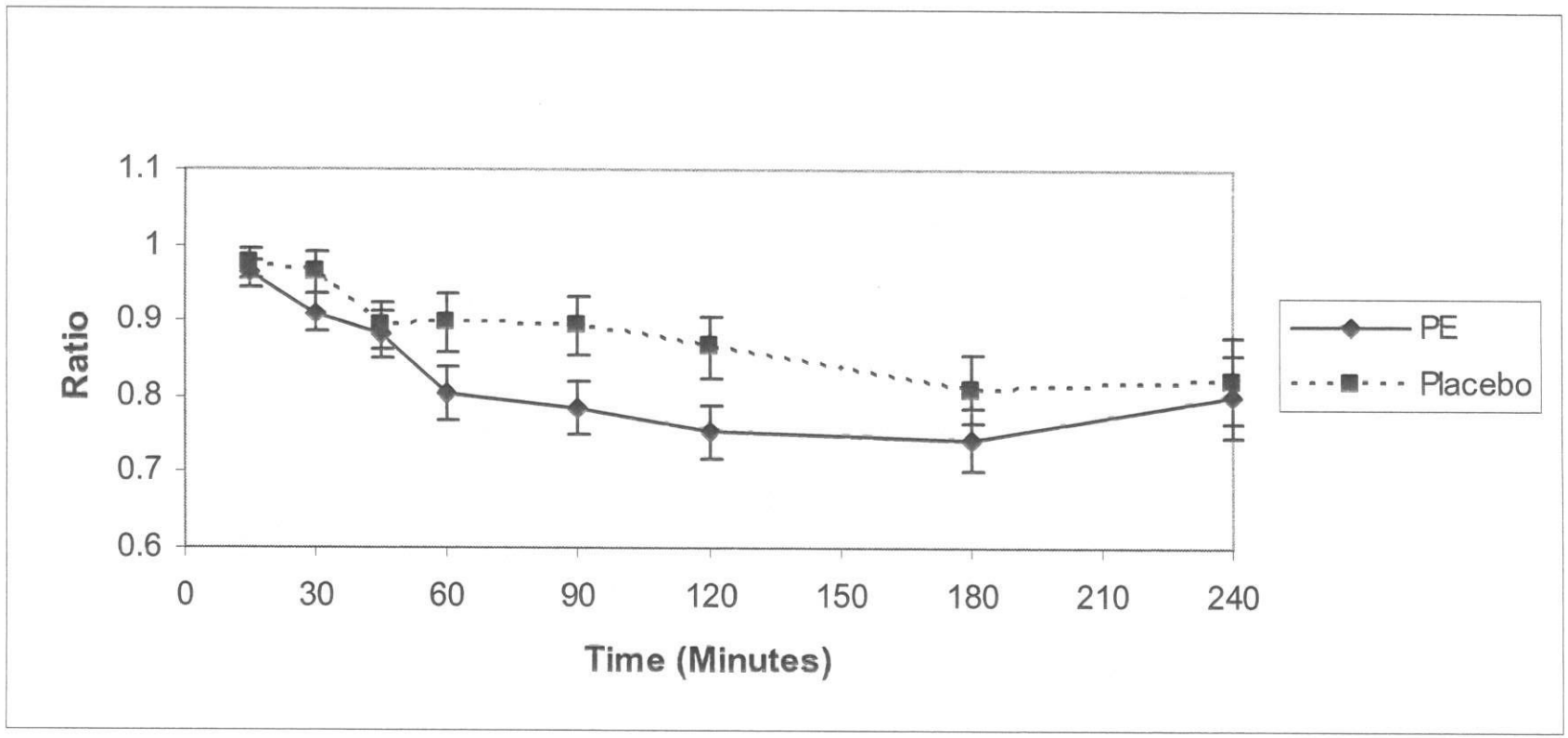
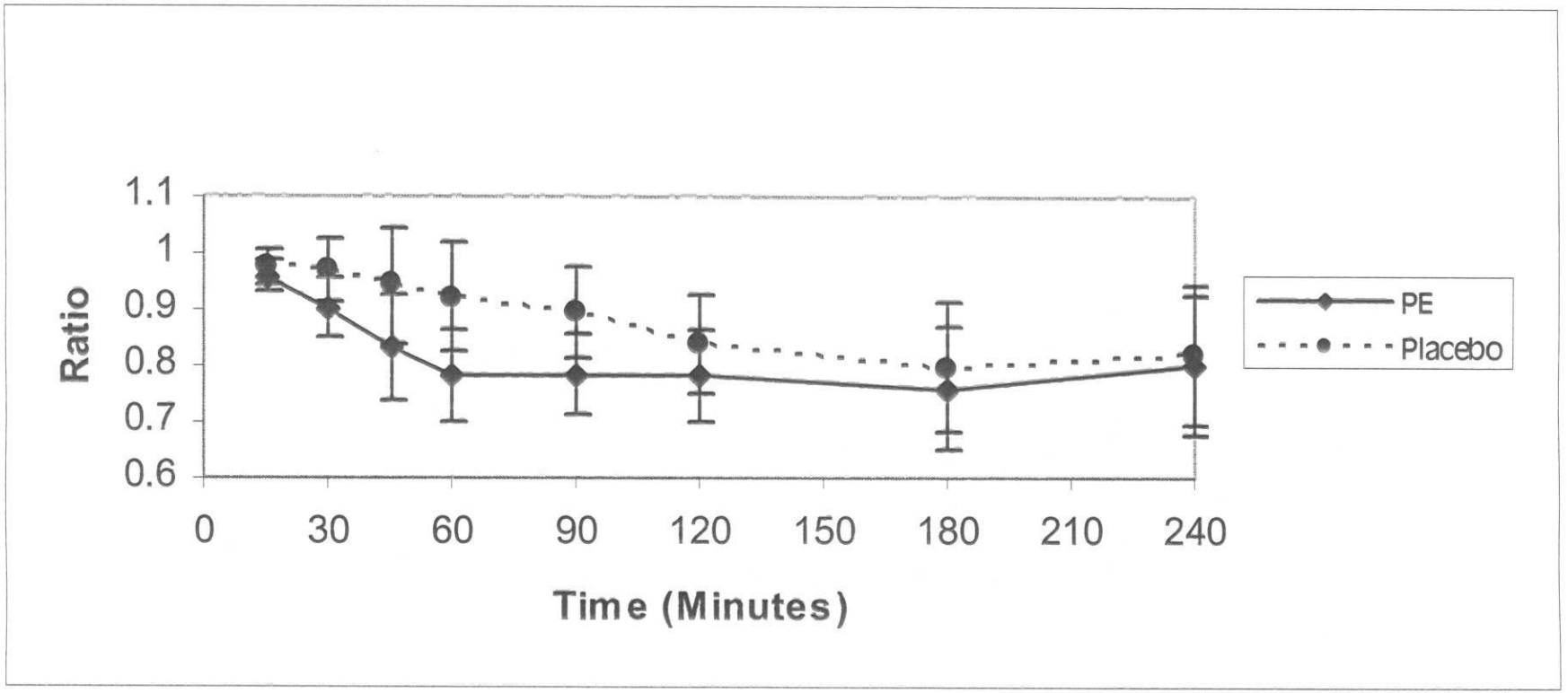


Figure 16
LN-Ratio by Time (minutes) with 95% Confidence Limits for Each Treatment
Model 3 – Patient, Study, and Treatment-by-Study Interaction are Random
LN-Ratio Has Been Back-transformed from the ln scale to the Base10 Scale



MEMORANDUM

To: Heinz Schneider

From: Michael Stoto

Re: Phenylephrine meta-analysis

Date: January 27, 2007

I have reviewed the January 23 draft of the CHPH Phenylephrine Task Group's "Efficacy Meta-Analysis of Single-Dose 10 mg Phenylephrine vs. Placebo in Adults with Acute Nasal Congestion due to Common Cold" and am pleased to report that I find that the task group has addressed all of the issues raised in the December 20, 2006 conference call, and that in my judgment the analysis meets professional standards. As a result, I believe that the conclusions are justified.

There are, however, a number of aspects of the written report that I believe can be improved. They are the following:

p. 6 — In presenting the study objectives, it should be noted that (a) individual studies will be reanalyzed in a parallel fashion and (b) a pooled (individual-level) meta analysis will be performed.

p. 12 — The footnote to Table 2 is an important point to make, but it should be made in the conclusions section rather than here.

p. 13 — The discussion of logs and ratios is overly complicated and confusing. It is well known that the log transformation is appropriate for ratio measures, and that the results of analyses done in the log scale should be transformed back to the original scale for presentation. A geometric mean is indeed equivalent to the re-transformed mean of the logs, but this not actually being done in this analysis, so the term "geometric mean" should not be used.

p. 14 — The results of study #8, now discussed in the pooled analysis section, should be moved to the conclusions section of the paper.

p. 15, l. 2 — Add s to "statistical models"

p. 15 — I would have labeled the second model as #1 and visa versa since that way the three would be increasingly complex.

p. 16 — The second complete paragraph, beginning with "The results …", is a result and should be moved to the results section.

pp. 17 & 18 Tables 3 and 4 should present the estimated difference or summary difference and a 95% confidence interval, i.e. the information in Figures 1-8.

Figures 1-8 Units should be given for the horizontal scale.

Comments on Phenylephrine Meta-analysis
M. A. Stoto, December 17, 2006

1. Choice of studies
    a. Why limit studies to before '76?
    b. Did you search for other studies, before or after '76?
    c. Complete references should be given for all studies
    d. "Site" looks like it might be the company performing some of the trials
2. Non-included studies
    a. Should list references and specific reason for exclusion
    b. Were results qualitatively consistent with the included studies?
    c. Was lack of individual-level data a reason for exclusion?
3. A priori choices
    a. should be made clear, including reason, at the start
    b. Rationale for excluding study #8 seems to depend on knowing that results would be significant without it
    c. Was choice of ΔNAR vs. ΔlnNAR a priori?
    d. Model for individual study and M-A
    e. 30 and 60 minute time points as most important output?
4. Time line
    a. Note at the start that studies tested outcomes at different points
    b. Were there results at other time points not reported here?
5. Data entry
    a. Note more clearly that individual-level data were used.
6. Outcome measure
    a. ln-ratio NAR = ΔlnNAR, which seems like a reasonable measure if NAR is a ratio; why was transformation used instead?
    b. ΔlnNAR might help with the departure from normality noted
7. Statistical model
    a. make more clear that this is a **pooled** meta-analysis (MA-P)
    b. List in text and tables as Model 1.a, 1.b, 2.a, 2.b, 3
8. Results
    a. If ΔNAR was chosen vs. ΔlnNAR a priori, it would be better to present it as such, with the alternative as a sensitivity analysis
    b. Report effect sizes and 95% C.I., not P-values
    c. Table 2 is hard to read since it does not make clear which studies has results at which levels and which didn't
    d. Better to present Table 2 in tabular form (e.g. rows = time points, columns = study) with effect and 95% C.I. for each available effect estimate. Base on a priori choice of statistical model, then indicate differences where they appear
    e. Table 2 (M-A results): Use same format as suggested above, with columns for Model 2 and Model 3
    f. Note that time scale on graphs is not equally spaced
    g. Show a forest plot for each key time point, with major analysis only

Department of Statistics
and Statistical Laboratory
101 Dickens Hall
Manhattan, KS 66506 -0802
785-532-6883
Fax: 785-532-7736
E-mail: statdept@stat.ksu.edu
http://www.ksu.edu/stats

January 18, 2007

Dr. Heinz Schneider
Vice President, Regulatory & Scientific Affairs
Consumer Healthcare Product Association
900 19th Street, NW, Suite 700
Washington, DC 20006

Dear Dr. Schneider:

Thank you very much for giving me an opportunity to review the report entitled "Efficacy Meta-Analysis of 10 mg Phenylephrine vs. Placebo in Adults with Acute Nasal Congestion Due to Common Cold" prepared by the CHPA Phenylephrine Task Group.

When reviewing the report, I have concentrated on the statistical analyses of each of the individual studies, as well as the Meta Analysis involving seven of the eight studies. I have also had an opportunity to review Appendices 1-5 and the individual study analyses and the Meta analyses.

Statistical analyses on each of the individual studies were performed using Mixed Model analyses, and in my opinion, these analyses were correctly performed and the results have been accurately described in Tables 3 and 4 and nicely illustrated in Figures 1-8, 9, and 13.

Meta analyses were performed using each of the five models 1.a, 1.b, 2.a, 2.b, and 3 with the report emphasizing the results of models 2.b and 3. Of the five models considered, I believe that Model 2.b is the most appropriate and most accurately describes the efficacy of Phenylephrine when compared to placebo. The results are accurately described in Table 5 and effectively illustrated in Figures 1-8, 10-12, and 14-16.

Finally, I agree with the report's basic conclusion that Phenylephrine at a dose of 10 mg is an effective decongestant.

If I can provide you with anything else, please let me know.

Sincerely,

Dallas E. Johnson
Professor Emeritus

CHPA

founded 1881

5578 7 FEB -9 P4:23

February 6, 2007

Dockets Management Branch
Food and Drug Administration (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Appendices to Letter dated February 1, 2007 – OTC Monograph for Nasal Decongestant Drug Products; Docket 76N-052N

Dear Sir or Madam:

Enclosed is a CD-rom containing the Appendices to the comments submitted by Consumer Healthcare Products Association on Thursday, February 1, 2007.[1]

Sincerely,

Heinrich Schneider, Dr. Med.
Vice President, Regulatory and Scientific Affairs

[1] All appendices are releasable.

1976N-0052N

SUP 13

Consumer Healthcare Products Association
900 19th Street, NW, Suite 700
Washington, DC 20006
T 202.429.9260 F 202.223.6835
www.chpa-info.org

The enclosed, sent with this cover letter, can be found at the following web address:

http://www.fda.gov/ohrms/dockets/dockets/76n0052n/76n-0052n-sup0013-00-toc.htm

CHPA

founded 1881

2548 7 AUG -3 P3:55

August 2, 2007

Dockets Management Branch
Food and Drug Administration (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: OTC Monograph for Nasal Decongestant Drug Products; Docket 76N-052N

Enclosed is a reprint of our article in *Clinical Therapeutics*, Vol. 29, No. 6, pp. 1057-1070 with the title "Meta-Analysis of the Efficacy of a Single Dose of Phenylephrine 10 mg Compared with Placebo in Adults with Acute Nasal Congestion Due to the Common Cold." The article presents and discusses the data of the meta-analysis study report submitted to the FDA Docket on February 1, 2007.

Sincerely,

Heinrich Schneider, Dr. Med.
Vice President, Regulatory and Scientific Affairs

C 253

1976N-0052N

Consumer Healthcare Products Association
900 19th Street, NW, Suite 700
Washington, DC 20006
T 202.429.9260 F 202.223.6835
www.chpa-info.org

Kollar C, Schneider H, et al. Meta-Analysis of the Efficacy of a Single Dose of Phenylephrine 10 mg Compared with Placebo in Adults with Acute Nasal Congestion Due to the Common Cold. Clinical Therapeutics, Vol. 29, No. 6, pp 1057-1070.

Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Lauren Quinn JD
Director
Regulatory Affairs
973.660.6167
quinnL4@wyeth.com

Wyeth

November 16, 2006

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD, 20852

RE: OTC Monograph for Nasal Decongestant Drug Products
Docket 76N-052N

Dear Sir or Madam:

Reference is made to a recent series of communications between Representative Waxman and the FDA on the efficacy of 10 mg phenylephrine. As a result of these communications, Wyeth Consumer Healthcare (WCH) has reviewed its records and is submitting information on three unpublished studies conducted between 1967 and 1983 that were not previously submitted to the OTC Monograph for Nasal Decongestant Drug Products, Docket 76N-052N. Accompanying the study reports is a review of the data supplied to the docket, as well as a review of the literature from 1976 to the present.

After reviewing the data, WCH concurs with the Agency opinion that at a dose of 10mg, phenylephrine is a safe and efficacious oral nasal decongestant.

Sincerely,

Lauren Quinn

WYETH CONSUMER HEALTHCARE
Lauren Quinn, JD
Director, Regulatory Affairs

cc: C. Ganley, Office of Nonprescription Drug Products

enc.

MAY 30 1973

A. H. ROBINS COMPANY

1407 Cummings Drive

Richmond, Virginia 23220

PROTOCOL EVALUATION REPORT

DIMETAPP ELIXIR

(AHR-G1-A) Protocol 01

Investigator: Burton Marcus Cohen, M.D.
230 W. Jersey Street
Elizabeth, New Jersey 07202

May 10, 1973

AHP2-REG-004-0044733

PROTOCOL EVALUATION REPORT

Dimetapp Elixir (AHR-GI-A) Protocol 01

Prepared by:

Dorothy K. Ervin, B.S.	Manager, Data Management and Analysi Section
Lester W. Preston, Jr., Ph.D.	Director, Scientific Information Department

The above report has been reviewed and approved by the undersigned.

5/10/73
Date

R. William Dent, M.D.
Associate Physician, Medical Service

AHP2-REG-004-0044734

INVESTIGATOR

Investigator:	Cohen, Burton Marcus, M.D.
Address:	230 W. Jersey Street Elizabeth, New Jersey 07202
Academic Affiliati	Associate Clinical Professor of Medicine The New Jersey College of Medicine
Type of Practice:	Internal Medicine
Study Number:	0101
Date Initiated:	05/69
Study Status:	Complete
Status Date:	02/71
Patients Reported:	48

AHP2-REG-004-0044735

TABLE OF CONTENTS

* (NA) Not Applicable

AHP2-REG-004-0044736

AHP2-REG-004-0044737

0. SUMMARY

This well controlled clinical trial was conducted to compare the effects of Dimetapp Elixir with those of its components on nasal airway resistances and on nasal mucosal characteristics.

48 subjects were randomly assigned to one of four treatment groups. Single doses of test medication were administered as follows:

1. 24 subjects received 10 cc Dimetapp Elixir (8 mg brompheniramine, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride).
2. 8 subjects received 10 cc Neosynephrine Elixir (10 mg phenylephrine hydrochloride).
3. 8 subjects received 2.5 cc Propadrine Elixir (10 mg phenylpropanolamine).
4. 8 subjects received 20 cc Dimetane Elixir (8 mg brompheniramine maleate)

In order to preserve blindness, test medications were administered by a disinterested third party since the test medications were not identical in appearance and concentration.

Measurements of nasal inspiratory and expiratory resistances and subjective evaluations of nasal mucosal characteristics (viz. Nasal Serous Secretions, Nasal Mucosal Congestion, Nasal Mucosal Hyperemia, and Ease of Nasal Breathing) were made pre-drug and every 30 minutes post-drug for 4.5 hours. At the end of 4 hours (*i.e.* 240 minutes) post-drug, each subject received Afrin Nasal Spray.

Analyses of covariance were performed on the measurements of nasal inspiratory and expiratory resistances. The results of these analyses may be found in Figures 0-1 and 0-2. As shown, the effects of Dimetapp on both nasal inspiratory and expiratory resistances are consistently better than those of any of its components; in fact, many of the differences observed are statistically significant.

Analyses of variance were performed on the ratings of the nasal mucosal characteristics. Prior to these analyses, a covariance-like procedure was utilized, and the resultant variables were transformed to ridits. Results of these analyses may be found in Figures 0-3 through 0-6. These results are consistent with those for the nasal

AHP2-REG-004-0044738

airway resistances - *i.e.* Dimetapp is consistently better than any of its components, and many of the differences observed are statistically significant.

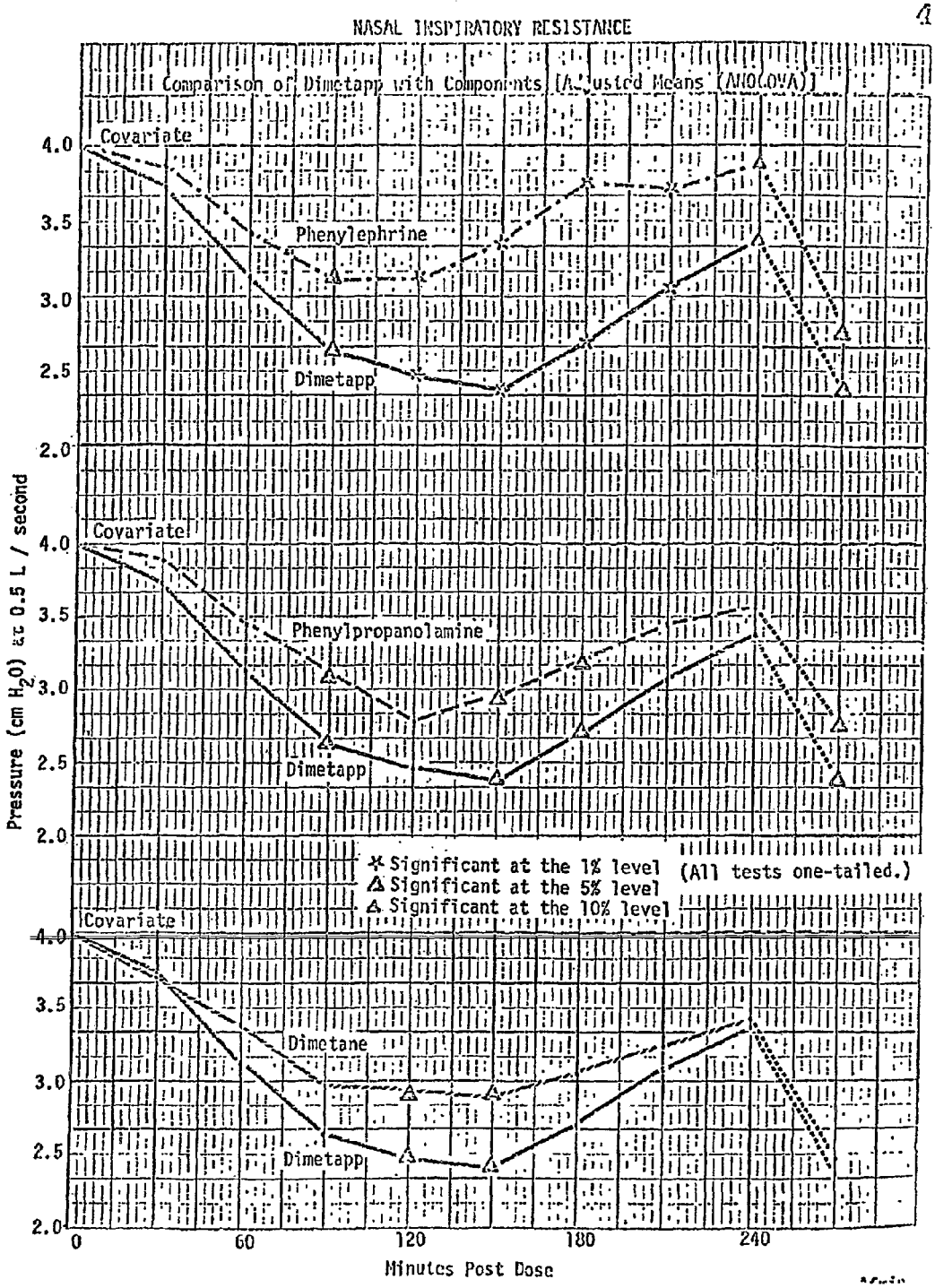
A more detailed discussion of the analyses performed on these data may be found in Section 4 of this report.

As anticipated, few adverse effects were observed, and none of those reported are considered to be significant.

AHP2-REG-004-0044739

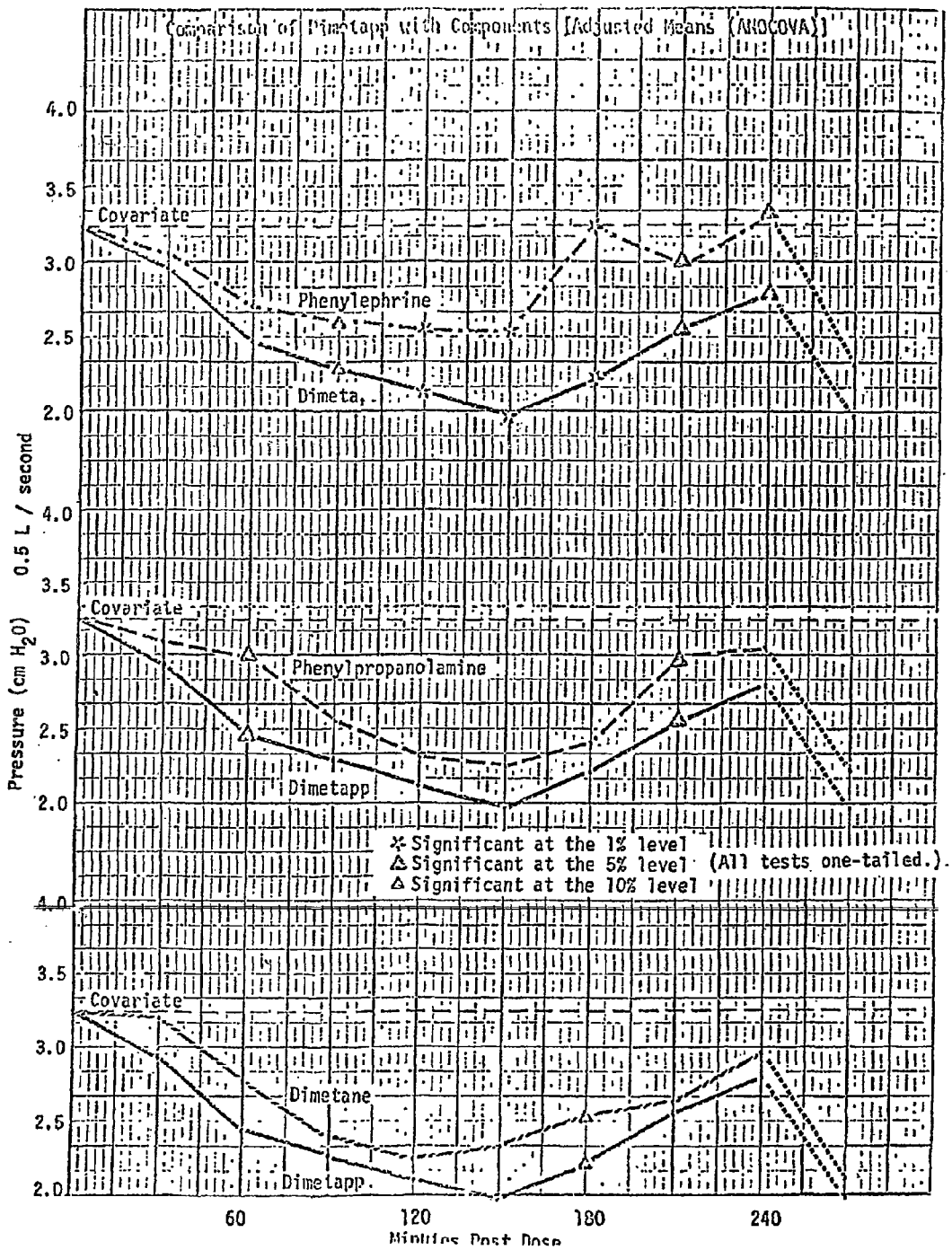
Nasal Inspiratory and Expiratory Resistances

AHP2-REG-004-0044740



AHP2-REG-004-0044741

NASAL EXPIRATORY RESISTANCE



AHP2-REG-004-0044742

Nasal Mucosal Characteristics

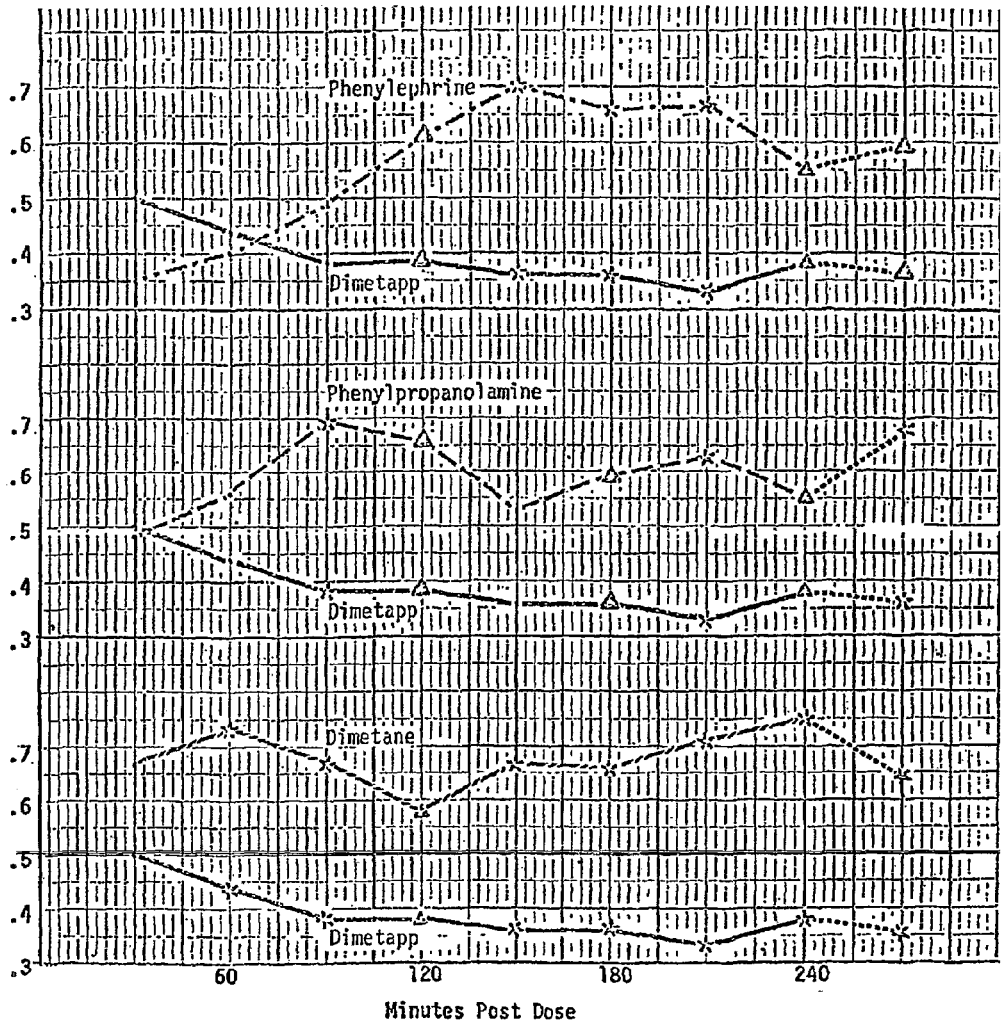
AHP2-REG-004-0044743

Figure 0-3

7

NASAL SEROUS SECRETIONS

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



☆ Significant at the 1% level
△ Significant at the 5% level
△ Significant at the 10% level.
(All tests one-tailed.)

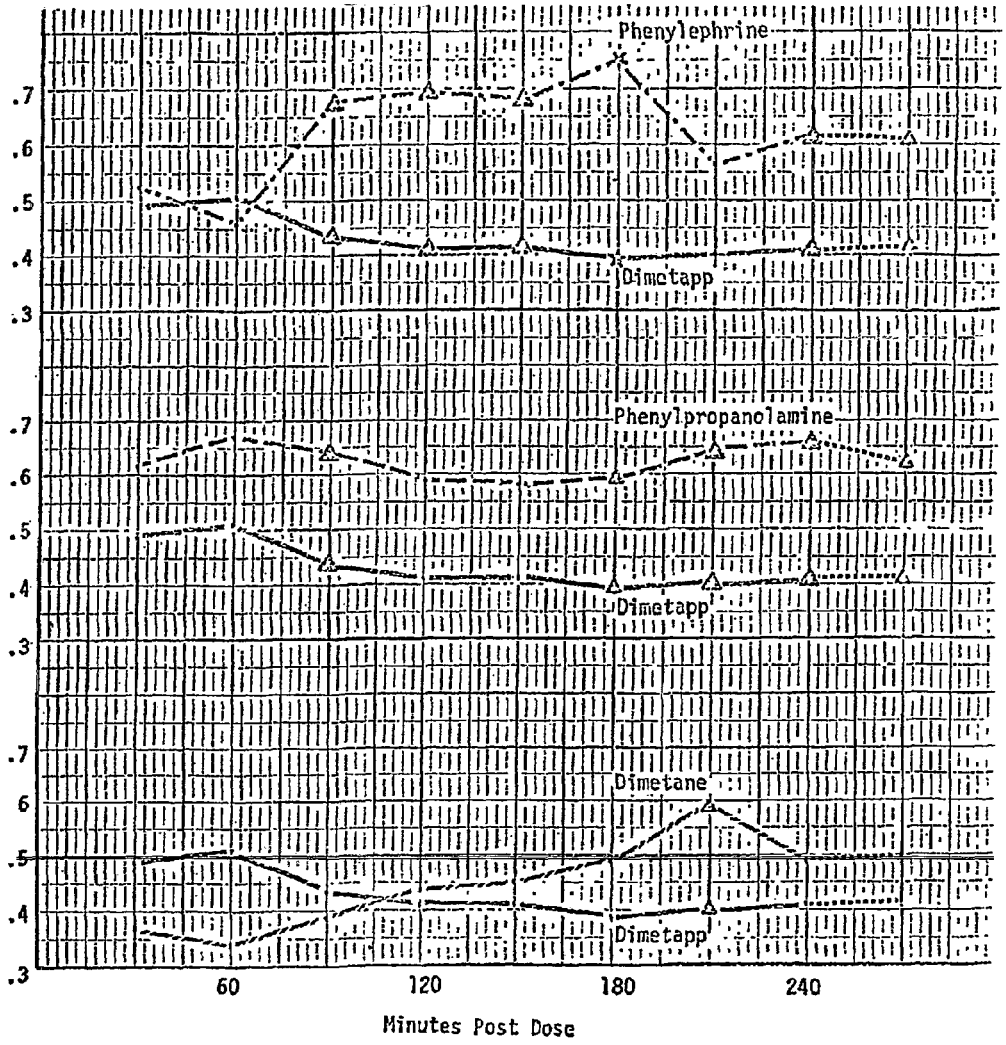
..... Afrin

AHP2-REG-004-0044744

Figure 0-4

NASAL MUCOSAL CONGESTION

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



☆ Significant at the 1% level
△ Significant at the 5% level (All tests one-tailed.)
△ Significant at the 10% level

..... Af

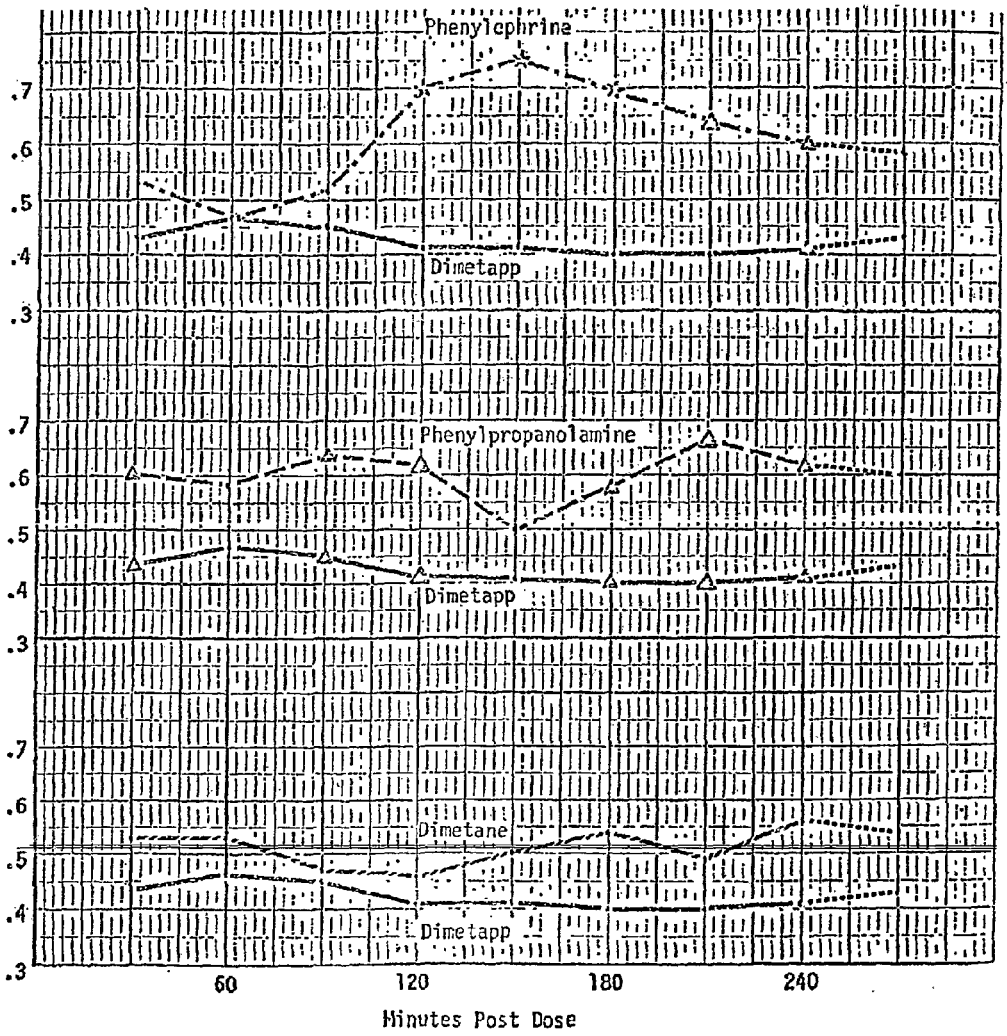
AHP2-REG-004-0044745

Figure 0-5

9

NASAL MUCOSAL DIFFERENTIA

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



☆ Significant at the 1% level
△ Significant at the 5% level (All tests one-tailed.)
△ Significant at the 10% level

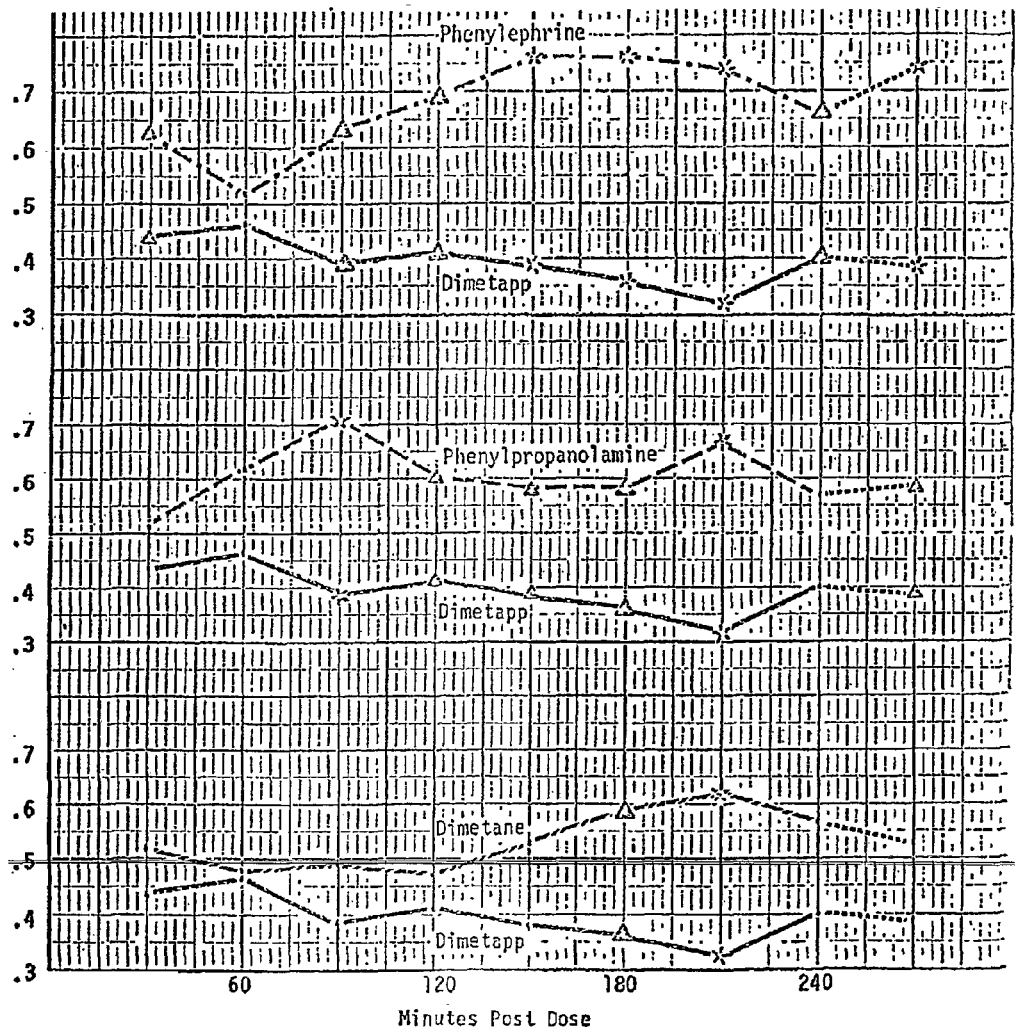
..... Af

AHP2-REG-004-0044746

Figure 0-6

EASE OF NASAL BREATHING

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



✱ Significant at the 1% level
△ Significant at the 5% level
△ Significant at the 10% level
(All tests one-tailed.)

..... Afrin

AHP2-REG-004-0044747

1. Study Protocol

AHP2-REG-004-0044748

1. STUDY PROTOCOL

1.1 PROTOCOL DESCRIPTION

1.1.1 Objective

To compare the effects of single doses of Dimetapp Elixir with each of its components on nasal airway resistance in patients with upper respiratory infections.

1.1.2 Study Design

This is a single investigator well controlled special study in which each of the patients with upper respiratory infections received a single dose of Dimetapp Elixir (24 patients) or one of its three components (8 patients/component) on a single test day; measurements of nasal airway resistance and subjective evaluations of nasal mucosal characteristics were made every 30 minutes after drug administration for 4.5 hours.

1.1.3 Patient Description

A. Selection Criteria

1. Treated Condition(s) and Diagnostic Criteria

   Nasal congestion due to upper respiratory infections whose duration was not less than 24 hours and not more than 72 hours at time of test day.

2. Prior Treatment Criteria

   48 hours off all drugs having the same general pharmacological actions as the study medication.

3. Safety Exclusion Criteria

   a. Chronic pulmonary disease

   b. Allergic rhinitis

   c. Pregnancy

4. Miscellaneous Criteria

   a. Adults

   b. Males and females

   c. Outpatients (office)

   d. Willingness to participate in a one day study.

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B. The patients were numbered serially as they entered the study and were assigned to one of the study medications on the basis of a randomization schedule (see Appendix A4.3) prepared by the Biometry Unit, A. H. Robins Company.

1.1.4 Treatment Groups

A. Test Groups

1. Dimetapp Elixir containing 4 mg of brompheniramine maleate, 5 mg of phenylephrine hydrochloride, and 5 mg of phenylpropanolamine hydrochloride per 5 cc.

B. Control Groups

1. Dimetane Elixir containing 2 mg of brompheniramine maleate per 5 cc.

2. Neosynephrine Elixir containing 1 mg of phenylephrine hydrochloride per 1 cc.

3. Propadrine Elixir containing 4 mg of phenylpropanolamine hydrochloride per 1 cc.

C. Dosage Schedules

Using the Randomization Schedule in Appendix A4.3 each patient received single doses of test medication on the morning of the test day according to the following schedules:

Treatment Group 1: 10 cc of Dimetapp Elixir (8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride).

Treatment Group 2: 20 cc of Dimetane Elixir (8 mg brompheniramine maleate).

Treatment Group 3: 10 cc of Neosynephrine Elixir (10 mg phenylephrine hydrochloride).

Treatment Group 4: 2.5 cc of Propadrine Elixir (10 mg phenylpropanolamine hydrochloride).

Since the test medications were not identical in appearance they were administered by a disinterested third party; hence, the investigator and the technician making the measurements and assessments were "blind" to the test medication received by each subject.

At four hours (240 minutes) after dosing, each patient received Afrin (oxymetazoline hydrochloride) nasal solution.

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C. Concomitant Treatments

1. Excluded

Nasal decongestants (oral and topical)

2. Included

Any medications and/or treatments needed for concurrent conditons were permitted but were to be recorded on data sheets.

1.1.5 Assessment of Special Findings

At "0 hour" and at 30, 60, 90, 120, 180, 240 and 270 minutes after test medication was administered, the following assessments were made:

A. Nasal Airway Resistance

Using the Respiron both nasal inspiratory and expiratory resistances were measured. The results were reported as pressure (cm H_2O) at 0.5 5/sec.

See Appendix A5.3 for the following reference on Respiron methodology.

Cohen, Burton M., "Nasal Airway Resistance and the Effects of Bronchodilator Drugs in Expiratory Airflow Disorders." *Respiration* 26:35-46, 1969.

B. Characteristics of Nasal Mucosa

Evaluations were made of the following:

1. Nasal mucosal congestion
2. Nasal mucosal hyperemia
3. Nasal secretion
4. Ease of nasal breathing

Items 1-3 above were rated on a 5-point scale as follows:

0 = absent
1 = mild
2 = moderate
3 = severe
4 = very severe

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Item 4 above was rated on a 5-point scale as follows:

0 = normal
1 = only mildly impaired
2 = moderately impaired
3 = severely impaired
4 = total obstruction

[It should again be noted that Afrin (oxymetazoline hydrochloride) nasal solution was administered immediately after the above measurements were made at 240 minutes.]

1.1.6 Effectiveness Assessment: See Special Findings (1.1.5)

1.1.7 Safety Assessment

The investigator observed particularly for the following adverse effects: nervousness, headache, nausea, dizziness or light-headed, drowsiness, dry mouth, urticaria, palpitation, and blurred vision.

Blood pressures (right arm, sitting three minutes) and pulse rates (sitting three minutes) were measured pre-drug and post drug according to the following schedule:

"0 hour"	120 minutes
30 minutes	180 minutes
60 minutes	240 minutes
90 minutes	270 minutes

1.1.8 Data Management and Analysis

After initial medical screening by the Data Monitor (M.D.), primarily from a safety viewpoint, the data sheets were carefully monitored by a research physician in order to ascertain if they met the selection and treatment criteria of the protocol (see 4.1.3 and 4.1.4). Standard statistical methods were used to analyze the special findings (see Section 5).

~~1.1.9~~ Summary of "Bias Minimization" Aspects

1. Assignment of patients to treatment groups by a pre-determined randomization schedules.

2. Drug administration of the differing test medications by a disinterested third party (i.e. the investigator and technician were "blind" to the medication each patient received).

3. Careful and independent medical auditing of the data sheets for "acceptability" (e.g. with respect to patient selection criteria, etc.) prior to biometric evaluation of the special findings.

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2.1 PROTOCOL DEVIATIONS: None

AHP2-REG-004-0044753

4. Investigator Information

AHP2-REG-004-0044754

2. INVESTIGATOR INFORMATION

One clinician supplied the data on the 48 patients participating in this study. The name and address of the investigator and pertinent information about the investigation may be found at the front of this report. The *curriculum vitae* of the investigator follows in this section.

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Curriculum Vitae: Burton Marcus Cohen, M.D.

AHP2-REG-004-0044756

MANG-3

MAY 5 1969

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CARDIOPULMONARY DISEASES
RESPIRATORY PHYSIOLOGY

7/7/67

18

CURRICULUM VITAE

Name: Burton Marcus Cohen, M.D.

Personal Data: Born: December 13, 1925, Elizabeth, N.J.
Married, four children.

Education: 1945 A.B. Columbia University
1948(March) M.D. University of Rochester School of Medicine and Dentistry.

Positions:
1948-50 Intern, Medical Services, Maimonides Hospital, Brooklyn, N.Y.
1950-51 Assistant Resident Physician, Maimonides Hospital
1951-52 Assistant Resident Physician, Strong Memorial Hospital & Hochstetter Fellow in Medicine, University of Rochester

1952-55 Active Duty-Surgeon(Lieutenant-Commander) U.S. Public Health Service:
Internist, Phoenix Area
Deputy Chief of Medicine(Chest Diseases), U.S. Marine Hospital, Detroit, Michigan
Chief of Medicine, U.S.P.H.S. Out-patient Clinic, New York, N.Y.

1954-57 Goldwater Memorial Hospital, Welfare Island, New York:
First (Columbia University) Research Service:
Research Fellow, 1954-56
Assistant Visiting Physician, 1956-57

1955-63 Saint Elizabeth Hospital, Elizabeth, New Jersey:
Assistant Attending Cardiologist 1955-58
Associate Attending Cardiologist 1958-59
Senior Attending Cardiologist 1959-61
Attending in Medicine 1960-61
Consultant in Internal Medicine and Cardiology 1961-63

1955-- Elizabeth General Hospital, Elizabeth, N.J.
Assistant Attending Physician 1958-60
Associate Attending Physician 1960-63
Attending Physician 1963-
Electrocardiographer 1966-

1963-- Jersey City Medical Center, Jersey City
Assistant Attending Physician 1963-D65
Attending Physician 1965-1967

1967-- Chairman, Department of Medicine-Elizabeth General Hospital

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1955-- Alexian Brothers Hospital, Elizabeth, N.J.
Assistant Attending Physician 1958-59
Consultative Courtesy Staff 1959--

1959-63 Medical Board, Deborah Hospital, Browns Mills, N.J.

1959-64 Associate Director, T.J. White Cardiopulmonary Institute, B.S. Pollak Hospital, JerseyCity, N.J.

1955-57 Consultant in Cardiology, U.S.P.H.S. Outpatient Clinic, New York

Consultant to:
Baxter Laboratories, Morton Grove, Illinois
Irwin, Neisler & Co., Decatur, Illinois
Riker Laboratories, Northridge, California
Squibb Institute for Therapeutic Research, New Brunswick, N.J.
Schering Corporation, Bloomfield, N.J.
Strasenburgh Laboratories, Rochester, N.Y.
A.M. Christians Co., Brussels, Belgium.
A.H. Robins Co., Richmond, Virginia

Academic Positions:

1951-52 Assistant in Medicine, University of Rochester
1954-57 Assistant in Medicine, Columbia University College of Physicians and Surgeons
1959-61 Assistant Professor of Clinical Medicine, Seton Hall College of Medicine
1959-60 Assistant Professor of Clinical Preventive Medicine, Seton Hall College of Medicine
1961-63 Clinical Assistant Professor of Medicine, Seton Hall College of Medicine
1963-65 Associate Professor of Clinical Medicine, Seton Hall College of Medicine
1960-61 Postgraduate Advisory Curriculum Committee, Seton Hall College of Medicine.
1965- Associate Clinical Professor of Medicine, The New Jersey College of Medicine.

Qualifications:

1955 Diplomate, American Board of Internal Medicine
1956 Fellow, American College of Chest Physicians
1957 Fellow, American College of Cardiology
1961 Fellow, AMERICAN COLLEGE OF PHYSICIANS
1961 Fellow, American Society of Clinical Radiology
1955 Fellow, Academy of Medicine of New Jersey
1963 Fellow(Charter), American College of Clinical Pharmacology and Chemotherapy
1965 Fellow, The Royal Society of Medicine (London)
1967 Fellow, American Geriatrics Society

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Memberships:

American College of Physicians
American College of Chest Physicians
American College of Cardiology
American Society of Clinical Radiology
International Cardiovascular Society and North American Chapter
International Society of Internal Medicine
American and New Jersey Societies of Internal Medicine
American Federation for Clinical Research and N.J. Chapter
American Thoracic Society
American Heart Association
N.J. Heart Association
Union County Heart Association (Past President)
Reserve Officers Association of the U.S.
Association of Military Surgeons of the United States
Reserve Officers Association of the U.S.P.H.S.
Clinical Society, U.S.P.H.S.
P & S Club (N.Y.)
Medical Alumni Association, University of Rochester (former Class Chairman)
American Association of Inhalation Therapits (Medical Advisor)
Association of American Physicians and Surgeons
American Association of University Professors
American Association for the Advancement of Science
Fellow, New York Academy of Science
Drug Information Association (Charter Member)
Academyof Science of N.J.
American Geriatrics Society
American Therapeutic Society

Cardiology Editor: MEDECINE et HYGIENE, Geneva Switzerland. 1959--1965

Section on Physiologic Therapy (Committee on Inhalation Therapy), American College of Chest Physicians. 1960--

International Committee on Emphysema, IX International Congress on Diseases of the Chest, Copenhagen, August 20-25, 1966.

ALEXANDER COCHRAN BOWEN-HARLOW BROOKS SCHOLAR, New York Academy of Medicine, 1949-1950.

CIVIC: Rotary Club of Elizabeth, N.J.
Honorary Member, Rotary Club of St. Marylebone, London, England.
Columbia University Club (N.Y.C.)

Military:
U.S.N.R. 1943-44
U.S.P.H.S.(R) and U.S.P.H.S.(Regular Corps) 1952-54
Surgeon, USPHS(R)-Inactive 1955-1966.
Senior Surgeon(Commander) 1966-

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18. Chlorothiazide therapy of the ambulatory patient with hypertension. Observations in 140 patients treated for up to two years of continuous therapy. 1959 Scientific Sessions, 25th annual meeting,. Am. Coll. Chest Physicians, Atlantic City, N.J.

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EXHIBITS, PAPERS PRESENTED:

Clinical Exhibit: The treatment of Ambulatory Patients with Hypertension. A.M.A. Annual Meeting, San Francisco, July, 1959.

Indiana Academy of General Practice, March, 1959.

Clinical Exhibit: The importance of weight reduction in Internal Medicine. A.M.A. Clinical Meeting, Dallas, Texas, December, 1959.

Bahamas Medical Conference on Hypertension, January, 1961.

Bahamas Conference on Internal Medicine, April, 1962.

VI INTERNATIONAL CONGRESS OF INTERNAL MEDICINE, Basle, Switzerland, Aug. 1960.

American College of Angiology, New York, N.Y. (Symposium on Atherosclerosis), June, 1961.

International Cardiovascular Society and International Congress of Cardiovascular Surgery, Dublin, Ireland, September, 1961.

European Cardiovascular Surgical Congress, Stockholm, Sweden, July, 1962.

University of Liege, Faculty of Medicine, June, 1962.

VII INTERNATIONAL CONGRESS OF INTERNAL MEDICINE, Munich, Federal Republic of Germany, September, 1962.

Scientific Exhibit (Certificate of Merit). 196th Annual Meeting, The Medical Society of New Jersey, May 12-16, 1962.: Aerosol-Induced Sputum.

18th Annual Meeting, Medical Alumni Association, The University of Rochester, Rochester, N.Y.; October 11-13, 1962.

Scientific Sessions, American College of Cardiology, Los Angeles, California, February 28-March 3, 1963.

~~Medical Society of the State of New Jersey, Atlantic City, N.J.; May 13-20, 1963.~~

Scientific Exhibit: Physiologic Therapy of Obstructive Ventilatory Disorders, Annual Meeting, American Academy of General Practice, Atlantic City, N.J., April 13-16, 1964 and Annual Meeting, American Medical Association, June 21-25, San Francisco, California.

Third Annual Meeting, American College of Clinical Pharmacology & Chemotherapy, Philadelphia, Pa. April 29-30, 1966.

Oxygen Toxicity: Mid-Atlantic Society of Nurse Anesthetists. Mid-Atlantic Hospital Meeting, May 18, 1966, Atlantic City, N.J.

Diagnosis of Obstructive Lung Diseases. N.J. Acad. Gen. Practice, Atlantic City, Jan. 1966.

AHP2-REG-004-0044766

Bronchoperviant effects of Pimetine HCl. Annual Scientific Sessions, American College of Chest Physicians. June 23-27, 1966. Chicago, Illinois.

IX International Congress on Diseases of the Chest, H. C. Orsted Institute, Copenhagen, August 20-25, 1966.

Appraisal of the worth of bronchodilator microaerosols: III. Cardiovascular and nervous system effects as indices of broncholytic potency in clinical trials. Annual Meeting, American Medical Association (Meeting of Sections on Diseases of the Chest and Preventive Medicine-June 19, 1967), Atlantic City, N. J., June 18-24, 1967.

Airway Resistance Measurements in the Internist's Office:Routine Determinations in the Diagnosis and Care of Breathless Patients.

VI. International Congress of Allergology, Montreal, Canada, Nov. 5-11, 1967.

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AHP2-REG-004-0044768

3. DRUG/ASSAY INFORMATION

3.1 Drug Information

The test medications were taken from commercial lots. They were as follows:

1. Dimetane Elixir - 2 mg brompheniramine maleate per 5 cc
2. Dimetapp Elixir - 4 mg brompheniramine maleate, 5 mg phenylephrine hydrochloride, and 5 mg phenylpropanolamine hydrochloride per 5 cc
3. Neosynephrine Elixir (Winthrop) - 1 mg phenylephrine hydrochloride per 1 cc
4. Propadrine Elixir (Merck, Sharp, and Dohme) - 4 mg phenylpropanolamine hydrochloride per 5 cc

Since the test medications were not identical in appearance, they were administered by a disinterested third party; hence, the investigator and the technician making the measurements were "blind" to the test medication received by each subject.

AHP2-REG-004-0044769

AHP2-REG-004-0044770

4. SPECIAL FINDINGS

4.1 Patient Accountability

Forty-eight patients with upper respiratory infections were enrolled in the study. Each successfully completed his single test day. A listing of the patients enrolled may be found in Table 4.1-01.

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Table 4.1-01

PATIENT CHARACTERISTICS

TREATMENT GROUP: Dimetapp Elixir

Subject No.	Age	Sex	Race	Weight (lbs.)	Height (inches)
1	38	F	C	125	65.0
3	41	M	C	178	73.0
5	64	F	C	129	61.0
8	46	F	C	136	66.0
9	44	M	C	191	69.0
11	51	F	C	134	65.0
12	69	M	C	201	68.0
14	46	M	C	169	66.0
16	40	F	C	149	65.0
21	40	F	C	138	65.0
23	74	F	C	169	68.0
24	64	M	C	161	68.0
25	39	F	C	123	65.0
26	53	M	C	192	73.0
28	40	F	C	137	65.0
32	48	F	C	147	69.0
34	55	M	C	179	70.5
35	23	F	C	137	65.0
38	69	F	C	149	64.0
39	19	M	C	247	75.5
41	71	M	C	164	69.0
43	58	F	C	154	64.0
44	40	F	C	132	63.0
48	54	M	C	161	68.0

Continued

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Table 4.1-01 (Cont'd.)

PATIENT CHARACTERISTICS

TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

Subject No.	Age	Sex	Race	Weight (lbs.)	Height (inches)
7	42	F	C	161	67.0
15	68	F	C	141	63.0
18	56	M	C	194	70.0
19	42	F	C	139	67.0
37	38	M	C	199	69.0
40	37	F	C	137	66.0
42	43	M	C	170	73.0
46	60	F	C	149	65.0

TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

Subject No.	Age	Sex	Race	Weight (lbs.)	Height (inches)
2	62	F	C	168	67.0
4	36	F	C	123	72.0
6	71	F	C	143	64.0
10	64	M	C	156	65.0
29	67	F	C	191	67.0
30	36	F	C	139	67.0
33	64	M	C	179	72.0
47	59	M	C	175	67.0

Continued

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Table 4.1-01 (Cont'd.)

PATIENT CHARACTERISTICS

TREATMENT GROUP: Dimetane Elixir (8 mg brompheniramine maleate)

Subject No.	Age	Sex	Race	Weight (lbs.)	Height (inches)
13	52	F	C	139	67.0
17	56	F	C	106	61.0
20	51	M	C	184	72.0
22	58	M	C	179	65.0
27	46	F	C	128	65.0
31	39	M	C	171	68.0
36	39	M	C	168	67.0
45	70	F	C	149	63.0

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4.2 Special Findings

4.2.1 Nasal Inspiratory and Expiratory Resistances (Respiron)

Analyses of covariance were performed on both the nasal inspiratory and expiratory resistances using the pre-drug measurements as the covariates. For both parameters, the adjusted means of the components were compared with the adjusted means of Dimetapp using Dunnett's t (one-tailed). The results of these analyses may be found in Tables 4.2.1-01 and 4.2.1-02 and Figures 4.2.1-01 and 4.2.1-02.

As shown, Dimetapp is consistently better than any of its components and many of the differences are statistically significant.

In addition, the adjusted means for each of the treatment groups were compared with the "control value" (covariate). As shown in Tables 4.2.1-03 and 4.2.1-04 and Figures 4.2.1-03 and 4.2.1-04, Dimetapp and each of its components demonstrate significant decreases in both nasal inspiratory and expiratory resistances - most of these differences are highly significant (i.e., $p < 0.01$).

Listings of the data discussed above and more detailed information on the analyses may be found in Appendix A4.

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Table 4.2.1-01

NASAL INSPIRATORY RESISTANCE: COMPARISON OF DIMETAPP WITH COMPONENTS

Analysis of Covariance and Results of Dunnett's t (HRT Dimetapp)

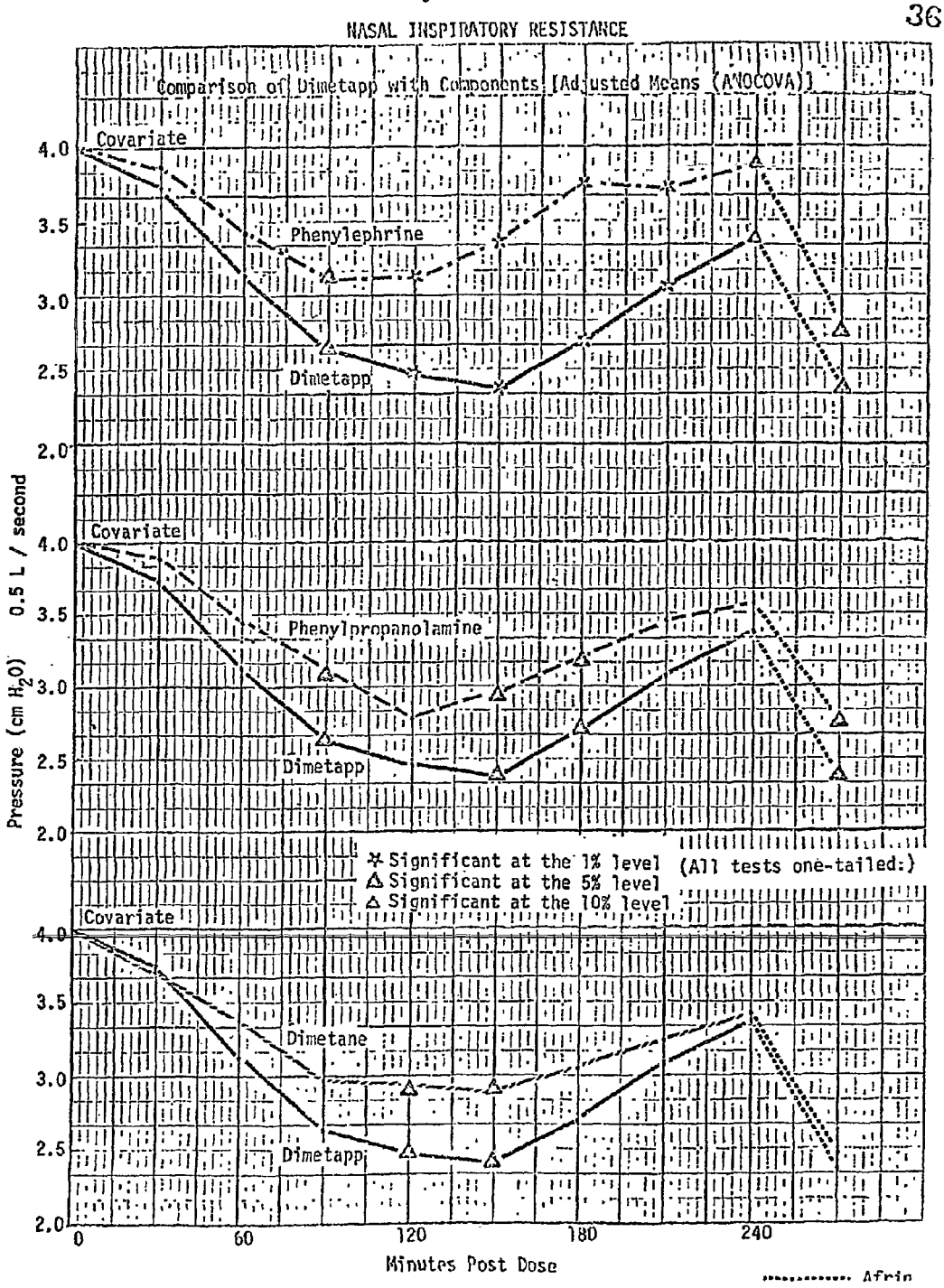
	Minutes Post Dose								
	30	60	90	120	150	180	210	240	270
Mean Square Error	0.055376	0.295830	0.302532	0.210785	0.220289	0.295846	0.300635	0.336042	0.188783
DF	43	43	43	43	42	43	43	43	43
F	1.36	1.21	2.75	4.63	8.62	7.66	3.10	1.50	2.77
P	NS	NS	<0.10	<0.01	<0.001	<0.001	<0.05	NS	<0.10
Adjusted Treatment Means									
Dimetapp (24)	3.735	3.119	2.624	2.485	2.405	2.680	3.070	3.350	2.354
Phenylephrine (8)	3.864	3.405	3.118**	3.123***	3.328***	3.721**	3.710***	3.837	2.768**
Phenylpropanolamine (8)	3.888	3.472	3.121**	2.763	2.942**	3.174**	3.463	3.547	2.752**
Dimetane (8)	3.718	3.367	2.985	2.921**	2.872**	3.053	3.210	3.385	2.472

*** Significantly different from Dimetapp at the 1% level
** Significantly different from Dimetapp at the 5% level (All tests one-tailed.)
* Significantly different from Dimetapp at the 10% level

( ) Sample size

AHP2-REG-004-0044776

Figure 4.2.1-01



AHP2-REG-004-0044777

Table 4.2.1-02

NASAL EXPIRATORY RESISTANCE: COMPARISON OF DIMETAPP WITH COMPONENTS

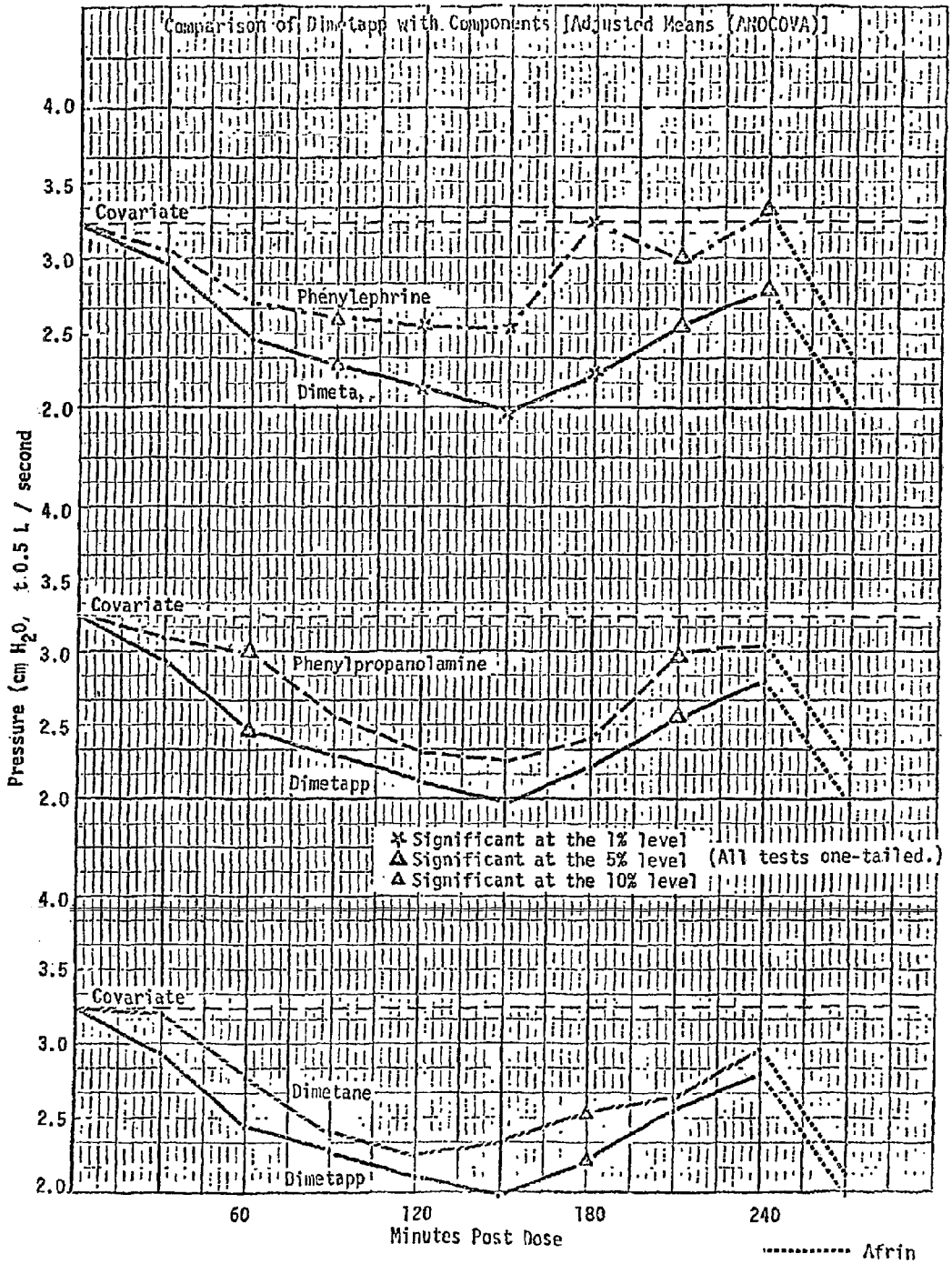
Analysis of Covariance and Results of Dunnett's t (WRT Dimetapp)

	Minutes Post Dose								
	30	60	90	120	150	180	210	240	270
Mean Square Error	0.125899	0.246921	0.206566	0.140656	0.202280	0.195096	0.224118	0.243040	0.215026
DF	43	43	43	43	42	43	43	43	43
F	1.31	3.02	1.80	2.70	2.96	9.69	2.68	2.01	0.90
P	NS	<0.05	NS	<0.10	<0.05	<0.001	<0.10	NS	NS
Adjusted Treatment Means									
Dimetapp (24)	2.922	2.418	2.236	2.087	1.985	2.204	2.560	2.780	1.992
Phenylephrine (8)	3.040	2.687	2.602 *	2.528 ***	2.522 ***	3.211 ***	2.990 **	3.276 **	2.288
Phenylpropanolamine (8)	3.089	2.988 **	2.562	2.288	2.216	2.388	2.987 **	3.019	2.181
Dimetane (8)	3.188	2.758	2.353	2.233	2.304	2.556 *	2.611	2.973	2.111

*** Significantly different from Dimetapp at the 1% level
** Significantly different from Dimetapp at the 5% level (All tests one-tailed.)
* Significantly different from Dimetapp at the 10% level

( ) Sample size

AHP2-REG-004-0044778



AHP2-REG-004-0044779

Table 4.2.1-03

NASAL INSPIRATORY RESISTANCE

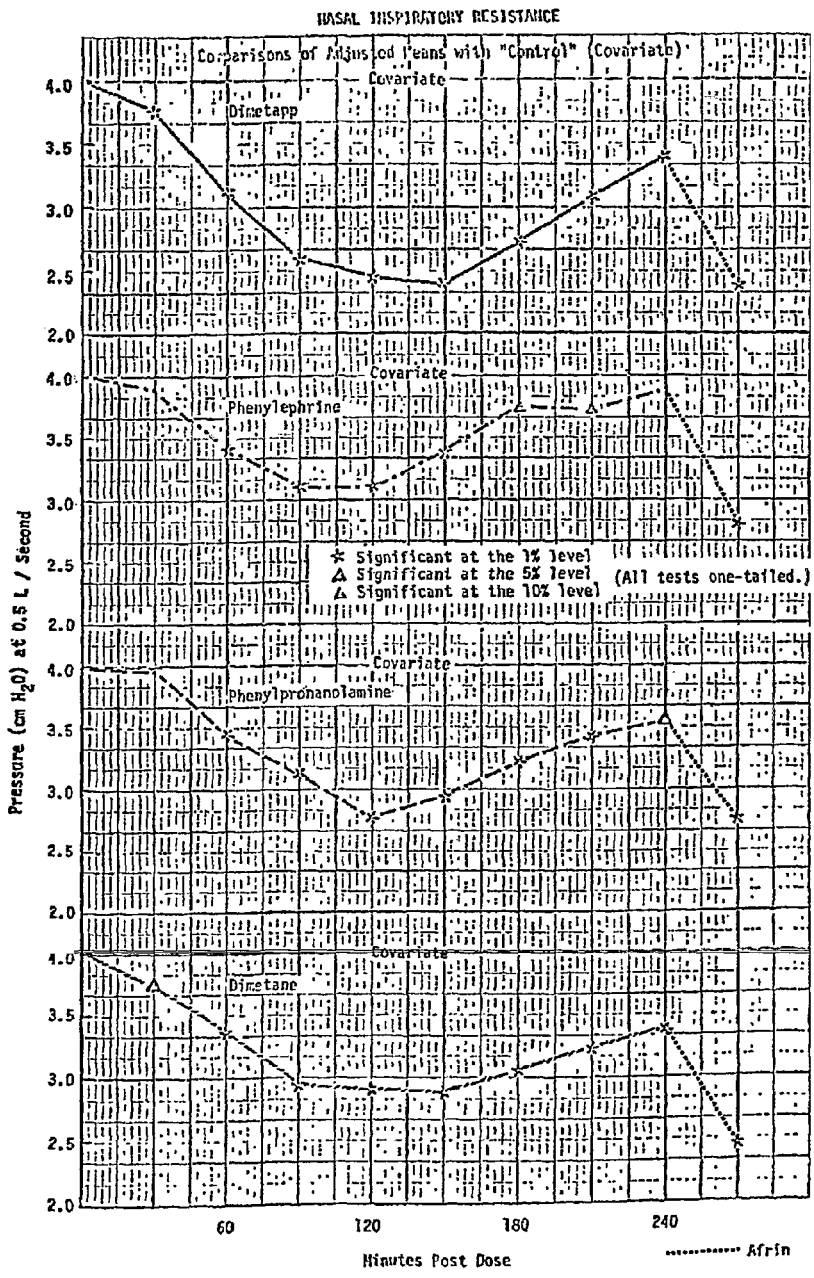
Comparisons of Adjusted Means with "Control" (Covariate)

Minutes Post Dose	Adjusted Treatment Means		Covariate	t	P +
30	Dimetapp	3.74	4.0135	-2.784	<0.005
	PE	3.86		-0.979	NS
	PPA	3.89		-0.821	NS
	Dimetane	3.72		-1.934	<0.05
60	Dimetapp	3.12	4.0135	-6.284	<0.005
	PE	3.41		-3.039	<0.005
	PPA	3.47		-2.704	<0.005
	Dimetane	3.37		-3.229	<0.005
90	Dimetapp	2.62	4.0135	-10.539	<0.005
	PE	3.12		-4.446	<0.005
	PPA	3.12		-4.432	<0.005
	Dimetane	2.98		-5.107	<0.005
120	Dimetapp	2.48	4.0135	-12.631	<0.005
	PE	3.12		-4.817	<0.005
	PPA	2.76		-6.765	<0.005
	Dimetane	2.92		-5.910	<0.005
150	Dimetapp	2.41	4.0213	-12.960	<0.005
	PE	3.33		-3.698	<0.005
	PPA	2.94		-5.757	<0.005
	Dimetane	2.87		-6.131	<0.005
180	Dimetapp	2.68	4.0135	-10.173	<0.005
	PE	3.72		-1.461	<0.10
	PPA	3.17		-4.192	<0.005
	Dimetane	3.05		-4.797	<0.005
210	Dimetapp	3.07	4.0135	-7.168	<0.005
	PE	3.71		-1.509	<0.10
	PPA	3.46		-2.738	<0.005
	Dimetane	3.21		-3.996	<0.005
240	Dimetapp	3.35	4.0135	-4.893	<0.005
	PE	3.84		-0.852	NS
	PPA	3.55		-2.252	<0.025
	Dimetane	3.38		-3.034	<0.005
270	Dimetapp	2.35	4.0135	14.032	<0.005
	PE	2.77		-6.894	<0.005
	PPA	2.75		-6.983	<0.005
	Dimetane	2.47		-8.533	<0.005

+ One-tailed tests

AHP2-REG-004-0044780

Figure 4.2.1-03



AHP2-REG-004-0044781

Table 4.2.1-04

NASAL EXPIRATORY RESISTANCE

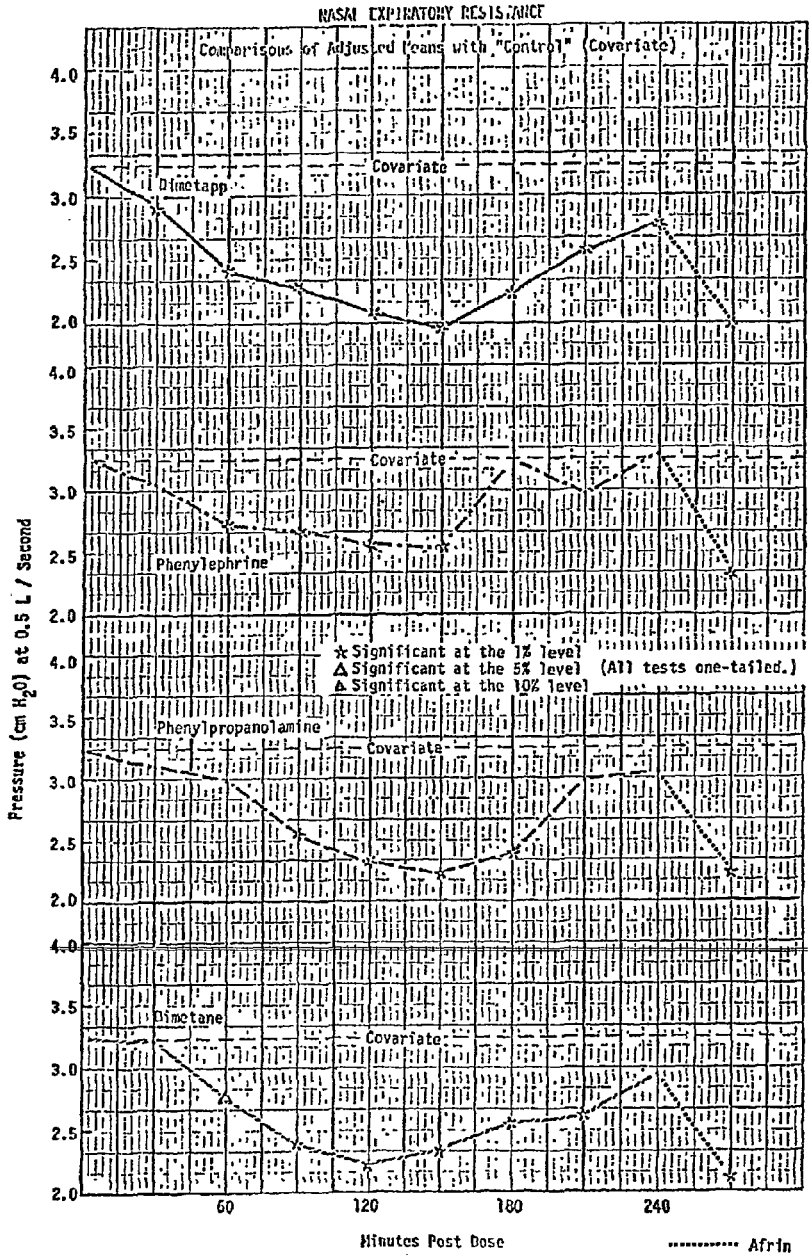
Comparisons of Adjusted Means with "Control" (Covariate)

Minutes Post Dose	Adjusted Treatment Means		Covariate	t	P+
30	Dimetapp	2.92	3.2052	-2.646	<0.01
	PE	3.04		-1.011	NS
	PPA	3.09		-0.711	NS
	Dimetane	3.19		-0.105	NS
60	Dimetapp	2.42	3.2052	-6.413	<0.005
	PE	2.69		-2.764	<0.005
	PPA	2.99		-1.158	NS
	Dimetane	2.76		-2.385	<0.025
90	Dimetapp	2.24	3.2052	-8.232	<0.005
	PE	2.60		-3.354	<0.005
	PPA	2.56		-3.576	<0.005
	Dimetane	2.35		-4.738	<0.005
120	Dimetapp	2.09	3.2052	-10.253	<0.005
	PE	2.53		-4.065	<0.005
	PPA	2.29		-5.506	<0.005
	Dimetane	2.23		-5.836	<0.005
150	Dimetapp	1.98	3.1989	-10.190	<0.005
	PE	2.52		-3.796	<0.005
	PPA	2.22		-5.496	<0.005
	Dimetane	2.30		-5.007	<0.005
180	Dimetapp	2.20	3.2052	-8.611	<0.005
	PE	3.21		+0.033	NS
	PPA	2.39		-4.601	<0.005
	Dimetane	2.56		-3.655	<0.005
210	Dimetapp	2.56	3.2052	-5.379	<0.005
	PE	2.99		-1.175	NS
	PPA	2.99		-1.191	NS
	Dimetane	2.61		-3.243	<0.005
240	Dimetapp	2.78	3.2052	-3.477	<0.005
	PE	3.28		+0.379	NS
	PPA	3.02		-0.997	NS
	Dimetane	2.97		-1.243	NS
270	Dimetapp	1.99	3.2052	-10.211	<0.005
	PE	2.29		-5.054	<0.005
	PPA	2.18		-5.644	<0.005
	Dimetane	2.11		-6.029	<0.005

+ One-tailed tests

AHP2-REG-004-0044782

Figure 4.2.1-04



AHP2-REG-004-0044783

4.2.2 Nasal Mucosal Characteristics

Parameters evaluated: Nasal Serous Secretion
Nasal Mucosal Congestion
Nasal Mucosal Hyperemia
Ease of Nasal Breathing

In order to compensate for any differences in severity of initial symptomatology among the four treatment groups, a covariance-like procedure was utilized for the four parameters above prior to making ridit transformations. More explicitly, ridit variables were derived on the basis of "Score Changes" between the initial (pre-drug) and each of the serial post-drug evaluations. Analyses of variance were performed on these covariance-like ridit transformed variables. For all four parameters, the mean ridits of the components were compared with those of Dimetapp using Dunnett's t (one-tailed).

The results of these analyses may be found in Tables 4.2.2-01 through 4.2.2-04 and in Figures 4.2.1-01 through 4.2.2-04. As shown, Dimetapp is consistently better than any of its components and many of the differences observed are statistically significant.

In addition, the means for each of the treatment groups were compared with the "No Change" ridits (i.e., the ridit score representing a change = 0). As shown in Tables 4.2.2-05 through 4.2.2-08 and Figures 4.2.2-05 through 4.2.2-08, Dimetapp and each of its components show a definite improvement with respect to all four parameters throughout the study period. In fact, most of the differences are highly significant (i.e. $p < 0.01$).

AHP2-REG-004-0044784

AHP2-REG-004-0044785

Table 4.2.2-01

NASAL SEROUS SECRETIONS: COMPARISONS OF DIMETAPP WITH COMPONENTS

Analysis of Variance on Ridit Transformed Variables and Results of Dunnett's t (WRT Dimetapp)

	Minutes Post Dose								
	30	60	90	120	150	180	210	240	270
Mean Square Error	0.05161	0.04640	0.05522	0.05369	0.05464	0.05550	0.03954	0.04112	0.05295
DF	44	44	44	44	43	44	44	44	44
F	2.56	4.45	5.01	3.58	6.21	5.69	11.45	7.03	5.99
P	<0.10	<0.01	<0.005	<0.025	<0.005	<0.005	<0.001	<0.001	<0.005
Adjusted Treatment Means									
Dimetapp (24)	0.500	0.438	0.384	0.383	0.360	0.362	0.334	0.393	0.362
Phenylephrine (8)	0.354	0.398	0.490	0.610 **	0.704 ***	0.664 ***	0.667 ***	0.552 *	0.591 **
Phenylpropanolamine (8)	0.480	0.560	0.685 ***	0.660 **	0.533	0.586 **	0.625 ***	0.548 *	0.620 ***
Dimetane (8)	0.657	0.728 ***	0.672 ***	0.580 *	0.668 ***	0.664 ***	0.708 ***	0.750 ***	0.645 ***

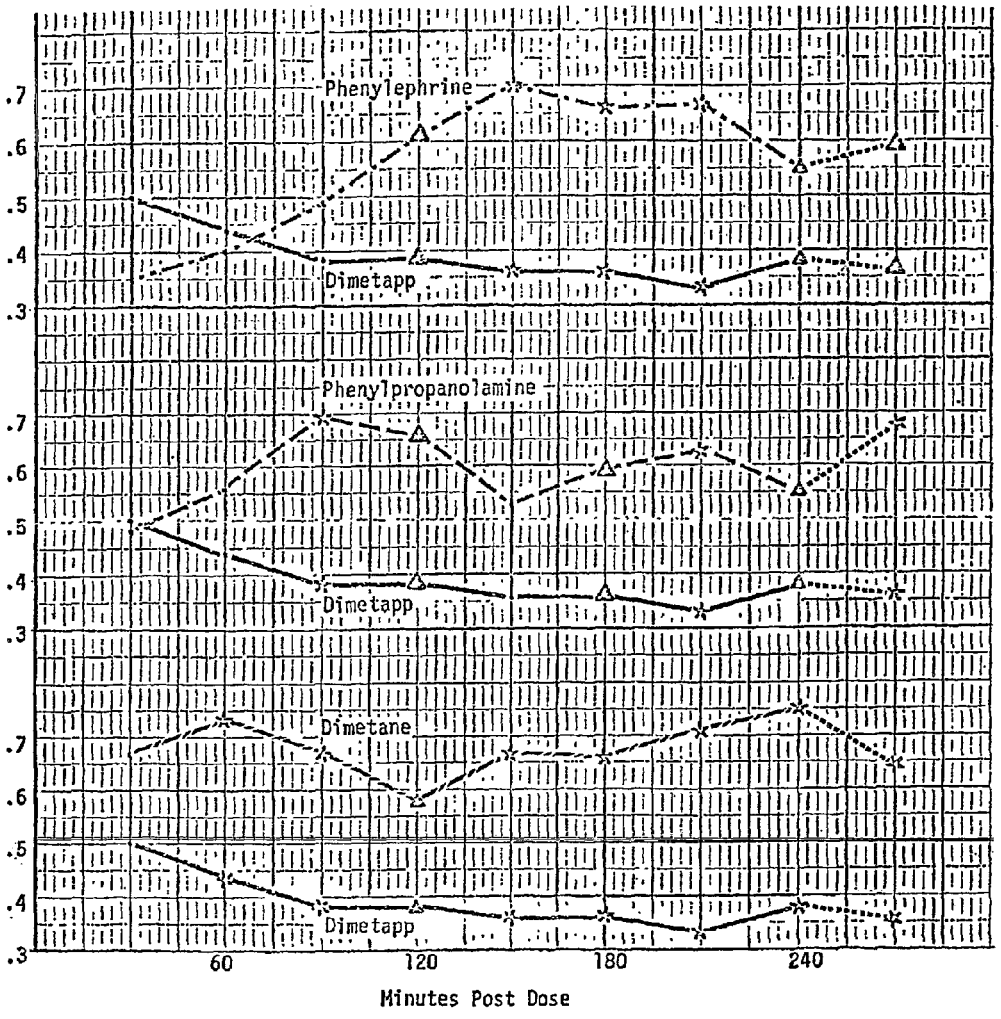
*** Significantly different from Dimetapp at the 1% level
** Significantly different from Dimetapp at the 5% level (All tests one-tailed.)
* Significantly different from Dimetapp at the 10% level

( ) Sample size

Figure 4.2.2-01

NASAL SEROUS SECRETIONS

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



✱ Significant at the 1% level
Δ Significant at the 5% level
▵ Significant at the 10% level
(All tests one-tailed.)

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AHP2-REG-004-0044786

Table 4.2.2-02

NASAL MUCOSAL CONGESTION: COMPARISONS OF DIMETAPP WITH COMPONENTS

Analysis of Variance on Ridit Transformed Variables and Results of Dunnett's t (WRT Dimetapp)

	Minutes Past Dose								
	30	60	90	120	150	180	210	240	270
Mean Square Error	0.04824	0.05784	0.05318	0.06399	0.06752	0.05326	0.05036	0.05376	0.05807
DF	44	44	44	44	43	44	44	44	44
F	1.85	2.61	3.99	2.55	2.33	5.20	2.82	3.06	2.10
P	NS	<0.10	<0.025	<0.10	<0.10	<0.005	<0.10	<0.05	NS
Adjusted Treatment Means									
Dimetapp (24)	0.488	0.509	0.432	0.427	0.424	0.392	0.399	0.412	0.423
Phenylephrine (8)	0.554	0.457	0.682 **	0.685 **	0.682 **	0.747 ***	0.570	0.615 **	0.611*
Phenylpropanolamine (8)	0.615	0.672	0.638 **	0.590	0.584	0.587 *	0.643 *	0.659 **	0.625*
Dimetane (8)	0.370	0.342	0.386	0.444	0.452	0.490	0.588 *	0.491	0.496

*** Significantly different from Dimetapp at the 1% level
** Significantly different from Dimetapp at the 5% level (All tests one-tailed.)
* Significantly different from Dimetapp at the 10% level

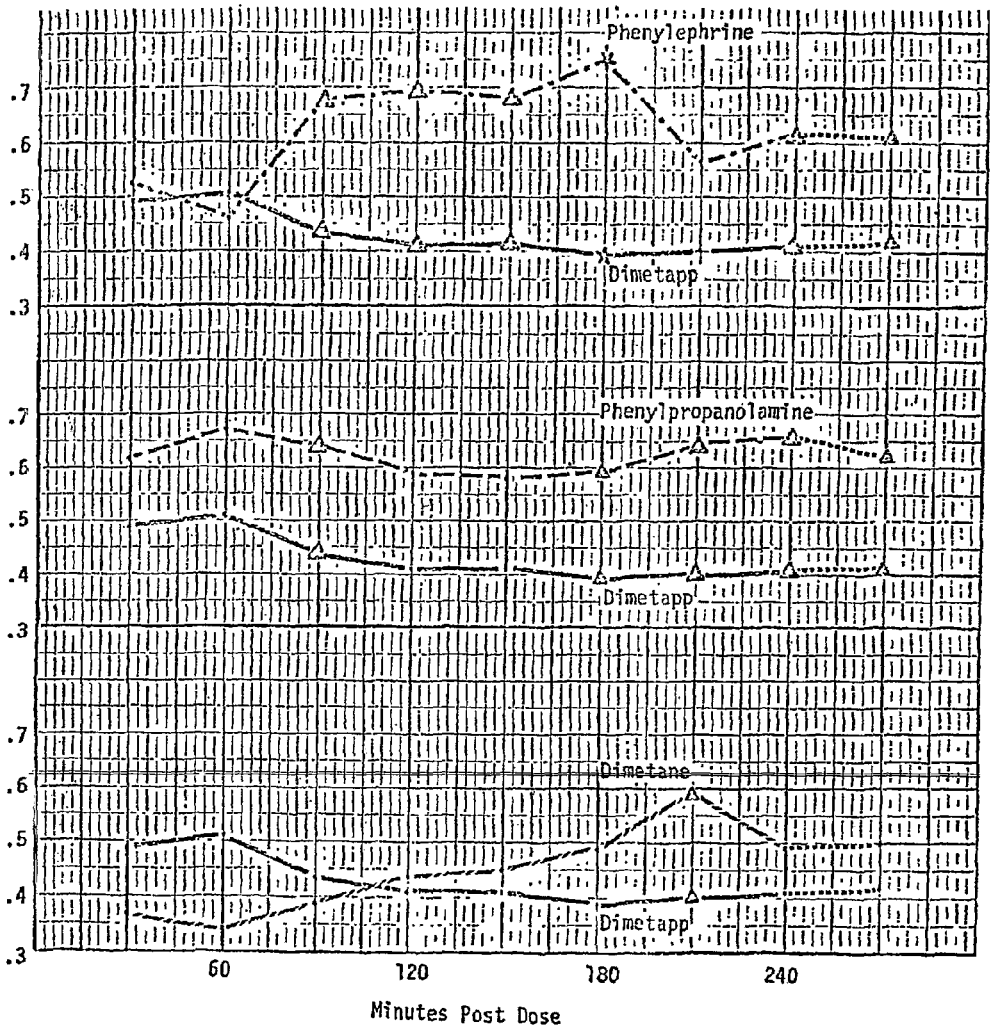
( ) Sample size

AHP2-REG-004-0044787

Figure 4.2.2-02

NASAL MUCOSAL CONGESTION

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



☆ Significant at the 1% level
△ Significant at the 5% level (All tests one-tailed.)
△ Significant at the 10% level

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AHP2-REG-004-0044788

NASAL MUCOSAL HYPEREMIA: COMPARISONS OF DIMETAPP WITH COMPONENTS

Analysis of Variance on Ridit Transformed Variables and Results of Dunnett's t (WRT Dimetapp)

Minutes Post Dose

	30	60	90	120	150	180	210	240	270
Mean Square Error	0.06060	0.04696	0.04949	0.04950	0.05700	0.05660	0.05706	0.05757	0.06112
DF	44	44	44	44	43	44	44	44	44
F	1.57	0.60	1.49	4.57	3.82	3.54	3.84	2.35	1.35
P	NS	NS	NS	<0.10	<0.025	<0.025	<0.025	<0.10	NS
Adjusted Treatment Means									
Dimetapp (24)	0.434	0.473	0.454	0.405	0.414	0.398	0.396	0.410	0.430
Phenylephrine (8)	0.525	0.473	0.522	0.704 ***	0.746 ***	0.690 ***	0.644 **	0.596 *	0.577
Phenylpropanolamine (8)	0.647 *	0.584	0.642 *	0.620 **	0.500	0.581 *	0.670 **	0.617 *	0.596
Dimetane (8)	0.525	0.526	0.474	0.461	0.500	0.537	0.494	0.557	0.536

*** Significantly different from Dimetapp at the 1% level
** Significantly different from Dimetapp at the 5% level (All tests one-tailed.)
* Significantly different from Dimetapp at the 10% level

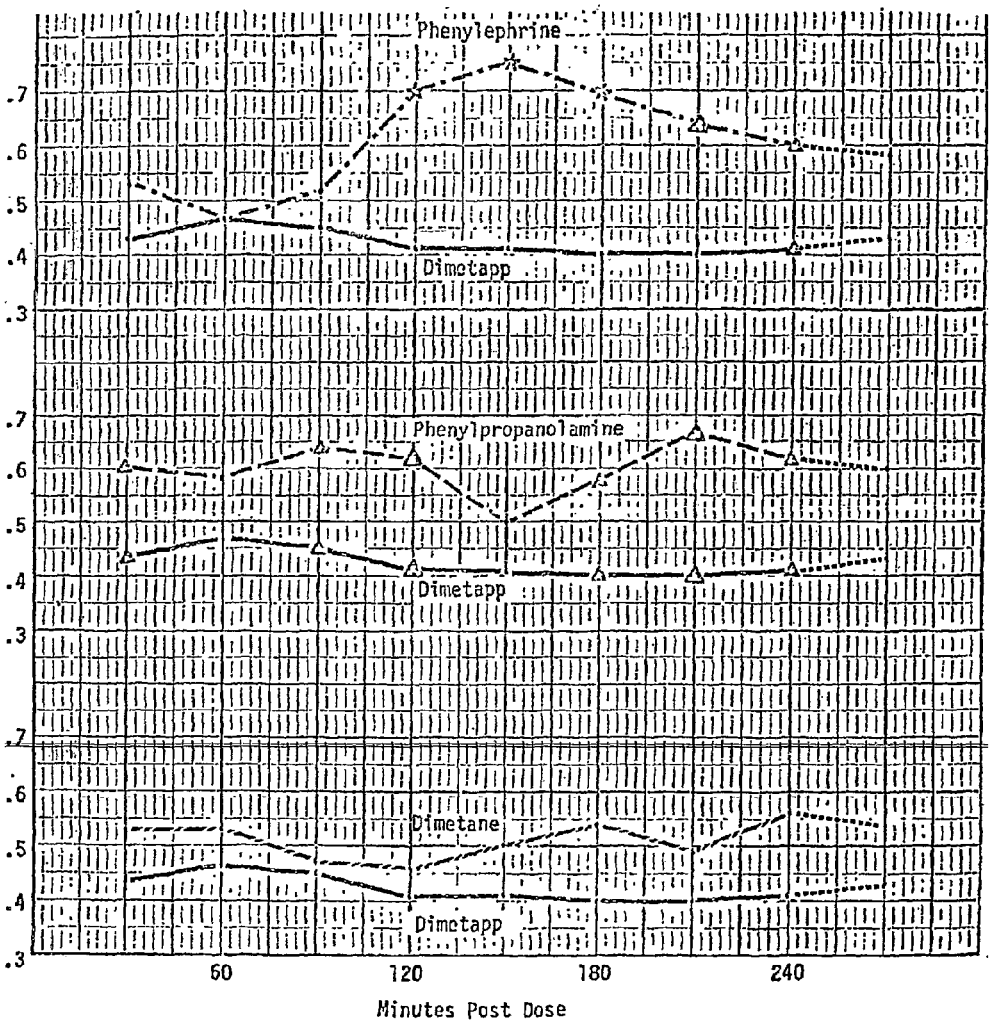
( ) Sample size

AHP2-REG-004-0044789

Figure 4.2.2-03

NASAL MUCOSAL HYPEREMIA

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



★ Significant at the 1% level
△ Significant at the 5% level (All tests one-tailed.)
△ Significant at the 10% level

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AHP2-REG-004-0044790

Table 4.2.2-04

EAST OF NASAL BREATHING: COMPARISONS OF DIMETAPP WITH COMPONENTS

Analysis of Variance on Ridit Transformed Variables and Results of Dunnett's t (WRT Dimetapp)

	Minutes Post Dose								
	30	60	90	120	150	180	210	240	270
Mean Square Error	0.05629	0.06396	0.06069	0.06515	0.05583	0.05385	0.03999	0.05122	0.05756
DF	44	44	44	44	43	44	44	44	44
F	1.31	.82	4.07	2.85	5.60	7.16	12.98	3.22	4.95
P	NS	NS	<0.025	<0.05	<0.005	<0.001	<0.001	<0.05	<0.01
Adjusted Treatment Means									
Dimetapp (24)	0.442	0.464	0.394	0.412	0.375	0.357	0.323	0.403	0.382
Phenylephrine (8)	0.628 *	0.521	0.625**	0.685 **	0.757 ***	0.763 ***	0.737***	0.656 **	0.740 ***
Phenylpropanolamine (8)	0.524	0.620	0.707***	0.608 *	0.577 *	0.581 **	0.674***	0.568	0.584 *
Dimetane (8)	0.524	0.469	0.488	0.470	0.525	0.586 **	0.620***	0.568	0.521

*** Significantly different from Dimetapp at the 1% level
** Significantly different from Dimetapp at the 5% level . (All tests one-tailed.)
* Significantly different from Dimetapp at the 10% level

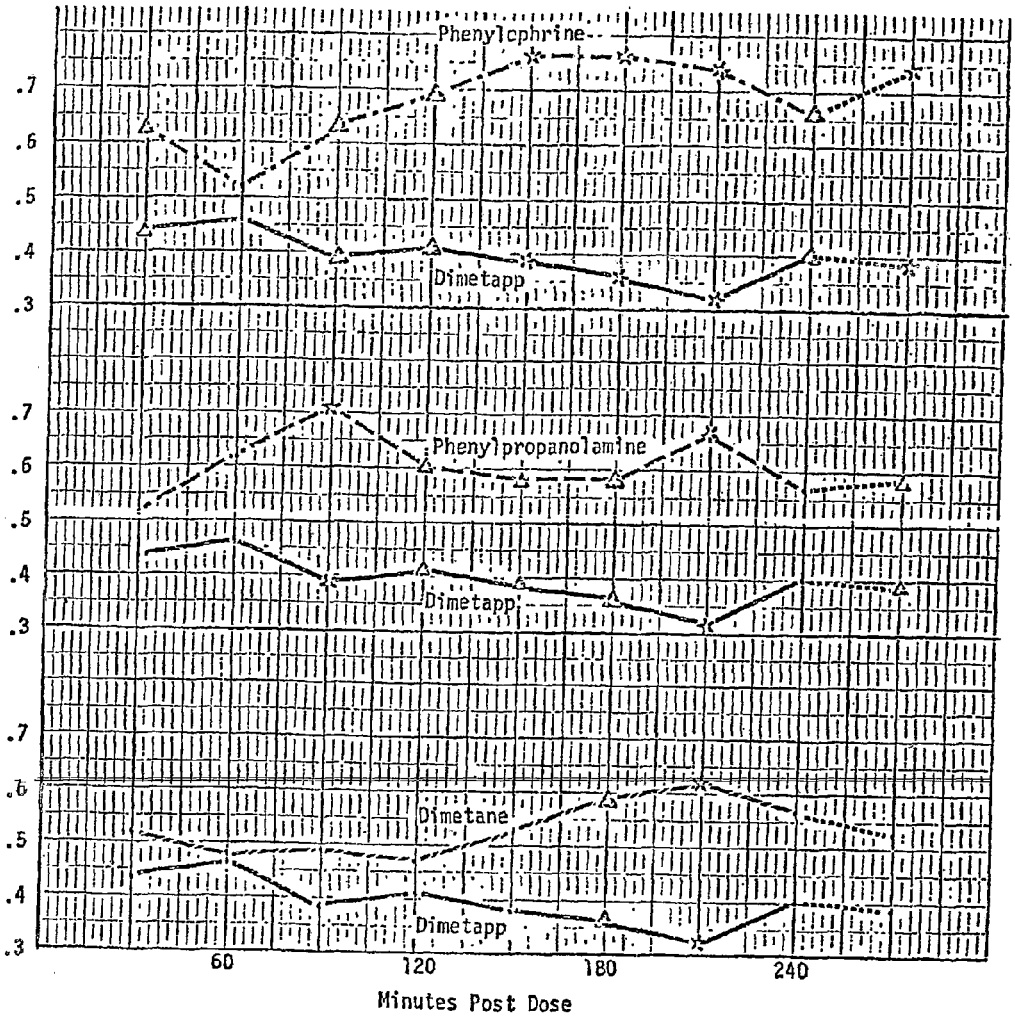
( ) Sample size

AHP2-REG-004-0044791

Figure 4.2.2-04

EASE OF NASAL BREATHING

Comparison of Dimetapp with Components [Mean Ridits (ANOVA)]



* Significant at the 1% level
Δ Significant at the 5% level (All tests one-tailed.)
Δ Significant at the 10% level

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AHP2-REG-004-0044792

Table 4.2.2-05

NASAL SEROUS SECRETIONS

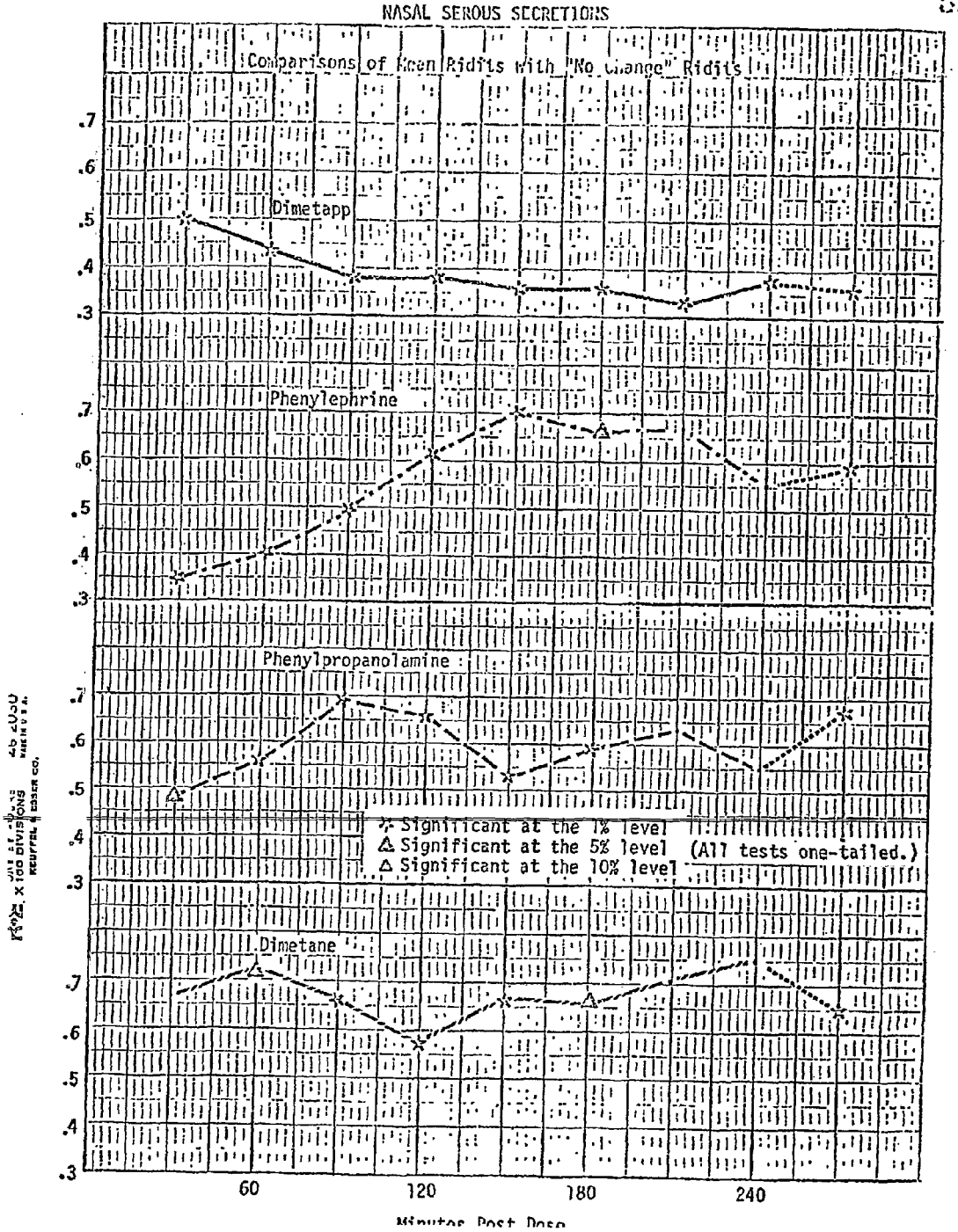
Comparison of Mean Ridits with "No Change" Ridits

Minutes Post Dose	Treatment Means (Ridits)		"No Change" Ridits	t	P+
30	Dimetapp	0.500	0.667	-3.601	<0.005
	PE	0.354		-3.897	<0.005
	PPA	0.480		-2.328	<0.025
	Dimetane	0.667		0	NS
60	Dimetapp	0.438	0.896	-10.417	<0.005
	PE	0.398		-6.539	<0.005
	PPA	0.560		-4.412	<0.005
	Dimetane	0.728		-2.205	<0.025
90	Dimetapp	0.384	0.958	-11.966	<0.005
	PE	0.490		-5.633	<0.005
	PPA	0.685		-3.286	<0.005
	Dimetane	0.672		-3.442	<0.005
120	Dimetapp	0.383	0.969	-11.376	<0.005
	PE	0.610		-4.024	<0.005
	PPA	0.660		-3.463	<0.005
	Dimetane	0.580		-4.360	<0.005
150	Dimetapp	0.360	0.915	-11.387	<0.005
	PE	0.704		-2.553	<0.01
	PPA	0.533		-4.623	<0.005
	Dimetane	0.668		-2.989	<0.005
180	Dimetapp	0.362	0.813	-9.379	<0.005
	PE	0.664		-1.789	<0.05
	PPA	0.586		-2.725	<0.005
	Dimetane	0.664		-1.789	<0.05
210	Dimetapp	0.334	0.625	-7.169	<0.005
	PE	0.667		0.597	NS
	PPA	0.625		0	NS
	Dimetane	0.708		1.180	NS
240	Dimetapp	0.383	0.552	-4.083	<0.005
	PE	0.552		0	NS
	PPA	0.548		- .056	NS
	Dimetane	0.750		2.762	NS
270	Dimetapp	0.362	0.979	-13.136	<0.005
	PE	0.591		-4.769	<0.005
	PPA	0.680		-3.675	<0.005
	Dimetane	0.645		-4.106	<0.005

+ One-tailed test

AHP2-REG-004-0044793

Figure 4.2.2-05



AHP2-REG-004-0044794

Table 4.2.2-06

NASAL MUCOSAL CONGESTION

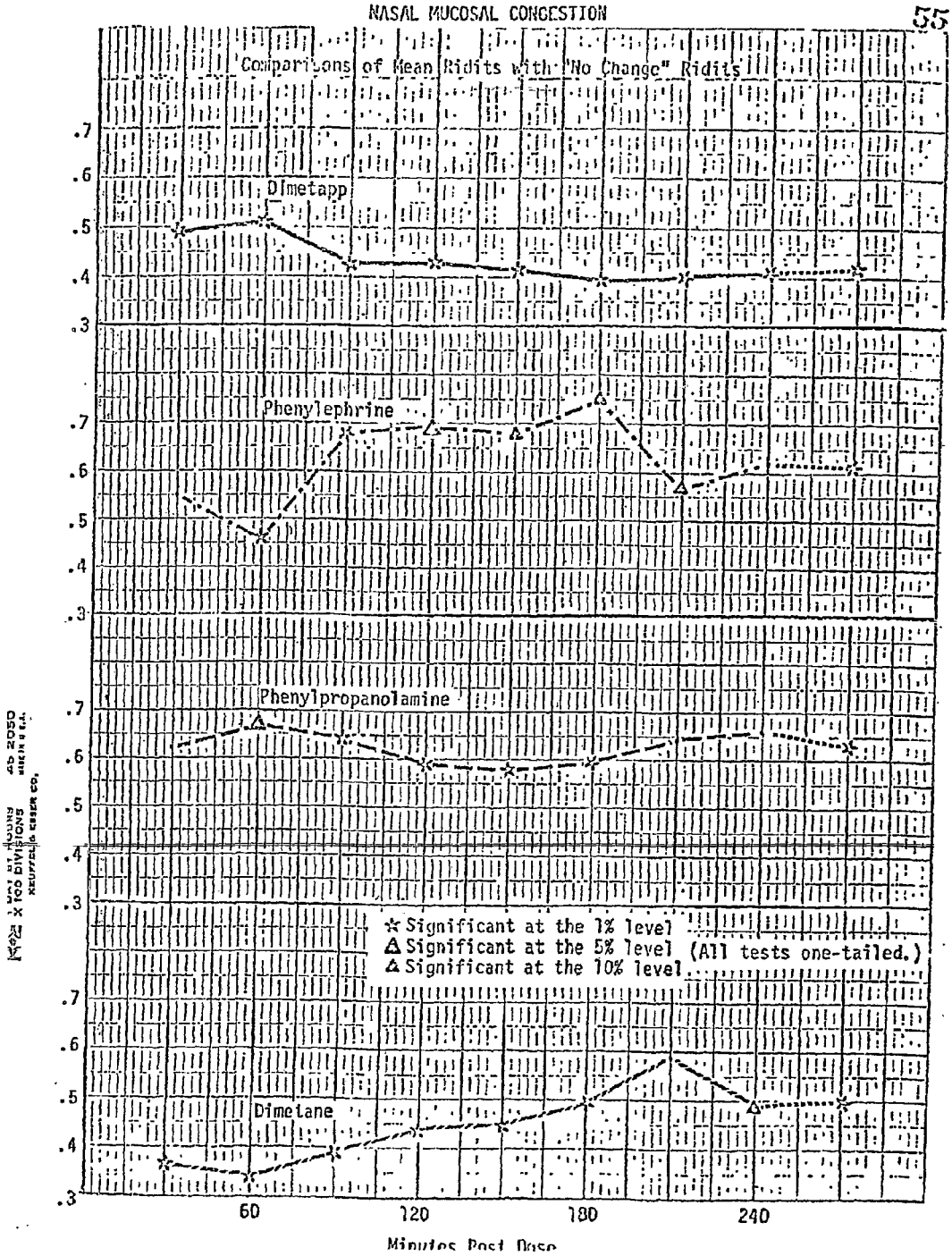
Comparison of Mean Ridits With "No Change" Ridits

Minutes Post Dose	Treatment	Means (Ridits)	"No Change" Ridits	t	P +
30	Dimetapp	0.488	0.615	-2.832	<0.005
	PE	0.554		-0.785	NS
	PPA	0.615		0	NS
	Dimetane	0.370		-3.155	<0.005
60	Dimetapp	0.509	0.844	-6.824	<0.005
	PE	0.457		-4.551	<0.005
	PPA	0.672		-2.023	<0.025
	Dimetane	0.342		-5.904	<0.005
90	Dimetapp	0.432	0.927	-10.516	<0.005
	PE	0.682		-3.005	<0.005
	PPA	0.638		-3.545	<0.005
	Dimetane	0.386		-6.636	<0.005
120	Dimetapp	0.427	0.906	-9.277	<0.005
	PE	0.685		-2.471	<0.01
	PPA	0.590		-3.533	<0.005
	Dimetane	0.444		-5.166	<0.005
150	Dimetapp	0.424	0.830	-7.488	<0.005
	PE	0.682		-1.610	<0.10
	PPA	0.584		-2.676	<0.005
	Dimetane	0.452		-4.111	<0.005
180	Dimetapp	0.392	0.854	-9.807	<0.005
	PE	0.747		-1.311	<0.10
	PPA	0.587		-3.272	<0.005
	Dimetane	0.490		-4.461	<0.005
210	Dimetapp	0.399	0.698	-5.962	<0.005
	PE	0.570		-1.474	<0.10
	PPA	0.643		-0.633	NS
	Dimetane	0.588		-1.266	NS
240	Dimetapp	0.412	0.615	-4.289	<0.005
	PE	0.615		0	NS
	PPA	0.659		0.537	NS
	Dimetane	0.491		-1.513	<0.10
270	Dimetapp	0.423	0.969	-11.100	<0.005
	PE	0.611		-4.202	<0.005
	PPA	0.625		-4.038	<0.005
	Dimetane	0.496		-5.552	<0.005

+ One-tailed tests

AHP2-REG-004-0044795

Figure 4.2.2-06



AHP2-REG-004-0044796

Table 4.2.2-07

NASAL MUCOSAL HYPEREMIA

Comparison of Mean Ridits with "No Change" Ridits

Minutes Post Dose	Treatment Means (Ridits)		"No Change" Ridits	t	P+
30	Dimetapp	0.434	0.708	-5.453	<0.005
	PE	0.525		-2.103	<0.025
	PPA	0.647		-0.701	NS
	Dimetane	0.525		-2.103	<0.025
60	Dimetapp	0.473	0.927	-10.264	<0.005
	PE	0.473		-5.926	<0.005
	PPA	0.584		-4.477	<0.005
	Dimetane	0.526		-5.234	<0.005
90	Dimetapp	0.454	0.979	-11.451	<0.005
	PE	0.522		-5.810	<0.005
	PPA	0.642		-4.285	<0.005
	Dimetane	0.474		-6.421	<0.005
120	Dimetapp	0.405	0.948	-11.957	<0.005
	PE	0.704		-3.102	<0.005
	PPA	0.620		-4.170	<0.005
	Dimetane	0.461		-6.191	<0.005
150	Dimetapp	0.414	0.894	-9.642	<0.005
	PE	0.746		-1.753	<0.05
	PPA	0.500		-4.668	<0.005
	Dimetane	0.500		-4.668	<0.005
180	Dimetapp	0.398	0.854	-9.389	<0.005
	PE	0.690		-1.950	<0.05
	PPA	0.581		-3.245	<0.005
	Dimetane	0.537		-3.768	<0.005
210	Dimetapp	0.396	0.729	-6.830	<0.005
	PE	0.644		-1.007	NS
	PPA	0.670		-0.699	NS
	Dimetane	0.494		-2.783	<0.005
240	Dimetapp	0.410	0.677	-5.451	<0.005
	PE	0.596		-0.955	NS
	PPA	0.617		-0.707	NS
	Dimetane	0.557		-1.414	<0.10
270	Dimetapp	0.430	0.979	-10.879	<0.005
	PE	0.577		-4.599	<0.005
	PPA	0.596		-4.382	<0.005
	Dimetane	0.536		-5.068	<0.005

+ One-tailed test

AHP2-REG-004-0044797

Figure 4.2.2-07

NASAL MUCOSAL HYPEREMIA

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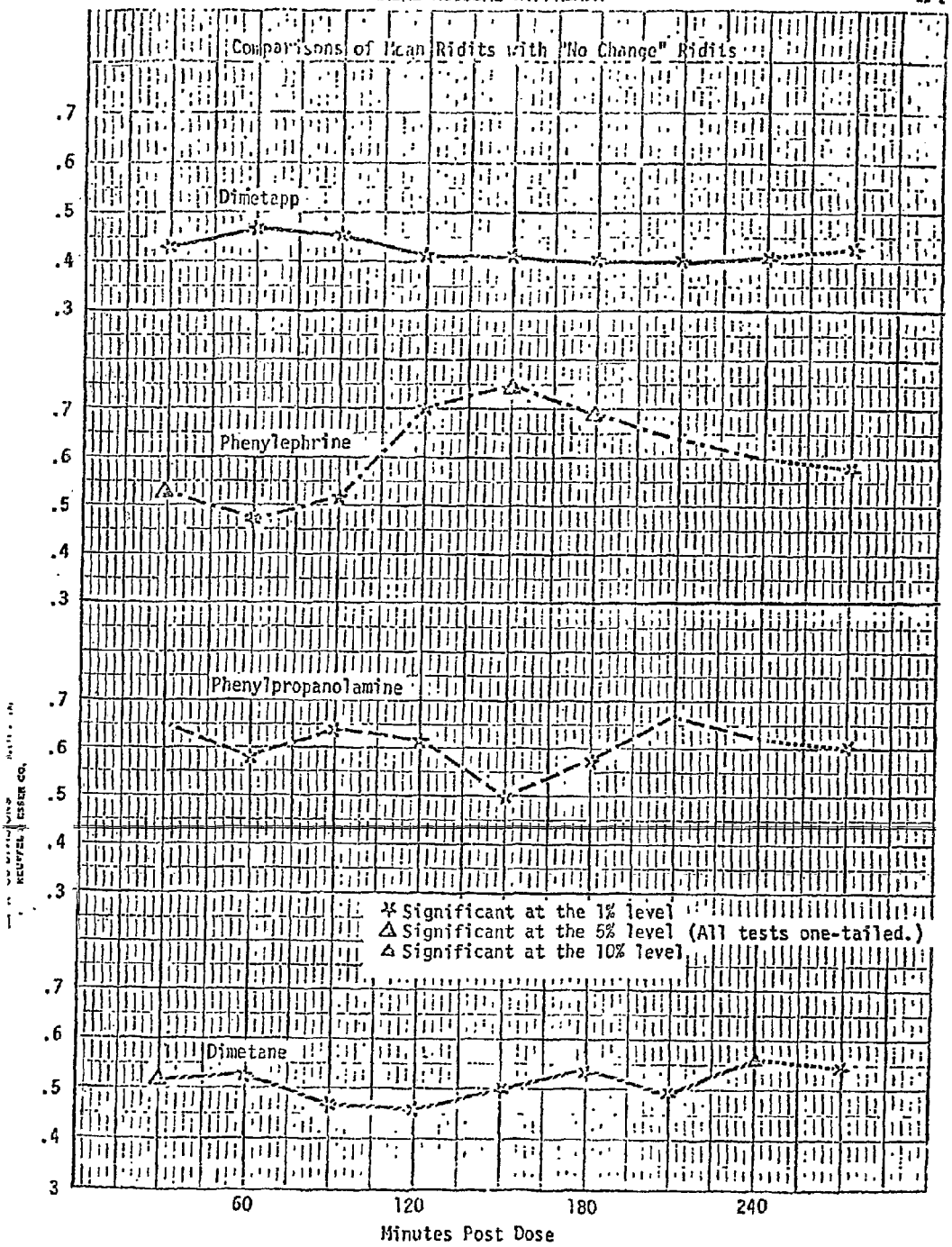


AHP2-REG-004-0044798

Table 4.2.2-08

EASE OF NASAL BREATHING

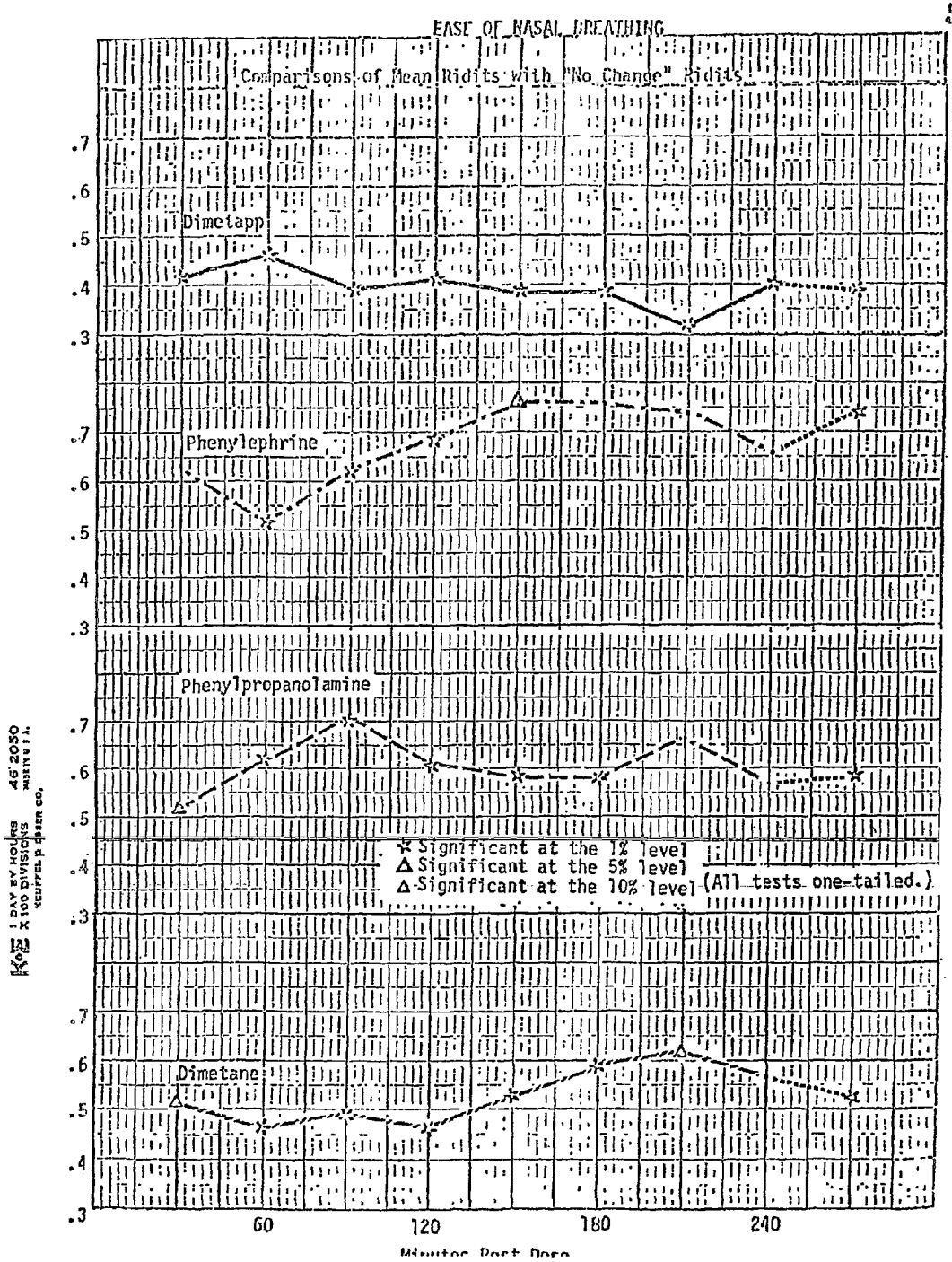
Comparison of Mean Ridits with "No Change" Ridits

Minutes Post Dose	Treatment Means (Ridits)		"No Change" Ridits	t	P +
30	Dimetapp	0.442	0.646	-4.212	<0.005
	PE	0.628		-0.214	NS
	PPA	0.524		-1.454	<0.10
	Dimetane	0.524		-1.454	<0.10
60	Dimetapp	0.464	0.917	-8.775	<0.005
	PE	0.521		-4.429	<0.005
	PPA	0.620		-3.322	<0.005
	Dimetane	0.469		-5.010	<0.005
90	Dimetapp	0.394	0.969	-11.434	<0.005
	PE	0.625		-3.949	<0.005
	PPA	0.707		-3.008	<0.005
	Dimetane	0.488		-5.522	<0.005
120	Dimetapp	0.412	0.969	-10.691	<0.005
	PE	0.685		-3.147	<0.005
	PPA	0.608		-4.000	<0.005
	Dimetane	0.470		-5.530	<0.005
150	Dimetapp	0.375	0.936	-11.387	<0.005
	PE	0.757		-2.143	<0.025
	PPA	0.577		-4.297	<0.005
	Dimetane	0.525		-4.920	<0.005
180	Dimetapp	0.357	0.854	-10.492	<0.005
	PE	0.763		-1.109	NS
	PPA	0.581		-3.328	<0.005
	Dimetane	0.586		-3.267	<0.005
210	Dimetapp	0.323	0.729	-9.946	<0.005
	PE	0.737		-0.113	NS
	PPA	0.674		-0.778	NS
	Dimetane	0.620		-1.542	<0.10
240	Dimetapp	0.403	0.625	-4.805	<0.005
	PE	0.656		0.387	NS
	PPA	0.568		-0.712	NS
	Dimetane	0.568		-0.712	NS
270	Dimetapp	0.382	0.990	-12.405	<0.005
	PE	0.740		-2.945	<0.005
	PPA	0.584		-4.782	<0.005
	Dimetane	0.531		-5.407	<0.005

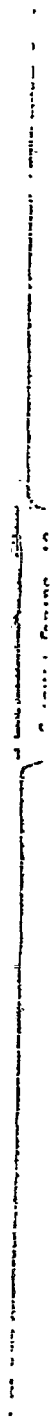
+ One-tailed test

AHP2-REG-004-0044799

Figure 4.2.2-08



AHP2-REG-004-0044800



AHP2-REG-004-0044801

6. SAFETY FINDINGS

6.1 CLINICAL FINDINGS

6.1.1 Relationship of Drug to Adverse Effect

The relationship of the study medication to an adverse effect has been classified as (1) probable, (2) possible, or (3) unlikely. Judgements have been made primarily on the basis of information collected over the years the study medications have been marketed. An adverse effect has been declared probably or possibly related to study medication if the effect has been known to occur or has been reported in connection with the use of the drug. All other adverse effects have been judged unlikely to be related to the study medication.

6.1.2 Significance of an Adverse Effect

For this study no adverse effects have been categorized as "significant."

6.1.3 Listings of Adverse Reactions and Experiences

AHP2-REG-004-0044802

Table 6.1.3-01

ADVERSE REACTIONS AND EXPERIENCES

TREATMENT GROUP: Dimetapp Elixir (single 10 cc dose)

STUDY NO.	INVESTIGATOR	PATIENT NO.	AGE	SEX	DESCRIPTION	FUNCTION DISORDER	SIGNIFICANT	DRUG RELATED	STOPPED THERAPY
0101	Cohen, B.M.	5	64	F	VPC*	Cardio-vascular	No	Unlikely	No
		8	46	F	Drowsiness	CNS	No	Probably	No
		14	46	M	Drowsiness Dry mouth	CNS ANS	No No	Probably Probably	No No
		21	40	F	Drowsiness	CNS	No	Probably	No
		24	64	M	Frequent urination	Genito-urinary	No	Possibly	No
		35	23	F	Visual blurring	Ophthalmic	No	Probably	No
		44	40	F	Dryness of mouth and nose	ANS	No	Probably	No
		48	54	M	Light headed	CNS	No	Probably	No

Comments:

*Patient #5 had rare VPC prior to treatment and during study. The investigator did not consider this to be related to the test medication.

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Table 6.1.3-02

ADVERSE REACTIONS AND EXPERIENCES

TREATMENT GROUP: Dimetane Elixir (single 20 cc dose)

STUDY NO.	INVESTIGATOR	PATIENT NO.	AGE	SEX	DESCRIPTION	FUNCTION DISORDER	SIGNIFICANT	DRUG RELATED	STOPPED THERAPY
0101	Cohen, B.M.	13	52	F	Circumoral numbness	ANS	No	Possibly	No
		20	51	M	Nervousness	CNS	No	Possibly	No
					Flatulence	Digestive	No	Unlikely	No
		27	46	F	Nervousness	CNS	No	Possibly	No
		36	39	M	Drowsiness	CNS	No	Probably	No

Table 6.1.3-03

ADVERSE REACTIONS AND EXPERIENCES

TREATMENT GROUP: Propadrine Elixir (single 2.5 cc dose)

STUDY NO.	INVESTIGATOR	PATIENT NO.	AGE	SEX	DESCRIPTION	FUNCTION DISORDER	SIGNIFICANT	DRUG RELATED	STOPPED THERAPY
0101	Cohen, B.M.	2	62	F	Dry mouth	ANS	No	Probably	No
		4	36	F	Drowsiness	CNS	No	Probably	No
		29	67	F	"Jittery"	CNS	No	Possibly	No

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Table 6.1.3-04

ADVERSE REACTIONS AND EXPERIENCES

TREATMENT GROUP: Neosynephrine Elixir (single 10 cc dose)

STUDY NO.	INVESTIGATOR	PATIENT NO.	AGE	SEX	DESCRIPTION	FUNCTION DISORDER	SIGNIFICANT	DRUG RELATED	STOPPED THERAPY
0101	Cohen, B.M.	15	68	F	Nervousness	CNS	No	Possibly	No
					VPC's	Cardio-vascular	No	Possibly	No
		37	38	M	Headache	CNS	No	Possibly	No
					Visual blurring	CNS	No	Possibly	No
					Palpitations	Cardio-vascular	No	Probably	No

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6.2 Measurements of Blood Pressures and Pulse Rates

A listing of the serial observations of blood pressures and pulse rates may be found in Appendix A6. Although rises in pulse rates from pre-drug values are occasionally noted, in no case, are these changes regarded as being clinically significant.

AHP2-REG-004-0044807

AHP2-REG-004-0044808

7. OVERALL DISCUSSION AND CONCLUSIONS

On the basis of the data collected under the conditions of this study, one may conclude that the effects of Dimetapp Elixir on nasal airway resistances and on nasal mucosal characteristics are consistantly much better than those of any of its components.

AHP2-REG-004-0044809

APPENDICES

AHP2-REG-004-0044810

APPENDICES

AHP2-REG-004-0044811

AHP2-REG-004-0044812

A1.1 Study Protocol 01 (03/69)

AHP2-REG-004-0044813

3-6-67

STUDY PROTOCOL

FINAL

A. H. ROBINS COMPANY
Medical Research Department
1407 Cummings Drive
Richmond, Virginia 23220

Name: Burton Marcus Cohen, M. D.
Address:
AHR Drug Number: GI Drug Name: Dimetapp Elixir
Study Number: Protocol Number: 01
Study Type: Special X ; Dose-range
Controlled Therapeutic ; Uncontrolled Therapeutic

(Attach extra sheets, if necessary, and indicate by outline numbers shown below.)

A. OBJECTIVE(S): To compare the effect on nasal airway resistance and clinical observatic following a single dose of Dimetapp Elixir to that from a single dose of components.

B. PATIENTS or SUBJECTS: 1. Total number in study: 48 2. Number receiving "study" drug: 24

3. Disease(s) or symptoms being studied: Nasal congestion from URI

4. Age Range (yrs.) Adult 5. Male 24 (approx.) Female 24 (approx) Pregnant No

6. Hospitalized No ; Outpatients: Clinic No Office Yes

7. Other specific criteria for inclusion: Duration of URI not less than 24 hours, not more than 72 hours, at time of first test day.

8. Specific criteria for exclusion: Chronic pulmonary disease, allergic rhinitis

C. STUDY DESIGN

1. Open No Single-blind Yes (To physician and technician) Double-blind No

2. Continuous treatment Yes Crossover No 3. Randomized (yes or no) Yes

4. If this is a comparison study:
a. Comparison between subjects (yes or no): Yes ; if yes, will subjects be paired (yes or no): No

If paired, give basis of pairing:

b. Comparison within subjects (yes or no): Yes

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TREATMENT: STUDY AND COMPARISON DRUG(S) INCLUDING PLACEBO

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1. a.	Drug (include placebo)	Dimetapp Elixir	Neosynephrine Elixir	Propadrine Elixir	Dimetane Elixir
b.	No. of Subjects	24 5	8	8	8
c.	Route of Administration	Oral	Oral	Oral	Oral
d.	Single Dose (show unit size)	10 cc.	10 cc.	2.5 cc.	20 cc.
e.	Frequency of Administration (e.g., single dose, od, bid, tid, qid, etc.)	Single dose	Single dose	Single dose	Single dose
f.	Fixed or Variable Dosage (if variable, explain here or in Section K)	Fixed	Fixed	Fixed	Fixed
g.	Duration of Admin. (days)	1	1	1	1

2. If subjects are already on a drug with same general pharmacological action, for how long will they be taken off before being placed on the "study" or "comparison" drug? 48 hours

Given placebo during this "wash-out" period? No

3. What concomitant drug or other treatment will be given (or permitted) while subject is in this study? None

4. What concomitant drug or other treatment will be specifically excluded while subject is in this study?

Nasal decongestants (oral or topical)

E. CRITERIA FOR "EFFECTIVENESS" EVALUATION

~~1. Indicate specific clinical and/or laboratory parameters (and methods) to be used to evaluate drug effectiveness and~~ give schedule for these observations. For each lab test, show normal range of values for lab doing test:

OBSERVATION or TEST (and method)	SCHEDULE
A. Nasal airway resistance*	A. "0" time (drug given immediately thereafter), 30, 60, 90, 120, 180, 240, 270 minutes on each test day.
B. Observation of nasal mucosa	B. As above

*A.B. Craig., Jr., et.al: Resistanct to Airflow Through the Nose. An. of ORL, 74:589, Sept., 1965

(Continue in Section K or on extra page, if necessary)

AHP2-REG-004-0044815

Study Protocol

F. CRITERIA FOR "SAFETY" EVALUATION

1. Specific adverse clinical manifestations (i.e., "side effects") that warrant particular observation in connection with study drug: Nervousness, headache, nausea, dizziness or light-headed, drowsiness, dry mouth, urticaria, palpitation, blurred vision.

2. Laboratory determinations (for toxicity purposes) and schedule for these observations:

TEST	NORMAL RANGE OF VALUES FOR LAB. DOING TEST	SCHEDULE*
None		

*Pre-drug = within 3 days prior to drug initiation; interim = specify drug day(s); Post-drug = within 3 days following drug cessation.
Any abnormal test is to be repeated immediately, and supplemented by other tests considered desirable to assess situation.

3. Special Physical Examination:

PROCEDURE	SCHEDULE
BP (rt. arm sitting - 3 min)	0, 30, 60, 90, 120, 180, 240 and 270 minutes
Pulse (sitting 3 min)	

G. REPORTS

1. Attached is a copy of the special report form(s) to be used in this study. (An individual data sheet must be completed for each recipient of test drug or control medication. It must include patient's identification; symptom or diagnosis being treated; concurrent diagnosis; concurrent treatment; dosage of test drug administered; dates of drug administration; clinical observations and laboratory tests made to assess response or toxic effects; full statement of adverse effects noted and whether attributable to test drug; adequate statement of useful results observed and whether attributable to test drug; date of report and signature of investigator.)

H. ANALYSIS OF RESULTS

1. In addition to my own subjective evaluation of the over-all study, a statistical anaylsis will be performed by:

"Special" statistical techniques to be employed are:

2. Analysis will be performed by A.H. Robins statistician (yes or no): Yes

AHP2-REG-004-0044816

ADMINISTRATIVE ASPECTS

1. Study is contingent on approval by the following committee or panel (give name and address) (if none, please indicate

2. Name and address of hospital, clinic, institution or office where clinical work will be done:

3. Name and address of laboratory where laboratory work will be done:

4. Earliest date that study can start:

5. Estimated duration of the investigation as proposed:

6. First few reports will be submitted to A. H. Robins for checking:
Yes_____ No_____ ; then submitted: At end_____ Periodically_____

7. Comments:

J. LITERATURE REFERENCES

The following literature references are pertinent to this proposed study:
1. A. H. Robins Company Investigational Brochure

K. OTHER PERTINENT COMMENTS (e.g., general description of packaging and labeling of study medications, data forms, etc.) (attach supplemental page if needed):
SEE ATTACHED PAGE

TE: _____ INVESTIGATOR: _____

AHP2-REG-004-0044817

ADMINISTRATIVE ASPECTS

1. Study is contingent on approval by the following committee or panel (give name and address) (if none, please indicate):

2. Name and address of hospital, clinic, institution or office where clinical work will be done:

3. Name and address of laboratory where laboratory work will be done:

4. Earliest date that study can start:

5. Estimated duration of the investigation as proposed:

6. First few reports will be submitted to A. H. Robins for checking:
Yes _____ No _____ ; then submitted: At end _____ Periodically _____

7. Comments:

J. LITERATURE REFERENCES

The following literature references are pertinent to this proposed study:
1. A. H. Robins Company Investigational Brochure

K. OTHER PERTINENT COMMENTS (e.g., general description of packaging and labeling of study medications, data forms, etc.) (attach supplemental page if needed):
SEE ATTACHED PAGE

DATE: _____ INVESTIGATOR: _____

AHP2-REG-004-0044818

Section K - Protocol #01, Dimetapp Elixir

1. Each subject will have one test day. Drug combinations will be randomly assigned so that each subject will receive either Dimetapp Elixir, Dimetane, Neosynephrine or Propadrine.

2. Openly labeled commercial drugs will be used in this study. However, the randomization code will be kept, and the drugs will be administered, by someone other than the examining physician or the person conducting the airflow measurements.

3. Immediately after the 240 minute reading is taken, Afrin (oxymethazoline) nasal solution will be administered and a reading of nasal resistance will be taken 30 minutes later.

AHP2-REG-004-0044819

WORKSHEET FOR DETERMINING STUDY MEDICATION REQUIREMENTS AND PACKAGING INSTRUCTIONS

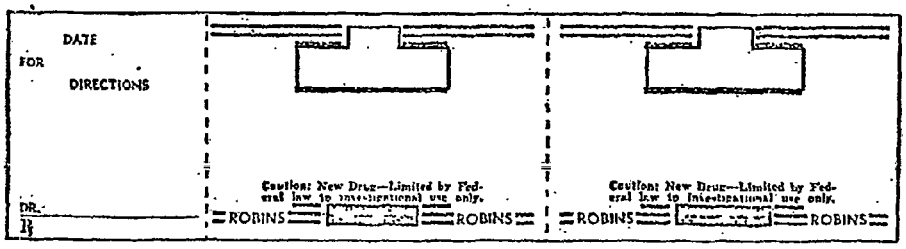
2.

stigator _____ Study Drug: Dimetapp Elixir Study No. _____ Protocol No. 01

DOSE FORM	UNIT SIZE	NUMBER DOSE UNITS PER PATIENT	NUMBER OF PATIENTS	TOTAL No. DOSE UNITS REQUIRED FOR ENTIRE STUDY
Dimetapp Elixir		10 cc.	24	240 cc.
(4 mg. brompheniramine, 5 mg.				
phenylephrine and 5 mg.				
phenylpropanolamine/5 cc.)				
Dimetane Elix. (2 mg. brom/5 cc.)		20 cc.	8	160 cc.
Neosynephrine Elix. (1 mg. PE/1 cc.)		10 cc.	8	80 cc.
Propadrine Elix. (4 mg. PE/1 cc.)		2.5 cc.	8	20 cc.
Afrin Nasal Spray		4 drops each	24	
		nostril x 2		

PACKAGING: Commercial medication ____; special packaging required No; Number dose units per bottle _____
number bottles per patient _____; total number bottles required _____

LABELING (show): Single part label _____; double part label _____; triple part label _____.



(1st Part) (2nd Part) (3rd Part)

Randomization code required Yes. (If yes, attach to copy here and to completed protocol form.)

Additional instructions: _____

AHP2-REG-004-0044820

A1.2 Sample Data Sheet

AHP2-REG-004-0044821

CLINICAL DATA FORM
DIMETAPP ELIXIR

A.H. ROBINS COMPANY
Medical Department
1407 Cummings Drive
Richmond, Virginia 23220

Case Number _____
Study Number _____
Protocol Number _____

(Section I-IV to be completed at time of admission to study: date _____)

I. PATIENT IDENTIFICATION: Initials _____ Age _____ Sex _____ Race _____

Weight _____ Height _____ Pregnant-No

II. DIAGNOSIS OR CONDITION. Nasal mucosal congestion from URI.

Concurrent medical diagnosis or condition: _____

III. GENERAL HISTORY. Hepatic disease _____ renal disease _____

cardiac disease _____ hypertension _____ allergy _____ drug hyper-

sensitivity _____ other _____

Give pertinent details of above (dates, severity, treatment, etc.) _____

_____

_____

IV. SPECIAL HISTORY. Date of onset of symptoms of URI _____ Symptoms present

cough _____ fever _____ sore throat _____ nasal stuffiness _____

headache _____ nasal secretion _____ muscular aching _____

weakness _____ other _____

V. DOSAGE AND SCHEDULE

Test Drug	Date	Time	Drug	Lot #	Dose
1st test day					
2nd test day					

VI. OBSERVATIONS AND ADVERSE EFFECTS (Record on other side).

AHP2-REG-004-0044822

VI. OBSERVATIONS AND ADVERSE EFFECTS (Drug Given Immediately After Making the "0" Minute Observation)

te _____ Case Number _____

st Day	Clinical Observation*					Ease**	Peak (V) L/minute		Pressure (cm H_2O) at 30 L/minute			Adverse Effects (see Protocol Fi, name at top of colum and indicate severity *** in tire block			
	PR	BP	MC	MH	SS		Insp.	Expir.	Insp.	Expir.	Total				
" time															
0 min.															
0 min.															
0 min.															
0 min.															
0 min.															
0 min															
0 min .															
0 min.															
0 min.															

* PR = pulse rate (give figures beats/min); BP = blood pressure (give figures mmHg); MC = Nasal mucosal congestion; MH = nasal mucosal hyperemia; SS = nasal secretion grade all as 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe.

** Ease of nasal breathing: 0 = normal; 1 = only mildly impaired; 2 = moderately impaired; 3 = severely impaired; 4 = total obstruction.

*** 1 = Did not significantly interfere with patient's functioning; 2 = significantly interfered with patient's functioning; 3 = nullified therapeutic effect; 4 = required withdrawal from study.

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VII. COMMENT (e.g., if prematurely dropped from study, give reason; etc): _____

_____

_____

_____

_____

_____ _____

Date of Report Signature of Investigator

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A1.3 Randomization Schedule

The randomization code may be broken as follows:

A - Dimetapp Elixir

B - Neosynephrine Elixir

C - Propadrine Elixir

D - Dimetane Elixir

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Randomization Schedule

Dimetapp Elixir Protocol #01

Investigator: Burton M. Cohen, M.D.

Pat. #	Drug	Pat. #	Drug
1	A	25	A
2	C	26	A
3	A	27	D
4	C	28	A
5	A	29	C
6	C	30	C
7	B	31	D
8	A	32	A
9	A	33	C
10	C	34	A
11	A	35	A
12	A	36	D
13	D	37	B
14	A	38	A
15	B	39	A
~~16~~	~~A~~	~~40~~	~~B~~
17	D	41	A
18	B	42	B
19	B	43	A
20	D	44	A
21	A	45	D
22	D	46	B
23	A	47	C
24	A	48	A

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A4. Special Findings

AHP2-REG-004-0044827

APPENDIX A4. SPECIAL FINDINGS

A4.1 Listing of Measurements of Nasal Airway Resistance

AHP2-REG-004-0044828

AHP2-REG-004-0044829

Table A4.1-01

MEASUREMENTS OF NASAL INSPIRATORY RESISTANCE*

TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
1	3.00	2.75	2.50	2.35	2.70	2.35	2.70	3.05	3.15	2.85
3	3.75	3.80	2.75	2.40	1.95	2.15	2.30	3.10	2.95	1.75
5	3.80	4.05	2.95	2.45	2.30	2.65	3.10	3.85	4.10	2.65
8	4.55	4.40	2.95	2.55	2.35	2.60	3.10	2.85	3.10	2.45
9	5.00	4.80	3.75	3.10	2.80	3.05	3.60	4.70	4.55	3.05
11	3.60	3.20	3.00	1.75	1.80	1.75	1.80	1.90	2.05	1.45
12	4.05	3.60	2.90	3.00	1.90	1.65	1.55	2.05	1.75	1.65
14	4.40	3.85	2.40	2.35	2.40	2.70	1.90	2.60	2.75	1.55
16	3.85	3.75	3.60	2.10	2.15	2.00	2.55	2.65	2.75	2.10
21	3.85	3.65	2.05	2.35	2.40	2.25	3.00	3.40	3.65	2.05
23	3.70	3.60	2.10	1.90	2.10	1.85	2.60	2.60	3.15	1.80
24	3.70	3.85	3.55	2.55	2.35	2.40	2.30	3.15	4.10	2.10
25	4.00	3.80	3.65	2.10	2.60	2.70	2.65	3.65	3.95	3.10
26	4.40	3.80	2.55	2.15	2.70	2.40	2.65	3.00	2.95	2.40
28	4.00	3.60	4.00	2.60	2.40	2.75	2.65	3.55	4.10	2.60
32	3.75	3.80	3.55	3.05	2.60	2.40	2.15	2.65	3.75	2.10
34	3.65	3.50	3.40	3.60	2.80		3.10	2.95	3.75	2.60
35	4.40	4.00	4.10	3.10	2.80	2.40	2.70	2.90	2.75	2.40
38	3.65	3.00	2.60	2.55	2.30	2.15	2.60	2.80	2.75	2.15
39	4.40	3.80	2.25	1.95	2.60	2.05	2.35	2.75	3.10	2.25
41	4.15	3.70	3.90	4.10	3.85	4.20	3.95	4.50	3.75	2.60
43	5.15	4.15	3.95	3.40	3.30	2.95	3.55	4.15	4.40	3.10
44	4.35	4.60	3.50	3.65	2.80	2.10	3.60	2.55	4.05	3.80
48	4.60	3.80	4.35	2.60	2.40	2.70	2.65	3.15	3.80	2.90
MEANS	4.07	3.78	3.15	2.65	2.51	2.42	2.70	3.10	3.38	2.38

* Pressure (cm H_2O) at 0.5 L/sec

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride

(Continued)

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Table A4. (Continued)

MEASUREMENTS OF NASAL INSPIRATORY RESISTANCE*

TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	0	MINUTES AFTER DOSE 30	60	90	120	150	180	210	240	270
7	3.10	3.25	2.75	2.65	2.55	2.75	3.05	2.85	3.15	1.95
15	3.75	3.80	3.60	3.40	2.70	2.95	2.80	3.05	3.55	2.65
18	4.55	4.30	2.80	2.70	3.10	2.90	3.75	4.15	3.95	3.00
19	4.45	4.40	3.70	3.65	3.80	3.45	4.10	3.95	4.10	2.90
37	3.85	3.55	3.40	2.60	2.40	2.75	3.60	3.55	3.60	2.60
40	3.75	3.40	3.30	2.60	3.10	3.80	4.15	3.35	4.05	3.00
42	4.15	3.95	3.50	4.25	3.70	4.10	4.25	4.15	3.95	2.65
46	3.85	3.75	3.80	2.75	3.40	3.75	3.80	4.25	4.00	3.10
MEANS	3.93	3.80	3.36	3.07	3.09	3.31	3.69	3.66	3.79	2.73

TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	0	MINUTES AFTER DOSE 30	60	90	120	150	180	210	240	270
2	4.25	4.30	3.95	4.10	2.75	3.10	3.75	3.40	4.55	3.10
4	3.75	3.60	3.50	2.75	3.05	3.30	4.10	3.95	3.05	2.55
6	4.20	3.95	3.45	3.10	2.10	3.00	2.95	3.85	3.75	2.75
10	4.80	4.55	4.40	3.65	2.80	2.60	2.55	3.80	3.75	3.10
29	2.60	2.55	2.40	2.10	2.40	2.65	2.70	2.65	3.05	2.25
30	3.80	3.75	3.20	2.80	2.60	3.10	3.40	3.20	3.60	2.60
33	4.05	3.75	3.50	3.00	3.15	3.00	2.85	3.75	3.60	2.80
47	3.95	4.10	2.95	3.10	3.00	2.60	2.80	2.70	2.65	2.55
MEANS	3.92	3.82	3.42	3.07	2.73	2.92	3.14	3.41	3.50	2.71

TREATMENT GROUP: Dimetane Elixir (8 mg brompheniramine maleate)

PAT. NO.	0	MINUTES AFTER DOSE 30	60	90	120	150	180	210	240	270
13	4.00	3.85	4.05	3.75	2.45	2.75	2.35	2.55	3.05	1.95
17	3.55	3.40	2.90	2.40	2.60	3.15	2.65	3.65	3.40	2.60
20	3.80	3.90	3.45	2.40	3.60	2.80	2.75	2.90	3.60	2.10
22	4.40	3.90	3.40	2.65	2.50	2.40	2.95	3.70	2.90	2.60
27	4.60	3.80	2.90	2.70	2.60	2.70	3.10	3.40	3.90	2.60
31	2.95	2.60	2.30	2.60	2.20	2.60	2.70	2.60	2.30	2.00
36	4.40	3.95	3.50	3.60	3.20	2.80	4.10	3.85	4.15	3.00
45	4.35	4.10	4.40	3.75	4.20	3.75	3.80	2.90	3.75	2.90
MEANS	4.01	3.71	3.36	2.98	2.97	2.87	3.05	3.21	3.30	2.47

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Table 4.1-02

MEASUREMENTS OF NASAL EXPIRATORY RESISTANCE*

TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
1	2.95	2.50	2.50	2.25	2.40	2.25	3.00	2.15	2.40	2.80
3	2.50	2.15	2.00	2.05	1.75	1.75	2.15	2.65	2.40	1.50
5	3.50	3.45	2.10	1.95	1.75	1.90	2.10	2.10	3.10	2.10
8	3.25	3.20	2.70	2.10	2.25	1.90	2.15	2.65	3.05	2.30
9	3.75	3.45	3.50	2.85	1.80	1.75	1.90	2.65	3.35	2.80
11	3.55	2.80	1.90	1.60	1.50	1.25	1.75	1.60	1.90	1.25
12	3.20	1.90	1.90	2.70	1.60	1.50	1.40	2.00	1.80	1.30
14	3.60	3.40	2.40	2.30	2.20	1.80	1.60	1.85	2.10	1.40
16	3.00	2.85	3.40	1.80	1.65	1.75	2.00	2.45	2.45	2.00
21	2.60	2.60	1.80	1.90	1.70	1.90	1.95	2.20	3.60	1.35
23	2.60	2.15	1.90	1.75	2.00	1.80	2.60	2.55	2.95	1.35
24	3.25	3.25	2.10	2.00	2.30	2.15	2.25	2.40	2.60	1.70
25	2.90	3.70	3.50	2.00	2.30	1.40	2.50	3.50	3.80	2.10
26	2.80	2.60	2.15	1.80	2.45	1.80	1.90	2.05	2.00	1.90
28	3.40	3.20	1.90	2.30	2.35	2.60	2.15	3.10	3.70	2.50
32	3.60	3.30	3.10	1.80	1.80	2.05	1.95	2.50	3.10	1.45
34	3.50	3.20	2.05	3.10	1.35		2.10	2.80	2.40	2.20
35	2.90	2.70	2.10	1.75	2.15	2.30	2.65	2.90	2.55	1.80
38	2.10	1.85	1.30	2.10	1.35	1.40	1.50	2.40	2.10	1.60
39	2.65	2.00	1.80	1.75	2.30	1.65	2.15	2.60	2.80	1.75
41	3.80	3.10	3.10	3.80	3.50	3.70	3.50	3.75	3.50	2.50
43	3.60	3.75	3.10	2.70	2.60	2.40	3.30	2.60	3.00	2.95
44	3.10	2.40	2.00	2.00	2.10	1.80	2.05	2.50	2.65	1.75
48	2.95	3.10	2.65	2.50	2.30	2.60	2.50	3.00	3.00	2.85
MEANS	3.13	2.86	2.37	2.20	2.07	1.97	2.20	2.54	2.76	1.97

*Pressure (cm H_2O) at 0.5 L/sec

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride

Continued

Tab I-02 (Continued)

MEASUREMENTS OF NASAL EXPIRATORY RESISTANCE*

TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE								
	0	30	60	90	120	150	180	210	240	270
7	2.95	2.65	2.65	2.55	2.20	2.60	2.85	2.60	2.95	1.40
15	3.75	3.35	2.95	3.35	2.65	2.80	2.40	3.00	3.40	2.15
18	4.00	3.60	2.60	2.50	2.60	2.35	3.40	3.50	3.85	2.10
19	4.10	3.95	3.45	3.10	3.10	3.30	3.45	3.70	3.00	2.80
37	3.60	3.20	2.60	2.60	2.30	2.55	3.10	3.10	3.20	2.10
40	3.75	3.10	2.80	2.10	2.95	2.00	3.10	2.60	3.80	2.75
42	2.90	3.00	2.80	3.10	2.40	2.40	4.00	3.15	3.40	2.55
46	3.00	3.50	3.10	2.60	2.60	2.50	3.40	2.80	3.15	3.00
MEANS	3.52	3.29	2.87	2.74	2.60	2.56	3.21	3.06	3.34	2.36

TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE								
	0	30	60	90	120	150	180	210	240	270
2	3.15	3.20	3.30	3.10	2.40	2.15	2.20	3.15	3.65	2.10
4	3.60	3.55	3.45	2.65	2.55	2.10	2.15	3.25	2.90	2.25
6	3.10	2.95	3.10	2.65	2.00	2.35	2.85	3.55	2.80	2.05
10	3.90	3.85	3.75	3.35	2.60	1.80	2.40	3.70	3.60	2.15
29	2.40	2.30	2.10	1.60	1.75	1.85	2.40	2.20	3.00	1.95
30	2.20	2.15	1.90	2.70	2.60	2.90	2.40	2.60	2.70	2.10
33	2.80	3.40	3.30	2.15	2.15	2.40	2.50	3.00	2.80	2.70
47	3.80	2.75	2.60	2.00	2.40	2.10	2.20	2.30	2.55	2.00
MEANS	3.12	3.02	2.94	2.52	2.27	2.21	2.39	2.97	3.00	2.16

TREATMENT GROUP: Dimetane Elixir (8 mg brompheniramine maleate)

PAT. NO.	MINUTES AFTER DOSE								
	0	30	60	90	120	150	180	210	240	270
13	3.65	3.50	2.45	3.00	2.10	2.25	2.05	2.15	3.00	1.75
17	3.60	3.10	2.85	1.90	1.90	2.05	2.55	2.75	2.60	1.85
20	3.10	3.20	3.55	1.80	2.30	2.65	2.75	2.65	2.80	2.05
22	2.05	3.40	3.20	2.50	2.45	2.30	2.80	3.40	2.90	2.50
27	3.10	3.60	2.60	2.50	2.30	2.05	2.60	2.20	3.00	2.20
31	2.60	2.60	2.25	2.40	1.95	2.05	2.75	2.15	2.40	1.60
36	3.40	3.40	3.00	2.60	2.40	2.10	2.40	3.00	3.75	2.45
45	2.80	2.75	2.20	2.15	2.60	3.00	2.55	2.60	3.35	2.50
MEANS	3.21	3.19	2.76	2.36	2.22	2.31	2.56	2.61	2.97	2.11

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A4.2 Listings of Ratings for Nasal Mucosal Characteristics

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Table A4.2-01

RATINGS OF NASAL MUCOSAL CONGESTION*

TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
1	3	3	2	2	3	3	2	3	3	3
3	4	4	2	1	2	2	3	2	3	2
5	3	3	2	2	2	3	2	2	4	2
8	3	4	3	2	2	2	2	3	3	2
9	3	3	3	2	2	2	2	4	3	2
11	3	3	2	2	2	2	2	3	3	2
12	3	3	2	2	2	2	2	3	3	2
14	3	3	2	2	2	2	2	3	3	2
16	3	3	2	2	2	2	2	3	3	2
21	3	3	2	2	2	2	2	3	3	2
23	4	4	2	2	2	2	2	3	3	2
24	4	3	3	3	2	2	2	3	3	2
25	3	3	2	2	2	2	2	3	3	2
26	3	4	3	3	2	3	3	3	3	2
28	4	4	3	2	2	2	3	3	3	2
32	4	3	2	2	2	2	2	3	3	2
34	4	3	3	2	2	2	2	3	3	2
35	3	2	2	2	2	2	2	3	3	2
38	3	2	3	2	2	3	2	3	3	2
39	3	3	2	2	2	2	2	3	3	2
41	4	4	3	3	4	2	2	3	4	2
43	4	4	3	2	2	4	4	3	3	2
44	4	4	3	2	2	2	3	3	3	2
48	4	4	3	2	2	2	3	3	3	2

*Rated on a five point scale: 0=absent; 1=mild; 2=moderate; 3=severe; 4=very severe.

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride.

Continued

Table A4.2-01 (Cont'd.)

RATINGS OF NASAL MUCOSAL CONGESTION*

2 3 TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
7	3	3	2	3	3	3	3	4	3	2
15	3	3	3	3	2	2	2	3	3	2
18	3	3	2	2	2	3	3	3	3	2
19	4	3	3	3	3	3	3	3	3	3
37	4	4	2	2	3	3	4	3	4	3
40	4	4	3	3	3	3	3	4	4	2
42	3	3	3	3	3	4	4	4	4	3
46	3	3	2	3	3	3	3	3	3	2

3 3 TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
2	4	4	4	3	2	3	3	4	4	3
4	4	4	4	3	3	3	3	3	4	3
6	3	3	2	2	2	3	3	3	4	3
10	3	3	3	3	3	3	2	3	3	2
29	3	3	3	3	3	3	2	3	3	2
30	3	3	2	2	2	3	3	3	4	2
33	3	3	3	2	2	2	2	3	3	2
47	3	3	2	3	3	2	3	3	3	2
					2	2	3	3	3	2

4 3 TREATMENT GROUP: Dimetane Elixir (8 mg brompheniramine maleate)

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
13	3	3	2	2	2	2	2	3	3	2
17	4	3	2	2	2	3	3	4	3	2
20	3	3	2	2	2	3	3	3	3	2
22	3	3	2	2	2	2	2	3	2	2
27	4	4	3	2	3	2	2	3	4	2
31	3	3	2	2	3	3	3	3	3	2
36	4	3	3	2	2	2	3	3	3	2
45	3	3	2	2	2	2	2	3	4	2

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Table A4.2-02

RATINGS ON NASAL MUCOSAL HYPEREMIA *

14. TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
1	3	2	2	2	?	?	2	3	3	3
3	3	3	2	2	2	2	2	3	3	1
5	3	3	2	2	2	2	2	3	3	?
8	3	3	2	2	?	2	3	3	3	?
9	3	3	2	2	?	?	2	3	3	?
11	3	?	3	2	2	2	2	2	2	1
12	3	2	?	2	?	2	3	?	2	?
14	3	3	?	?	?	2	2	?	?	?
16	4	3	3	2	2	?	?	2	3	2
21	3	3	?	2	2	2	2	3	2	2
23	4	4	?	2	?	2	2	3	3	2
24	4	3	2	2	?	2	?	3	3	?
25	3	3	3	2	2	3	?	?	2	?
26	3	3	2	2	?	2	2	?	3	?
28	4	3	3	3	?	2	3	3	3	?
32	4	3	3	2	2	2	2	?	?	?
34	4	3	3	2	?		3	3	3	?
35	3	?	2	2	?	3	3	3	3	?
38	3	2	2	2	?	2	2	3	3	2
39	3	3	3	2	?	2	2	2	3	2
41	4	3	3	3	3	3	3	3	4	?
43	4	3	3	3	?	3	2	3	3	?
44	4	4	3	2	?	2	3	3	3	2
48	4	2	2	2	2	2	3	3	3	2

*Rated on a five point scale: 0=absent; 1=mild; 2=moderate; 3=severe; 4=very severe.

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride.

Continued

Table A6.2-02 (Cont'd.)

RATINGS ON NASAL MUCOSAL HYPEREMIA *

2 4 TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
7	3	3	2	2	3	3	3	3	3	2
16	3	3	2	2	2	2	2	3	3	2
18	3	2	2	2	3	3	3	3	3	3
19	4	3	3	3	3	4	4	4	4	3
37	4	4	2	2	3	3	3	3	3	2
40	4	4	3	2	2	3	3	3	3	2
42	3	2	3	2	3	3	3	4	3	2
46	3	3	2	3	3	3	3	3	4	2

3 4 TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
2	4	4	3	3	3	3	3	4	4	3
4	4	4	3	3	3	2	4	3	3	2
6	3	3	2	2	2	2	2	3	3	2
10	3	3	3	2	2	2	2	3	3	2
29	3	3	3	2	2	3	3	3	3	2
30	3	3	2	2	2	2	2	3	3	2
33	3	2	2	2	3	2	3	3	3	2
47	3	3	2	3	2	2	2	3	3	2

4 4 TREATMENT GROUP: Dimetane Elixir (8 mg. brompheniramine maleate)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
13	3	3	2	2	2	2	3	3	3	2
17	4	4	3	3	3	3	3	3	3	3
20	3	3	2	2	2	2	2	2	3	2
22	3	3	3	2	2	3	3	3	3	2
27	4	3	3	2	2	2	2	3	4	2
31	3	2	2	2	2	3	3	4	3	2
36	4	3	3	2	2	2	3	3	3	2
45	3	3	2	2	2	2	2	3	3	2

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Table A4.2-03

RATINGS OF NASAL SEROUS SECRETIONS *

1 5

TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
1	3	2	2	2	2	2	2	3	3	3
3	3	3	2	1	2	2	2	2	3	1
5	3	3	2	2	2	2	2	3	3	2
8	4	3	2	2	2	2	2	3	3	2
9	4	3	2	2	2	2	2	2	2	2
11	3	3	2	2	1	1	2	2	2	1
12	3	3	2	1	1	0	1	2	2	0
14	2	2	1	0	1	1	1	1	2	0
16	3	3	3	0	1	1	1	2	2	0
21	3	2	1	1	1	1	2	2	3	0
23	3	3	2	0	0	1	1	2	3	0
24	3	3	2	0	0	0	1	1	1	1
25	2	2	1	1	0	1	1	2	2	1
26	3	2	1	0	0	0	0	2	2	0
28	3	2	2	1	1	1	2	2	2	2
32	3	3	3	1	0	1	2	2	3	1
34	3	3	2	1	0		2	3	3	2
35	3	3	2	2	2	2	3	2	3	1
38	3	2	2	1	0	1	1	3	3	1
39	3	2	2	2	0	0	2	2	3	1
41	3	3	3	3	3	3	4	4	3	2
43	3	3	2	2	2	2	2	2	2	2
44	3	3	2	2	1	2	3	3	3	1
48	3	2	2	2	1	2	2	3	3	1

*Rated on a five point scale: 0=absent; 1=mild; 2=moderate; 3=severe; 4=very severe.

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride.

Continued

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A4.2-03 (Cont'd.)

RATINGS OF NASAL SEROUS SECRETIONS*

2 5 TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
7	3	3	2	2	2	3	3	4	3	1
15	3	3	2	2	2	2	2	3	3	2
18	3	2	1	1	1	2	3	3	3	2
19	4	3	3	2	2	4	4	4	4	2
37	3	3	2	1	1	2	2	3	3	2
40	3	2	2	2	2	3	3	3	3	2
42	3	2	2	2	3	3	3	3	3	2
46	3	2	2	2	2	1	2	3	3	2

3 5 TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
2	4	4	3	3	3	2	3	4	4	3
4	4	4	3	3	2	2	4	4	4	2
6	3	3	2	2	2	2	2	3	3	2
10	3	3	3	2	2	2	2	3	3	2
29	3	2	2	2	2	2	3	3	3	2
30	3	2	2	2	2	2	2	3	3	2
33	2	2	2	2	2	2	3	2	3	2
47	3	2	2	2	2	2	2	3	2	2

4 5 TREATMENT GROUP: Dimetane Elixir (8 mg brompheniramine maleate)

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
13	2	2	2	0	0	1	2	2	3	1
17	3	3	3	3	2	3	3	3	3	2
20	2	2	2	1	1	1	2	3	3	1
22	2	2	2	2	1	2	2	3	3	1
27	3	3	3	2	1	2	2	3	4	2
31	3	3	2	2	2	2	2	3	3	2
34	3	3	2	1	1	2	3	3	3	2
44	3	3	2	2	2	2	2	3	3	2

AHP2-REG-004-0044840

Table A4.2-04

RATINGS OF EASE OF NASAL BREATHING*

TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
1	2	[illegible]	2	2	2	2	2	2	2	2
3	3	[illegible]	3	2	2	1	1	2	3	1
5	4	[illegible]	2	2	1	2	1	3	3	1
8	3	[illegible]	2	1	2	2	2	3	3	1
9	4	[illegible]	2	2	2	2	2	2	3	2
11	3	[illegible]	3	1	1	1	2	2	2	1
12	3	[illegible]	1	1	0	0	0	1	1	0
14	3	[illegible]	1	0	1	1	1	1	2	0
16	3	[illegible]	3	2	1	1	1	2	2	0
21	3	[illegible]	1	1	1	1	2	2	3	1
23	3	[illegible]	2	1	0	0	0	2	3	1
24	3	[illegible]	2	1	1	1	1	2	1	1
25	3	[illegible]	1	1	1	1	1	2	2	1
26	3	[illegible]	1	0	1	1	1	2	2	0
28	3	[illegible]	2	1	1	1	2	2	2	0
32	3	[illegible]	3	0	0	1	2	2	3	1
34	3	[illegible]	2	1	1		2	2	3	2
35	3	[illegible]	1	1	2	2	3	2	3	1
38	3	[illegible]	2	1	1	1	1	2	3	1
39	3	[illegible]	2	1	1	1	1	2	3	1
41	3	[illegible]	3	3	3	3	3	3	3	2
43	3	[illegible]	2	2	2	2	2	2	3	2
44	4	[illegible]	2	2	1	2	3	2	3	1
48	3	[illegible]	2	2	1	2	2	3	3	1

*Rated on a five point scale: 0=normal; 1=only mildly impaired; 2=moderately impaired; 3=severely impaired; 4=total obstruction.

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride.

Continued

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Table A4.2-04 (Cont'd.)

RATINGS OF EASE OF NASAL BREATHING*

2 6 TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
7	3	2	2	2	2	3	3	4	3	2
15	3	4	2	2	2	2	2	2	4	2
18	3	3	2	1	1	1	3	4	4	2
19	4	4	3	3	3	4	4	4	4	2
37	3	3	2	1	1	3	2	3	3	2
40	3	2	2	2	2	2	3	3	3	2
42	3	2	2	2	3	3	3	3	2	2
46	3	2	2	2	2	2	3	3	3	2

3 6 TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
2	3	3	3	3	2	2	2	3	3	2
4	4	4	3	3	3	2	3	4	4	2
6	3	3	2	1	1	2	2	3	3	1
10	3	3	3	2	1	2	2	3	3	1
29	3	2	2	2	2	2	3	3	3	2
30	3	3	2	2	1	2	2	3	2	2
33	3	3	2	2	2	1	3	2	3	1
47	3	2	2	2	2	2	2	3	3	2

4 6 TREATMENT GROUP: Dimetane Elixir (8 mg brompheniramine maleate)

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
13	3	3	2	1	1	1	2	2	3	1
17	4	4	3	3	2	3	4	4	4	3
20	3	3	2	1	1	1	2	3	2	1
22	3	3	2	2	2	2	2	3	3	2
27	4	3	2	1	1	2	2	3	4	2
31	3	3	2	2	2	2	3	3	3	1
36	3	3	2	1	1	2	3	3	3	1
45	3	2	2	2	2	2	2	3	3	2

A4.3 Analyses of Covariance - Nasal Inspiratory and Expiratory Resistances

Treatment 1 = Dimetapp

Treatment 2 = Neosynephrine (10 mg phenylephrine hydrochloride)

Treatment 3 = Propadrine (10 mg phenylpropanolamine hydrochloride)

Treatment 4 = Dimetane (8 mg brompheniramine maleate)

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NASAL INSPIRATORY RESISTANCE - 30 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	0.03490	0.05167	3			0.22668	3	0.075559	1.36449
ERROR	11.82177	9.24594	9.61250	44	0.78211	7.23135	2.38115	43	0.055376	
TRT 1	5.43990	4.06031	4.68906	23	0.74640	3.03060	1.65846	22		
TRT 2	1.46949	1.20750	1.16000	7	0.82160	0.99209	0.16791	6		
TRT 3	2.76500	2.55875	2.52969	7	0.92541	2.36788	0.16180	6		
TRT 4	2.14719	1.41938	1.23375	7	0.66104	0.93826	0.29549	6		
TOTAL	12.02370	9.27104	9.66417	47	0.76607	7.05634	2.60783			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	3.7812	3.7348
TRT 2	3.9312	3.8000	3.8644
TRT 3	3.9250	3.8187	3.8880
TRT 4	4.0062	3.7125	3.7182

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 0.412 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 3.269 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 0.946 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.3692 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 176.6620 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 3.7792

DISREGARDING COVARIATE, F IS 0.0788

COVARIATE = 0 MIN

OBSERVATION = 30 MIN

NASAL INSPIRATORY RESISTANCE - 60 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	-0.359060	0.662646	3			1.07729	3	0.359095	1.213H9
ERROR	11.82177	7.04177	16.91521	44	0.59566	4.19451	12.72070	43	0.295830	
TRT 1	5.43990	2.88271	10.13958	23	0.52992	1.52760	8.61198	22		
TRT 2	1.46949	0.29594	1.07719	7	0.20136	0.05959	1.01760	6		
TRT 3	2.76500	2.46125	2.56469	7	0.88044	2.08839	0.47933	6		
TRT 4	2.14719	1.41188	3.13375	7	0.68083	0.99529	2.13846	6		
TOTAL	12.02370	6.70917	17.54167	47	0.55800	3.74368	13.79798			

MEANS TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	3.1542	3.1188
TRT 2	3.9312	3.3562	3.4053
TRT 3	3.9250	3.4187	3.4715
TRT 4	4.0062	3.3625	3.3668

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 0.133 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 3.376 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 0.844 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS — F IS 0.5153 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO — F IS 13.6993 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 3.4267

DISREGARDING COVARIATE, F IS 0.5432

COVARIATE = 0 MIN

OBSERVATION = 60 MIN

AHP2-REG-004-0044844

NASAL INSPIRATORY RESISTANCE - 90 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	-0.59422	1.86818	3			2.49604	3	0.832014	2.75017
ERROR	11.82177	6.11240	16.16927	44	0.51705	3.16039	13.00888	43	0.302532	
TRT 1	5.43990	2.13271	8.37958	23	0.39205	0.83613	7.54346	22		
TRT 2	1.44969	0.78475	2.69500	7	0.52307	0.40211	2.29289	6		
TRT 3	2.76500	2.21750	2.52000	7	0.80199	1.77841	0.74159	6		
TRT 4	2.14719	0.99344	2.57469	7	0.46267	0.45963	2.11505	6		
TOTAL	12.02370	5.51618	18.03745	47	0.45896	2.53252	15.50493			

MEANS TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	2.6542	2.6235
TRT 2	3.9312	3.0750	3.1175
TRT 3	3.9250	3.0790	3.1208
TRT 4	4.0062	2.9817	2.9850

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 0.198 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 7.855 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 1.477 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.5318 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 9.9595 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 2.8490

DISREGARDING COVARIATE, F IS 1.6946

COVARIATE = 0 MIN

OBSERVATION = 90 MIN

AHP2-REG-004-0044845

NASAL INSPIRATORY RESISTANCE - 120 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	-0.57121	2.52667	3			2.93009	3	0.976697	4.63362
ERROR	11.82177	4.26594	10.60313	44	0.36085	1.53938	9.06374	43	0.210785	
TRT 1	5.43890	1.89406	4.93156	23	0.34816	0.65947	3.87209	22		
TRT 2	1.44969	-1.05556	1.89219	7	0.71800	0.75957	1.13262	6		
TRT 3	2.76500	0.35125	0.87969	7	0.12703	0.04482	0.83507	6		
TRT 4	2.14719	0.96406	3.29969	7	0.44899	0.43285	2.85683	6		
TOTAL	12.02370	3.69373	13.12979	47	0.30737	1.13596	11.99383			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	2.5062	2.4848
TRT 2	3.9312	3.0937	3.1234
TRT 3	3.9250	2.7312	2.7632
TRT 4	4.0062	2.9187	2.9214

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 2.174 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 9.553 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 2.517 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.1469 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 7.0722 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 2.7104

DISREGARDING COVARIATE, F IS 3.4950

COVARIATE = 0 MIN

OBSERVATION = 120 MIN

AHP2-REG-004-0044846

NASAL INSPIRATORY RESISTANCE 150 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.25359	-1.007358	5.28069	3			5.69172	3	1.899240	8.621SA
ERROR	11.63514	2.76810	9.91069	43	0.23791	0.65855	9.25214	42	0.2202R9	
TRT 1	5.25326	2.09185	6.20913	22	0.39820	0.83297	5.37616	21		
TRT 2	1.46969	0.44340	2.00219	7	0.30172	0.13379	1.86839	6		
TRT 3	2.76500	0.07125	0.49989	7	0.02577	0.00186	0.49785	6		
TRT 4	7.14719	0.14156	1.19969	7	0.07524	0.01216	1.18753	6		
TOTAL	11.88872	1.69452	15.19138	46	0.14253	0.24152	14.94986			

MEANS TREATMENT	X	Y	Y ADJ
TRT 1	4.0915	2.4217	2.4051
TRT 2	3.9317	3.3062	3.3277
TRT 3	3.9250	2.9187	2.9417
TRT 4	4.0062	2.8687	2.8729

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 1.670
WITH 7 AND 42 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 72.525
WITH 1 AND 42 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 4.382
WITH 6 AND 39 DF

TEST FOR EQUAL BETAS F IS 0.4691
WITH 3 AND 39 DF

TEST BETA BAR IS ZERO F IS 2.8761
WITH 1 AND 39 DF

OVERALL X MEAN 4.0213

OVERALL Y MEAN 2.7330

DISREGARDING COVARIATE, F IS 7.6372

COVARIATE = 0 MIN

OBSERVATION = 150 MIN

100

AHP2-REG-004-0044847

AHP2-REG-004-0044848

NASAL INSPIRATORY RESISTANCE - 180 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	-0.97448	6.05271	3			6.79564	3	2.265214	7.69474
ERROR	11.02177	4.86333	14.72208	44	0.41139	2.00072	12.72137	43	0.295846	
TRT 1	5.43990	2.83521	8.12458	23	0.48442	1.27655	6.84803	22		
TRT 2	1.46969	0.98063	1.91875	7	0.66724	0.65431	1.26444	6		
TRT 3	2.74500	-0.03250	2.13875	7	-0.01175	0.00038	2.13837	6		
TRT 4	2.14719	1.28000	2.54000	7	0.59613	0.76304	1.77696	6		
TOTAL	12.02370	3.88885	20.77479	47	0.32343	1.25778	19.51701			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	2.7042	2.6797
TRT 2	3.9312	3.6875	3.7214
TRT 3	3.9250	3.1375	3.1739
TRT 4	4.0062	3.0500	3.0530

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 2.282 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 18.407 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 4.151 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.7689 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 6.6536 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 2.9979

DISREGARDING COVARIATE, F IS 6.0299

COVARIATE = 0 MIN

OBSERVATION = 180 MIN

NASAL INSPIRATORY RESISTANCE - 210 Minutes

ANALYSES OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	-0.59193	2.08651	3			2.79162	3	0.9305539	3.09525
ERROR	11.82177	6.79177	16.82927	44	0.57451	3.90197	12.92730	43	0.300635	
TRT 1	9.43990	3.00521	10.88458	23	0.35244	1.66019	9.22439	22		
TRT 2	1.46969	1.36188	2.04875	7	0.92664	1.26197	0.78678	6		
TRT 3	2.76500	1.42250	1.87875	7	0.51447	0.73183	1.14692	6		
TRT 4	2.14719	1.00219	2.01719	7	0.46674	0.46777	1.54942	6		
TOTAL	12.02370	6.19984	18.91576	47	0.51564	3.19686	15.71892			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	3.1042	3.0701
TRT 2	3.9312	3.4625	3.4709
TRT 3	3.9250	3.4125	3.4634
TRT 4	4.0062	3.2062	3.2104

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 0.584 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 8.117 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 1.580 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.2306 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 12.2824 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 3.2656

DISREGARDING COVARIATE, F IS 1.8184

COVARIATE = 0 MIN

OBSERVATION = 210 MIN

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AHP2-REG-004-0044849

AHP2-REG-004-0044850

NASAL INSPIRATORY RESISTANCE - 240 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	-0.35568	1.09776	3			1.51118	3	0.503726	1.49900
ERROR	11.82177	6.23281	17.73594	44	0.52723	3.28614	14.44980	43	0.336042	
TRT 1	5.43990	2.49031	12.04406	23	0.45779	1.14003	10.90403	22		
TRT 2	1.46969	0.82156	0.76219	7	0.55900	0.45926	0.30293	6		
TRT 3	2.76500	1.28250	2.37500	7	0.46383	0.59487	1.78013	6		
TRT 4	2.14719	1.63844	2.55469	7	0.76306	1.25023	1.30446	6		
TOTAL	12.02370	5.87714	18.83370	47	0.48880	2.87272	15.96098			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	3.3812	3.3499
TRT 2	3.9312	3.7937	3.8371
TRT 3	3.9250	3.5000	3.5467
TRT 4	4.0062	3.3812	3.3851

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 9.701 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 3.095 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 0.779 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS — F IS 0.1476 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO — F IS 9.1974 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 3.4698

DISREGARDING COVARIATE, F IS 0.0078

COVARIATE = 0 MIN

OBSERVATION = 240 MIN

NASAL INSPIRATORY RESISTANCE - 270 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.20193	-0.47016	1.13109	3			1.57005	3	0.523349	2.77222
ERROR	11.82177	5.33156	10.52219	44	0.45100	2.40451	8.11768	43	0.188783	
TRT 1	5.43990	2.36831	7.83906	23	0.43539	1.02411	6.81495	22		
TRT 2	1.46969	-0.83219	0.94969	7	-0.56623	0.47121	0.47847	6		
TRT 3	2.76900	1.13750	0.58875	7	0.41139	0.26796	0.12079	6		
TRT 4	2.14719	1.00195	1.14469	7	0.46645	0.46718	0.67751	6		
TOTAL	12.02370	4.86141	11.65328	47	0.40432	1.96556	9.68772			

MEANS TREATMENT	X	Y	Y ADJ
TRT 1	4.0729	2.3812	2.3545
TRT 2	3.9312	2.7312	2.7684
TRT 3	3.9250	2.7125	2.7524
TRT 4	4.0062	2.4687	2.4720

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 0.096 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 8.124 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 1.319 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS — F IS 0.0428 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO — F IS 11.8863 WITH 1 AND 40 DF

OVERALL X MEAN 4.0135

OVERALL Y MEAN 2.5094

DISREGARDING COVARIATE, F IS 1.5766

COVARIATE = 0 MIN

OBSERVATION = 270 MIN

AHP2-REG-004-044851

NASAL EXPIRATORY RESISTANCE, 30 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	1.00078	1.46830	3			0.49373	3	0.164577	1.30721
ERROR	10.08802	8.15583	12.00740	44	0.80847	6.59372	5.41367	43	0.125899	
TRT 1	4.59990	4.21708	7.48833	23	0.91678	3.86613	3.62220	22		
TRT 2	1.41469	1.15094	1.11719	7	0.81356	0.93636	0.18083	6		
TRT 3	2.76969	1.92219	2.49969	7	0.69401	1.33402	1.16567	6		
TRT 4	1.30375	0.86563	0.90219	7	0.66395	0.57473	0.32746	6		
TOTAL	11.08120	9.15661	13.47370	47	0.82632	7.56629	5.90740			

MEANS TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	2.8583	2.9215
TRT 2	3.5187	3.2937	3.0403
TRT 3	3.1187	3.0187	3.0886
TRT 4	3.7125	3.1937	3.1879

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 1.818 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 0.285 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 0.769 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS — F IS 0.2958 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO — F IS 47.8000 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 3.0135

DISREGARDING COVARIATE, F IS 1.7910

COVARIATE = 0 MIN

OBSERVATION = 30 MIN

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AHP2-REG-004-0044852

NASAL EXPIRATORY RESISTANCE - 60 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	0.87594	2.92771	3			2.23710	3	0.745701	3.02000
ERROR	10.08802	5.26042	14.02208	44	0.58093	3.40448	10.61760	43	0.246921	
TRT 1	4.59990	3.16010	8.73990	23	0.68699	2.17097	6.56892	22		
TRT 2	1.41469	0.40969	0.59969	7	0.28960	0.11864	0.48104	6		
TRT 3	2.76969	2.09938	3.10375	7	0.75798	1.59129	1.51246	6		
TRT 4	1.30375	0.79125	1.57875	7	0.14609	0.02805	1.55070	6		
TOTAL	11.08120	6.13636	16.94979	47	0.60791	4.09509	12.85470			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	2.3729	2.4183
TRT 2	3.5187	2.8687	2.8868
TRT 3	3.1187	2.9375	2.9677
TRT 4	3.2125	2.7625	2.7583

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 4.364 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 0.332 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 1.807 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS — F IS 0.6651 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO — F IS 13.4656 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 2.6146

DISREGARDING COVARIATE, F IS 3.0623

COVARIATE = 0 MIN

OBSERVATION = 60 MIN

REG

AHP2-REG-004-0044853

AHP2-REG-004-0044854

NASAL EXPIRATORY RESISTANCE - 90 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	1.12865	1.95083	3			1.11710	3	0.372368	1.80267
ERROR	10.08802	4.35615	10.76333	44	0.43131	1.88104	8.88229	43	0.206565	
TRT 1	4.59990	2.07115	6.16740	23	0.58070	1.55113	4.61627	22		
TRT 2	1.41469	0.26938	1.17375	7	0.19041	0.05129	1.12246	6		
TRT 3	2.74969	0.98625	2.34500	7	0.35609	0.35119	1.99381	6		
TRT 4	1.30375	0.42938	1.07719	7	0.32934	0.14141	0.93578	6		
TOTAL	11.08120	5.48479	12.71417	47	0.49496	2.71477	9.99939			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	2.2021	2.2358
TRT 2	3.5187	2.7375	2.6021
TRT 3	3.1187	2.5250	2.5623
TRT 4	3.2125	2.3562	2.3531

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 1.618 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 2.173 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 1.024 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS — F IS 0.3291 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO — F IS 8.6801 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 2.3708

DISREGARDING COVARIATE, F IS 2.6583

COVARIATE = 0 MIN

OBSERVATION = 90 MIN

NASAL EXPIRATORY RESISTANCE - 120 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	1.20333	1.72292	3			1.13928	3	0.379759	2.69991
ERROR	10.08802	2.30250	6.57375	44	0.22824	0.52552	6.04823	43	0.140656	
TRT 1	4.59990	1.23781	5.04906	23	0.26910	0.33309	4.71597	22		
TRT 2	1.41469	0.53500	0.66500	7	0.37818	0.20232	0.46268	6		
TRT 3	2.76969	0.53469	0.53969	7	0.19309	0.10322	0.43647	6		
TRT 4	1.30375	-0.00500	0.32000	7	-0.00384	0.00002	0.31998	6		
TOTAL	11.08120	3.50583	8.29667	47	0.31638	1.10916	7.18750			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	2.0687	2.0866
TRT 2	3.5187	2.6000	2.5284
TRT 3	3.1187	2.2687	2.2885
TRT 4	3.2125	2.2250	2.2233

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 0.942 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 6.216 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 1.407 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.2541 WITH 3 AND 40 DF

TEST BETA WAY IS ZERO F IS 3.5418 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 2.2167

DISREGARDING COVARIATE, F IS 3.8440

COVARIATE = 0 MIN

OBSERVATION = 120 MIN

AHP2-REG-004-0044855

NASAL EXPIRATORY RESISTANCE - 150 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	1.04994	1.39293	2.27583	3			1.79338	3	0.597795	2.95529
ERROR	9.94291	1.26808	8.65747	43	0.12754	0.16173	8.49575	42	0.202280	
TRT 1	4.45478	1.99402	5.96435	22	0.44761	0.89255	5.07180	21		
TRT 2	1.41469	0.40563	0.99375	7	0.42810	0.25927	0.73448	6		
TRT 3	2.76969	-0.88444	0.85719	7	-0.32077	0.28499	0.57220	6		
TRT 4	1.30375	-0.44312	0.84219	7	-0.33988	0.15061	0.69158	6		
TOTAL	10.99245	2.66101	10.93330	46	0.24208	0.64417	10.28913			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	3.1109	1.9739	1.9851
TRT 2	3.5187	2.5625	2.5217
TRT 3	3.1187	2.2062	2.2165
TRT 4	3.2125	2.3062	2.3045

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 1.056 WITH 2 AND 42 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 6.754 WITH 1 AND 42 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 2.940 WITH 6 AND 39 DF

TEST FOR EQUAL BETAS — F IS 2.6215 WITH 3 AND 39 DF

TEST BETA BAR IS ZERO — F IS 0.8921 WITH 1 AND 39 DF

OVERALL X MEAN 3.1969

OVERALL Y MEAN 2.1702

DISREGARDING COVARIATE, F IS 3.7679

COVARIATE = 0 MIN

OBSERVATION = 150 MIN

AHP2-REG-004-0044856

NASAL EXPIRATORY RESISTANCE - 180 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	2.42297	6.21693	3			5.67111	3	1.890369	9.69942
ERROR	10.08802	0.03667	8.38927	44	0.00363	0.00013	8.38914	43	0.195096	
TRT 1	4.59990	1.03229	0.05458	23	0.22442	0.23166	5.82292	22		
TRT 2	1.41469	-0.20437	1.56375	7	-0.14447	0.02953	1.55422	6		
TRT 3	2.10687	-0.30312	0.35375	7	-0.10944	0.03318	0.32057	6		
TRT 4	1.30375	-0.48812	0.41719	7	-0.37440	0.18279	0.23443	6		
TOTAL	11.08120	2.45964	14.60620	47	0.22196	0.54599	14.06025			

MEANS TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	2.2042	2.2045
TRT 2	3.5187	3.2125	3.2114
TRT 3	3.1187	2.3875	2.3878
TRT 4	3.2125	2.5562	2.5562

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION: F IS 0.784 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG: F IS 27.501 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION: F IS 5.180 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS: F IS 0.8038 WITH 3 AND 40 DF

TEST BETA HAS IS ZERO: F IS 0.0007 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 2.4615

DISREGARDING COVARIATE, F IS 10.86AA

COVARIATE = 0 MIN

OBSERVATION = 180 MIN

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AHP2-REG-004-0044857

AHP2-REG-004-0044858

NASAL EXPIRATORY RESISTANCE - 210 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	0.99557	2.23401	3			1.80369	3	0.601231	2.692266
ERROR	10.08802	2.11906	10.08219	44	0.21006	0.44512	9.63706	43	0.224118	
TRT 1	4.59990	0.33906	5.42656	23	0.07371	0.02499	5.40157	22		
TRT 2	1.41469	0.88156	1.10719	7	0.62315	0.54935	0.55784	6		
TRT 3	2.76969	1.12719	2.15969	7	0.40697	0.45873	1.70095	6		
TRT 4	1.30375	-0.22815	1.38875	1	-0.17546	0.04014	1.34861	6		
TOTAL	11.08120	3.11464	12.31620	47	0.28107	0.87544	11.44076			

MEANS TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	2.5437	2.5602
TRT 2	3.5187	3.0562	2.9904
TRT 3	3.1187	2.9687	2.9869
TRT 4	3.2125	2.6125	2.6110

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION F IS 2.758 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG F IS 2.533 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION F IS 1.800 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS F IS 0.9296 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO F IS 1.9764 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 2.7115

DISREGARDING COVARIATE, F IS 3.2498

COVARIATE = 0 MIN

OBSERVATION = 210 MIN

NASAL EXPIRATORY RESISTANCE - 240 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	1.30609	2.09734	3			1.44871	3	0.489571	2.01437
ERROR	10.08802	2.19531	10.92844	44	0.21762	0.47773	10.45070	43	0.243040	
TRT 1	4.59990	1.12438	7.71125	23	0.24443	0.27484	7.43641	22		
TRT 2	1.41469	0.09594	0.80219	7	0.06782	0.00651	0.79568	6		
TRT 3	2.76969	0.47750	1.16500	7	0.17240	0.08232	1.08268	6		
TRT 4	1.30375	0.49750	1.25000	7	0.38159	0.18984	1.06016	6		
TOTAL	11.08120	3.50141	13.02578	47	0.31598	1.10636	11.91942			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	2.7625	2.7795
TRT 2	3.5187	3.3437	3.2755
TRT 3	3.1187	3.0000	3.0188
TRT 4	3.2125	2.9750	2.9734

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 0.781 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 4.481 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 0.992 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS — F IS 0.0974 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO — F IS 1.8419 WITH 1 AND 40 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 2.9344

DISREGARDING COVARIATE, F IS 2.8148

COVARIATE = 0 MIN

OBSERVATION = 240 MIN

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AHP2-REG-004-0044859

NASAL EXPIRATORY RESISTANCE - 270 Minutes

ANALYSIS OF COVARIANCE, ONE-WAY

SOURCE	SSX	SSXY	SSY	DF	SLOPE	REG SS	RES SS	DF	MS	F
TRTS	0.99318	0.83464	0.93026	3			0.57930	3	0.193101	0.89803
ERROR	10.08802	2.19719	9.72469	44	0.21780	0.47855	9.24614	43	0.215026	
TRT 1	4.59990	1.81375	6.55500	23	0.39430	0.71517	5.83983	22		
TRT 2	1.41469	0.43656	1.89219	7	0.30859	0.13472	1.75747	6		
TRT 3	2.76969	-0.03937	0.38875	7	-0.01422	0.00056	0.38819	6		
TRT 4	1.30375	-0.01375	0.88875	7	-0.01055	0.00015	0.88860	6		
TOTAL	11.08120	3.03182	10.65495	47	0.27360	0.82951	9.82544			

MEANS

TREATMENT	X	Y	Y ADJ
TRT 1	3.1271	1.9750	1.9920
TRT 2	3.5187	2.3562	2.2880
TRT 3	3.1187	2.1625	2.1613
TRT 4	3.2125	2.1125	2.1109

TEST FOR LINEARITY OF BETWEEN CLASS REGRESSION — F IS 0.532 WITH 2 AND 43 DF

TEST BETWEEN TRT REG EQUALS WITHIN TRT REG — F IS 1.630 WITH 1 AND 43 DF

TEST LINEARITY OF OVERALL REGRESSION — F IS 0.715 WITH 6 AND 40 DF

TEST FOR EQUAL BETAS — F IS 0.5590 WITH 3 AND 40 DF

TEST BETA BAR IS ZERO — F IS 2.1571 WITH 1 AND 46 DF

OVERALL X MEAN 3.2052

OVERALL Y MEAN 2.0927

DISREGARDING COVARIATE, F IS 1.4030

COVARIATE = 0 MIN

OBSERVATION = 270 MIN

AHP2-REG-004-0044860

A4.4 Analyses of Variance - Nasal Mucosal Characteristics

AHP2-REG-004-0044861

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 30 MIN.

	SS	DF	MS	F
TREATMENT	0.39583	3	0.13194	2.55657
ERROR	2.27083	44	0.05161	
TOTAL	2.66667	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.22718

AHP2-REG-004-044862

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS = 60 MIN.

	SS	DF	MS	F
TREATMENT	0.61935	3	0.20645	4.44940
ERROR	2.04157	44	0.04640	
TOTAL	2.66091	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.21540

AHP2-REG-004-0044863

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 90 MIN.

	SS	DF	MS	F
TREATMENT	0.83069	3	0.27690	5.01418
ERROR	2.42981	44	0.05522	
TOTAL	3.26050	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23500

AHP2-REG-004-0044864

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 120 MIN.

	SS	DF	MS	F
TREATMENT	0.68473	3	0.22824	3.58379
ERROR	2.80227	44	0.06369	
TOTAL	3.48701	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.25236

AHP2-REG-004-0044865

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 150 MIN.

	SS	DF	MS	F
TREATMENT	1.01848	3	0.33949	6.21379
ERROR	2.34932	43	0.05464	
TOTAL	3.36780	46		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23374

AHP2-REG-004-0044866

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 180 MIN.

	SS	DF	MS	F
TREATMENT	0.94787	3	0.31596	5.69326
ERROR	2.44186	44	0.05550	
TOTAL	3.38973	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23558

AHP2-REG-004-0044867

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 210 MIN.

	SS	DF	MS	F
TREATMENT	1.35839	3	0.45280	11.45093
ERROR	1.73986	44	0.03954	
TOTAL	3.09825	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.19885

AHP2-REG-004-0044868

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 240 MIN.

	SS	DF	MS	F
TREATMENT	0.86753	3	0.28918	7.03316
ERROR	1.80911	44	0.04112	
TOTAL	2.67663	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.20277

AHP2-REG-004-0044869

ANALYSIS OF VARIANCE
NASAL SEROUS SECRETIONS - 270 MIN.

	SS	DF	MS	F
TREATMENT	0.95197	3	0.31732	5.99341
ERROR	2.32959	44	0.05295	
TOTAL	3.28156	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23010

AHP2-REG-004-0044870

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 30 MIN.

	SS	DF	MS	F
TREATMENT	0.26773	3	0.08924	1.84986
ERROR	2.12274	44	0.04824	
TOTAL	2.39047	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.21965

AHP2-REG-004-0044871

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 60 MIN.

	SS	DF	MS	F
TREATMENT	0.45273	3	0.15091	2.60916
ERROR	2.54489	44	0.05784	
TOTAL	2.99762	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.24050

AHP2-REG-004-0044872

AHP2-REG-004-0044873

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 90 MIN.

	SS	DF	MS	F
TREATMENT	0.63584	3	0.21195	3.98581
ERROR	2.33973	44	0.05318	
TOTAL	2.97557	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23060

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 120 MIN.

	SS	DF	MS	F
TREATMENT	0.49019	3	0.16340	2.55367
ERROR	2.81535	44	0.06399	
TOTAL	3.30555	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.25295

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ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 150 MIN.

	SS	DF	MS	F
TREATMENT	0.47311	3	0.15770	2.33221
ERROR	2.90766	43	0.06762	
TOTAL	3.38078	46		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.26004

AHP2-REG-004-0044875

AHP2-REG-004-0044876

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 180 MIN.

	SS	DF	MS	F
TREATMENT	0.83125	3	0.27708	5.20267
ERROR	2.34336	44	0.05326	
TOTAL	3.17461	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23078

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 210 MIN.

	SS	DF	MS	F
TREATMENT	0.51032	3	0.17011	2.81823
ERROR	2.65581	44	0.06036	
TOTAL	3.16613	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.24568

AHP2-REG-004-0044877

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 240 MIN.

	SS	DF	MS	F
TREATMENT	0.49409	3	0.16470	3.06373
ERROR	2.36531	44	0.05376	
TOTAL	2.85940	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23186

AHP2-REG-004-0044878

ANALYSIS OF VARIANCE
NASAL MUCOSAL CONGESTION - 270 MIN.

	SS	DF	MS	F
TREATMENT	0.36599	3	0.12200	2.10080
ERROR	2.55518	44	0.05807	
TOTAL	2.92118	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.24098

AHP2-REG-004-0044879

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 30 MIN.

	SS	DF	MS	F
TREATMENT	0.28551	3	0.09517	1.57054
ERROR	2.66624	44	0.06060	
TOTAL	2.95175	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.24616

AHP2-REG-004-0044880

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 60 MIN.

	SS	DF	MS	F
TREATMENT	0.08483	3	0.02828	0.60221
ERROR	2.06608	44	0.04696	
TOTAL	2.15091	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.21669

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AHP2-REG-004-0044882

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 90 MIN.

	SS	DF	MS	F
TREATMENT	0.22104	3	0.07368	1.48881
ERROR	2.17757	44	0.04949	
TOTAL	2.39861	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.22246

AHP2-REG-004-0044883

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 120 MIN.

	SS	DF	MS	F
TREATMENT	0.67829	3	0.22610	4.56776
ERROR	2.17793	44	0.04950	
TOTAL	2.85622	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.22248

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 150 MIN.

	SS	DF	MS	F
TREATMENT	0.65385	3	0.21795	3.82387
ERROR	2.45087	43	0.05700	
TOTAL	3.10472	46		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23874

AHP2-REG-004-0044884

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 180 MIN.

	SS	DF	MS	F
TREATMENT	0.60254	3	0.20085	3.54829
ERROR	2.49058	44	0.05660	
TOTAL	3.09313	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23792

AHP2-REG-004-0044885

AHP2-REG-004-0044886

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 210 MIN.

	SS	DF	MS	F
TREATMENT	0.65672	3	0.21891	3.83674
ERROR	2.51044	44	0.05706	
TOTAL	3.16716	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23886

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 240 MIN.

	SS	DF	MS	F
TREATMENT	0.40593	3	0.13531	2.35020
ERROR	2.53328	44	0.05757	
TOTAL	2.93921	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23995

AHP2-REG-004-0044887

ANALYSIS OF VARIANCE
NASAL MUCOSAL HYPEREMIA - 270 MIN.

	SS	DF	MS	F
TREATMENT	0.24914	3	0.08305	1.35886
ERROR	2.68908	44	0.06112	
TOTAL	2.93822	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.24722

AHP2-REG-004-0044888

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 30 MIN.

	SS	DF	MS	F
TREATMENT	0.22060	3	0.07353	1.30637
ERROR	2.47665	44	0.05629	
TOTAL	2.69725	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23725

AHP2-REG-004-0044889

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 60 MIN.

	SS	DF	MS	F
TREATMENT	0.15823	3	0.05274	0.82464
ERROR	2.81427	44	0.06396	
TOTAL	2.97250	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.25290

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ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 90 MIN.

	SS	DF	MS	F
TREATMENT	0.74109	3	0.24703	4.07010
ERROR	2.67052	44	0.06069	
TOTAL	3.41160	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.24636

AHP2-REG-004-0044891

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 120 MIN.

	SS	DF	MS	F
TREATMENT	0.55746	3	0.18582	2.85238
ERROR	2.86639	44	0.06515	
TOTAL	3.42385	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.25524

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AHP2-REG-004-0044893

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 150 MIN.

	SS	DF	MS	F
TREATMENT	0.93837	3	0.31279	5.60259
ERROR	2.40066	43	0.05583	
TOTAL	3.33903	46		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23628

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 180 MIN.

	SS	DF	MS	F
TREATMENT	1.15595	3	0.38532	7.15558
ERROR	2.36934	44	0.05385	
TOTAL	3.52530	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.23205

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ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 210 MIN.

	SS	DF	MS	F
TREATMENT	1.55733	3	0.51911	12.98081
ERROR	1.75959	44	0.03999	
TOTAL	3.31692	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.19998

AHP2-REG-004-0044895

ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 240 MIN.

	SS	DF	MS	F
TREATMENT	0.49496	3	0.16499	3.22141
ERROR	2.25347	44	0.05122	
TOTAL	2.74843	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.22631

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ANALYSIS OF VARIANCE
EASE OF NASAL BREATHING - 270 MIN.

	SS	DF	MS	F
TREATMENT	0.85791	3	0.28597	4.95970
ERROR	2.53699	44	0.05766	
TOTAL	3.39490	47		

SQUARE ROOT OF ERROR MEAN SQUARE = 0.24012

AHP2-REG-004-0044897

A4.5 Reference on Respiron Methodology

Cohen, Burton M., "Nasal Airway Resistance and the Effects of Bronchodilator Drugs in Expiratory Airflow Disorders." *Respiration* 26:35-46, 1969.

AHP2-REG-004-0044898

Respiration
Editor: H. HERZOG, Basel
S. KARGER - BASEL/NEW YORK (Printed in Switzerland)
SEPARATUM

Respiration 26: 35–46 (1969)

Nasal Airway Resistance and the Effects of Bronchodilator Drugs in Expiratory Airflow Disorders[1]

BURTON M. COHEN[2]

Analysis of pressure, volume and flow characteristics has supplanted conventional spirometry for critical estimation of lower airway resistance and responsiveness [1–6] and determination of the locus of drug action [6] in critical trials. Parallel observations have defined the significant contribution of the upper airways, principally the nasal component, to total respiratory work and resistance [7–15], implying that the relationship between upper and lower airways dynamics and the effects of therapy is not simple [16–19]. Because these measurements have been made principally in normal, often trained, individuals, it seemed pertinent to determine respiratory partitioning in patients with expiratory airflow disorders and the possible influence of drugs directed at various sites on the resistance compartments.

Materials and Methods

Twenty-five normal adults were matched to 25 patients with chronic bronchitis or diffuse obstructive pulmonary emphysema [20] who were free of known nasal disease or anatomic obstruction. All of the latter had demonstrated the presence of a partial, potentially reversible physiologic defect on prior isoproterenol aerosol testing [21]. None had received steroids, xanthine derivatives or sympathomimetic agents for at least two weeks prior to study.

[1] Presented at the Fifth Annual Meeting, The American College of Clinical Pharmacology and Chemotherapy, Atlantic City, N.J., May 2–4, 1968.
[2] Attending Physician, Elizabeth General Hospital; Associate Clinical Professor of Medicine, The New Jersey College of Medicine.

Received: June 5, 1968.

AHP2-REG-004-0044899

The body volume plethysmograph used was a modification of Mead's adaptation [22] of the design of DuBois, Cohen, and associates [23]. The volume-flow and pressure-volume oscilloscopic loops inscribed were read directly with the calibrated disc attachment for the tube face described by BERGER [23] and were photographed. Nasal resistance (R_n) was calculated from these plots as the difference between the values recorded during nasal ($R_n + R_o$) and oral (R_o) breathing. Nasal resistance was also determined with the subjects outside the chamber by posterior electronic rhinometry (fig. 1). A clinical pneumotachograph[1] was inserted in the outlet of a B-L-B rebreathing pressure mask; the pressure drop across the wire mesh screen was measured with a bidirectional gas pressure transducer[2] which generated the flow signal. Two polyethylene tubes were sealed into separate perforations made in the body of the mask, so that one ended just inside the mask, while the other was positioned to pass between the closed lips of the subject to lie on the tongue, its open end sensing pressure changes in the posterior buccal cavity and in the oral pharynx. These tubes were connected to a physiologic pressure transducer[3] which generated a signal proportionate to the pressure difference between the oral pharynx and the point in the mask external to the nose but before the low resistance pneumotachograph. The flow and pressure signals were amplified[5] and displayed on the precalibrated axes of the oscilloscope and were photographed. Flow was displayed on the vertical axis and pressure on the horizontal axis, so that expiration occupied the right upper quadrant and inspiration the left lower quadrant (fig. 2). Increased flow resistance rotated the expiratory curve clockwise, whereas a decreased resistance induced a counter-clockwise displacement. Inspiratory and expiratory resistance were read at the reference flow rate of 0.5 l/sec.

Following calculation of resistance compartments for the 50 subjects, 10 patients with obstructive lung disease entered a double-blind, crossover protocol including isoproterenol aerosolized from a metered hand device[7], phenylephrine nasal drops[8] and their matched placebos, in four combinations for each subject (isoproterenol aerosol + placebo drops; isoproterenol aerosol + phenylephrine drops; placebo aerosol + phenylephrine drops and placebo aerosol + placebo drops). On each of four consecutive days, after three determinations each of R_n and R_o with the plethysmograph and three recordings of R_n rhinometrically, two inhalations of the aerosol were given and two drops of the nasal solution instilled in each nostril according to a randomized code; the tests were repeated in like order 5, 15, 30, 60 and 90 min after medication.

[1] Fleisch No. 3 Pneumotachograph, Instrumentation Associates, New York, N. Y.

[2] No. 270B Bidirectional Gas Pressure Transducer, Hewlett-Packard Medical Division, Waltham, Mass.

[3] ~~No. 268B Physiologic Differential Pressure Transducer, Hewlett-Packard.~~

[5] No. 760-3000 Carrier Pre-Amplifiers, Hewlett-Packard.

[7] Isoproterenol was given as Iso-Medihaler®, Riker Laboratories, Northridge, California. Each cc. of this dry micronized suspension contains 2.0 mg. of isoproterenol sulfate; 0.075 mg. of drug is delivered at each valve depression.

[8] Phenylephrine was given as Neo-Synephrine Hydrochloride Plain (intranasal) 0.25 % Solution®, Winthrop Laboratories, New York, N. Y.

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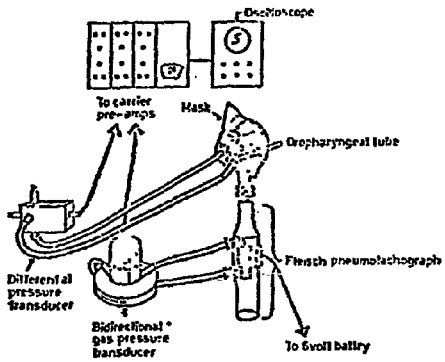

Fig. 1. Apparatus for measuring nasal air flow resistance by posterior rhinometry.

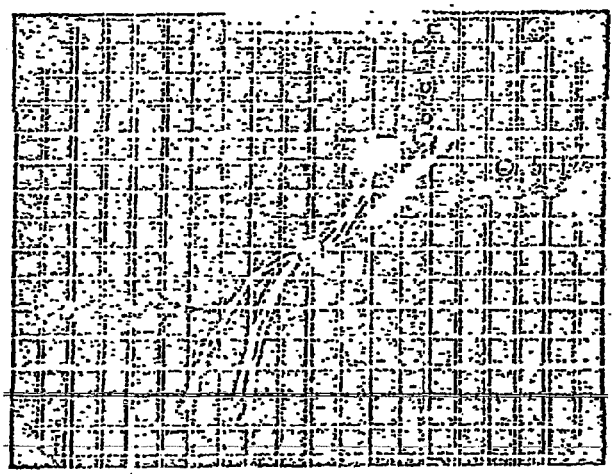

Fig. 2. Oscilloscope camera photograph demonstrating pressure-flow curves for both nasal passages and for each nasal passage, determined separately, in one normal subject.

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Table I. Respiratory flow partitioning in normal subjects and patients with expiratory airflow disorders

Subjects	Flow Resistances (cm H2O/l/sec		
	Lower Airways (R_L)	Nasal Airways (R_N)	Total Airways ($R_L + R_N$)
Normals (25)	1.49±0.14	2.47±0.41	3.96±0.
Expiratory Airflow Obstruction (25)	3.06±0.91	3.99±0.72	7.05±0.64
Intergroup Differences			
t	2.75	2.23	2.46
P	0.01–0.005	0.05–0.025	0.02–0.01
Significance at 0.05 level	Sig.	Sig.	Sig.

Results

A. Comparison of normal subjects and patients. Table I presents the values for resistances in the 25 patients with obstructive lung disorders and the 25 matched normal subjects. Mean values for lower airway, nasal and total resistances were 1.49, 2.47 and 3.96 cm H20/l/sec for the normal individuals, and 3.06, 3.99 and 7.05 cm H20/l/sec for the 25 patients, respectively. The differences between the three flow resistance indices were significant at the 0.05 level or better in distinguishing the two groups. Values for R_N obtained rhinometrically were in good general agreement with those calculated by plethysmographic subtraction. Mean R_N accounted for 56.5% of total airways resistance for patients with breathing handicaps, and 62.3% of the total for normal subjects during nasal breathing.

B. Behaviour of resistance indices in the clinical drug trial. Drug combinations including phenylephrine drops led to falls in mean R_N, while isoproterenol aerosol + placebo nose drops and the combination of two placebos did not alter this index (fig. 3). Mean R_N fell after isoproterenol aerosol + phenylephrine drops, isoproterenol aerosol + placebo drops and placebo aerosol + phenylephrine drops, in descending order of effectiveness, with a slight rise following the combined placebo (fig. 4). The greatest decline in total resistance ($[R_L + R_N]$) occurred with the two

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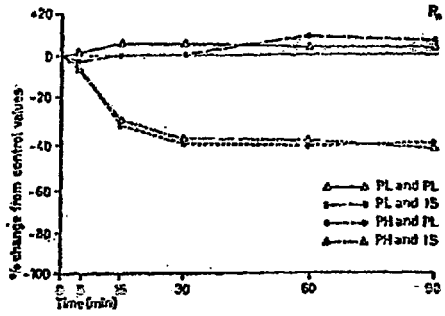

Fig. 3. Behaviour of mean nasal resistance (R_s) following the use of four nasal drops – aerosol combinations by 10 patients with obstructive ventilatory disease. (PL & PL represents placebo nose drops and placebo aerosol; PL & IS represents placebo nose drops and isoproterenol aerosol; PH & PL represents phenylephrine nose drops and placebo aerosol; PH & IS represents phenylephrine nose drops and isoproterenol aerosol).

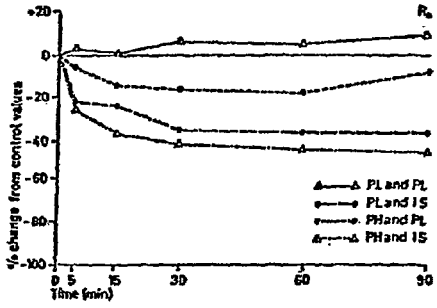

Fig. 4. Behaviour of mean lower airways resistance (R_L) following the use of four nasal-drops-aerosol combinations by 10 patients with obstructive ventilatory disease. The caption is described in the legend of figure 3.

active medications, placebo aerosol + phenylephrine drops was intermediate, and isoproterenol aerosol + placebo drops followed in effectiveness (fig. 5). Table II lists the ranking for each of the respiratory resist-

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Combined Nasal Airway Resistance and the Effects

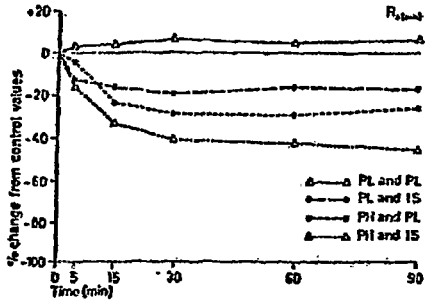

Fig. 5. Behaviour of total airways resistance ($R_a + R_e$) following the use of four nasal drops-aerosol combinations by 10 patients with obstructive ventilatory disease. The caption is described in the legend of figure 3.

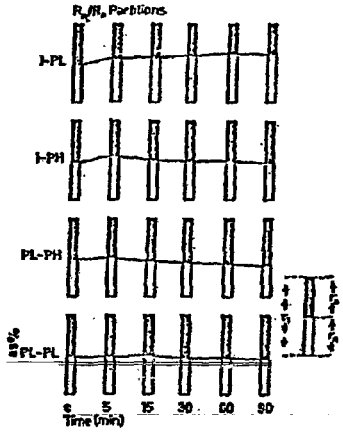

Fig. 6. Changes in R_a/R_e partitioning for 10 patients with chronic obstructive lung disease, presented as per cents of total airways resistance, following the use of four nasal drops-aerosol combinations. The drug schedules are captioned as in the legends of figures 3, 4 and 5.

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Table II. Relative ranking of aerosol-nasal drop combinations for airways resistance effects

Airways Resistance	Relative Ranking of Combinations[1]
Lower airways	Ph. + I. > Pl. + I. > Ph. + Pl. > Pl. + Pl.
Nasal airways	Ph. + Pl. = Ph. + I. > Pl. + I. = Pl. + Pl.
Total	Ph. + I. > Ph. + Pl. > Pl. + I. > Pl. + Pl.

[1] Ph. + I. = Phenylephrine drops and isoproterenol aerosol.
Pl. + I. = Placebo drops and isoproterenol aerosol.
Ph. + Pl. = Phenylephrine drops and aerosol placebo.
Pl. + Pl. = Placebo drops and aerosol placebo.

ances of the four combinations, which were significant at the 0.05 level or beter for the differences observed. Figure 6 presents the response to the various therapies as changes in the $\frac{R_n}{(R_n+R_o)}$ partitioning. Table III summarizes the mean values and standard deviations for the resistance indices, their per cent changes from control and their statistical significance at the 0.01 level, using Oldham's method [24] for t-test interpretation of repeated measurements made on the same subjects.

Discussion

Although the relationships of the respiratory functions of the nasal passages and the lower airway hinted at in antiquity were explored during the last century, it has only been within the past decade that acceptable methods have become available for critical assessment [25]. Electronic presentation of nasal ventilation now offers a practical, highly sensitive and reproducible approach to clinical drug studies yielding serial observations free of subjective bias or patient inconvenience. Because the nasal pressure-flow curve is essentially non-linear, protocols relating inspiratory and expiratory pressures to a uniform, specified rate of flow appear to be the most valid reflections of these changes [12,26–27]. At the lower flow rates during the initial inscription of the curves, when linearity is approached, resistance changes provide sensitive and objective measures of nasal patency and the impact of allergic, infectious and other influences, as well as therapy [26–29].

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Table III
Airways resistance behaviour of 10 patients with obstructive ventilatory

Medication and Indices	Mean Respiratory Resistances							
	Control			5 min			15 min	
	R_t	R_n	R_o	R_t	R_o	R_n	R_t	R_n
Isoproterenol aerosol and placebo drops								
mean	8.25	3.85	4.40	7.23	3.82	3.41	6.94	3.85
S.D.	1.04	0.76	0.93	1.07	0.79	0.66	0.98	0.82
% change	–	–	–	–12.3	–0.7	–22.5	–15.8	0
significance[1]				S	NS	S	S	NS
Isoproterenol aerosol and phenylephrine drops								
mean	8.36	3.92	4.44	7.06	3.72	3.34	5.54	2.75
S.D.	1.02	0.87	0.79	0.97	0.86	0.75	0.93	0.68
% change	–	–	–	–15.5	–5.1	–25.0	–33.7	–29.8
significance[1]				S	NS	S	S	S
Placebo aerosol and phenylephrine drops								
mean	8.41	4.05	4.36	8.03	3.89	4.14	6.50	2.78
S.D.	0.74	0.45	0.78	0.91	0.50	0.73	0.81	0.18
% change	–	–	–	–4.5	–3.9	–5.0	–22.7	–31.3
significance[1]				NS	NS	NS	S	S
Placebo aerosol and placebo drops								
mean	8.52	4.00	4.52	8.71	4.04	4.67	8.80	4.23
S.D.	1.00	0.54	0.84	1.01	0.32	0.94	0.96	0.27
% change	–	–	–	2.2	0.1	3.0	3.2	5.7
significance[1]				NS	NS	NS	NS	NS

[1] Significant at the 0.01 level or better, calculated by the method of Oldham for analysis of non-independent samples.

The physiology of the upper airway and the importance of nasal airflow and nasal respiratory reflexes in total ventilation have been authoritatively reviewed [30]. Nasal stenosis may be compensated for by an unusually powerful pulmonary action, but mouth breathing may occur, even with a normal nasal passage, if lung function is reduced by respiratory or

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diseases following treatment with combinations of aerosols and nasal drops

[cm H_2O/l/sec][a]

	30 min			60 min			90 min		
R_a	R_t	R_n	R_a	R_t	R_n	R_a	R_t	R_n	R_n
3.09	6.67	3.85	2.82	6.91	4.18	2.73	6.81	4.09	2.72
0.61	1.07	0.84	0.53	1.06	1.18	0.48	1.05	0.91	0.47
−29.7	−19.1	0	−35.9	−16.2	8.5	−37.9	−17.4	6.2	−38.1
S	S	NS	S	S	NS	S	S	NS	S
2.79	4.96	2.42	2.54	4.82	2.40	2.42	4.55	2.22	2.33
0.38	0.94	0.53	0.36	1.01	0.40	0.30	0.85	0.44	0.22
−37.1	−40.6	−38.2	−32.7	−42.3	−38.7	−45.4	−45.5	−43.3	−47.5
S	S	S	S	S	S	S	S	S	S
3.72	6.05	2.50	3.55	5.93	2.40	3.53	6.26	2.30	3.96
0.75	0.65	0.54	0.73	0.81	0.48	0.68	0.79	0.81	0.64
−14.7	−28.0	−38.2	−16.2	−29.4	−40.7	−19.0	−25.5	−43.2	−9.1
S	S	S	S	S	S	S	S	S	NS
4.57	9.01	4.20	4.81	8.88	4.14	4.74	9.04	4.13	4.91
0.73	1.02	0.36	0.79	1.17	0.33	0.72	0.91	0.39	0.73
0.1	5.7	5.0	6.4	4.2	3.5	4.8	6.1	3.2	8.6
NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

[a] R_t represents the sum of the resistance for the lower airways and the nasal airways;
R_n represents the resistance of the nasal airways;
R_a represents the resistance of the lower airways.

cardiac disease [7, 18, 19, 31]. Ogura describes the high nasal resistance of nasal obstruction as responsible for reductions in spirographic indices and compliance, increases in pulmonary resistance measured through the nose or mouth and in ventilatory work, variables significantly bettered by successful medical or surgical treatment [18, 19]. The lack of correlation

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between the degree of nasal obstruction relieved and the magnitude of improved lung function suggested that the stimulus response was mediated through a reflex arc [19]. Alveolar hypoventilation, hypoxia and hypercapnia have been incriminated in the genesis of pulmonary hypertension and cor pulmonale from obstructive lesions of the nasal passages [32].

Unlike our subjects, Ogura's five individuals with acute or chronic bronchopulmonary disorders had abnormal noses. In the only evaluation of subjects comparable to our own, NOLTE and ULMER reported an average R_n of 4.72 cm $H_2O/l/sec$ for 29 patients with 'chronic obstructive bronchitis', and an average of 3.74 cm $H_2O/l/sec$ for 43 persons with healthy lungs, data not dissimilar from the present estimates [13]. Our experience reinforces the data of NOLTE and ULMER in suggesting that nasal airflow resistance is frequently elevated in the presence of chronic obstructive lung disorders, making an important contribution to the total breathing handicap of these patients; although absolute values for R_n and R_a rise, respiratory resistance partitioning resembles that of subjects without upper or lower airways diseases. Although the absence of significant distant effects from systemic absorption from the medication instilled in the nasal passages cannot be excluded without definitive pharmacologic support[a] [33], analysis of the clinical drug trial suggests that this local therapy of the nasal airways was responsible for reduction in R_n, as well as R_a, and that the combination of such medication with an aerosol of isoproterenol, a sympathomimetic amine bronchodilator, was superior in its effects on these indices and total respiratory resistance, than either drug alone. Description of changes in nasal flow and lower respiratory tract resistances may be more informative and precise than reliance upon the latter only in judging the efficacy and site of action of drugs directed to the relief of airway obstruction.

Summary

Nasal resistance was calculated with the whole-body, volume displacement plethysmograph, and by electronic posterior rhinometry, for 25 patients with chronic bronchitis or pulmonary emphysema and 25 matched normal subjects. Ten patients entered a double-blind crossover protocol

[a] '...studies of either its absorption or fate have failed to come to my attention [Beckman, 33].

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in which isoproterenol aerosol, phenylephrine nasal drops and their respective placebos were given in four therapeutic combinations.

Mean values for lower airways, nasal airways and total resistances were significantly higher for the patient group, although respiratory partitioning was unchanged. Therapy directed to the nasal passages alone had helpful effects in lowering the abnormal lower and nasal airway resistances. Nasal respiratory dynamics can not be disregarded in the consideration of breathing handicaps nor in the therapy of airways disorders.

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APPENDIX A6. SAFETY FINDINGS

A6.1 Listings of Clinical Safety Findings

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Table A6.1-01

MEASUREMENTS OF PULSE RATES

1 7 TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE									
	0	30	60	90	120	150	180	210	240	270
1	60	64	72	64	60	64	72	64	68	64
3	60	64	56	60	64	72	60	56	60	64
5	76	80	76	80	72	76	72	80	72	80
8	76	72	80	72	64	60	64	68	72	68
9	96	90	84	88	76	76	76	72	76	68
11	72	76	68	72	64	68	72	64	68	72
12	64	60	56	64	72	76	68	72	68	64
14	68	64	72	64	68	72	76	66	56	64
16	72	76	72	68	72	68	64	72	64	64
21	80	76	84	72	76	72	76	80	72	68
23	84	80	76	76	72	76	80	76	80	80
24	60	64	60	72	60	60	56	64	60	60
25	80	84	80	76	88	80	72	84	80	76
26	68	60	60	56	64	60	60	64	60	60
28	88	84	80	76	84	72	84	80	88	76
32	80	80	80	72	80	76	72	76	80	72
34	76	80	64	64	64		72	64	60	72
35	92	88	76	80	88	76	80	84	88	92
38	88	92	84	80	84	76	80	72	76	72
39	64	68	60	64	60	56	64	60	72	68
41	76	80	72	76	72	76	72	80	72	72
43	88	84	80	80	76	76	84	80	80	76
44	60	64	60	72	68	64	60	60	64	60
48	76	80	64	60	64	60	88	88	76	84
MEANS	75	75	72	71	71	70	72	72	71	71

* Pressure (cm H_2O) at 0.5 L/sec

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride

Continued

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Table A6.1-c (Cont'd.)

MEASUREMENTS OF PULSE RATES

2 7 TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
7	76	92	88	84	72	72	80	72	76	80
15	60	64	56	64	60	60	68	60	72	68
18	56	52	60	64	56	56	52	56	60	56
19	80	84	72	76	72	68	72	68	68	68
37	60	64	88	88	92	96	80	74	72	72
40	60	64	72	64	68	68	72	64	64	72
42	60	68	72	64	60	72	68	64	68	72
46	68	72	68	68	64	76	72	64	76	72
MEANS	65	70	72	72	68	71	71	66	70	70

3 7 TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
2	76	72	76	80	72	68	64	72	64	72
4	80	88	76	84	80	80	76	84	84	80
6	68	72	64	68	64	72	76	72	64	72
10	68	72	68	76	72	64	68	76	72	76
29	76	80	72	68	64	68	72	76	72	72
30	76	80	60	60	60	72	64	68	60	60
33	64	60	52	56	60	64	56	52	56	56
47	80	76	72	76	72	76	76	76	72	76
MEANS	73	75	68	71	68	70	68	71	68	71

4 7 TREATMENT GROUP Dimetane Elixir (8 mg brompheniramine maleate)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
13	72	76	72	68	68	64	72	72	68	64
17	80	76	84	80	76	72	72	68	72	72
20	60	56	64	60	60	60	56	56	60	64
22	72	76	68	68	64	60	56	64	60	56
27	76	80	72	76	80	76	72	76	72	80
31	72	76	80	72	76	72	72	76	80	68
36	76	80	76	80	84	72	72	80	84	84
45	60	64	68	60	60	60	56	60	56	56
MEANS	71	73	73	70	71	67	66	69	69	71

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Table AG.1-02

MEASUREMENTS OF BLOOD PRESSURES

TREATMENT GROUP: Dimetapp Elixir +

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
1	125/70	120/70	125/65	120/70	130/70	125/70	130/70	125/70	120/65	120/65
3	120/70	125/75	120/70	115/70	125/70	130/70	125/80	130/70	125/60	125/70
5	125/70	130/70	125/70	130/70	125/70	130/80	120/70	125/70	130/70	130/75
8	130/80	125/70	130/70	125/70	130/70	140/75	135/70	125/70	130/70	125/80
9	120/75	130/60	120/70	125/70	120/70	125/80	130/70	125/70	130/70	125/70
11	130/80	125/70	125/70	120/80	115/75	125/75	120/70	125/70	130/70	125/80
12	125/70	130/70	125/75	120/70	130/70	130/70	125/70	125/75	130/70	125/70
14	120/65	125/70	115/70	120/70	115/65	120/70	125/70	130/65	120/70	125/70
16	130/70	125/70	130/70	125/70	130/75	140/70	125/70	130/70	125/80	130/75
21	120/65	125/70	130/70	115/75	120/80	125/65	115/70	120/70	115/70	120/75
23	135/70	140/70	130/75	125/75	130/75	130/75	140/80	135/65	130/70	130/70
24	140/70	145/70	135/70	130/70	130/70	125/70	135/70	140/70	130/70	125/85
25	135/70	125/70	130/75	125/80	130/70	125/70	130/80	125/70	130/75	125/70
26	115/80	120/80	110/65	120/70	130/70	125/80	130/75	125/80	130/70	115/75
28	135/70	125/70	130/75	130/70	125/70	130/70	125/70	120/70	125/70	130/70
32	120/80	125/70	130/70	115/70	110/70	120/70	115/70	120/70	125/70	125/70
34	140/80	135/80	140/80	125/70	140/70		140/75	135/70	140/70	140/70
35	120/70	125/70	130/70	125/70	130/70	125/75	130/70	125/70	130/70	125/70
38	140/70	130/70	125/70	130/70	125/70	140/70	135/70	140/70	135/70	140/80
39	125/70	130/70	125/80	130/70	120/65	115/65	120/70	125/70	115/70	115/70
41	130/70	125/70	135/70	125/70	130/70	135/70	135/70	125/80	130/70	125/70
43	150/70	135/75	140/70	135/75	140/70	140/70	145/70	140/80	140/70	140/70
44	120/65	130/70	115/70	120/70	130/70	125/70	120/70	125/70	130/70	125/70
48	135/65	140/70	130/70	125/70	125/70	130/70	135/70	140/70	130/65	140/75
MEANS	129/71	129/71	127/71	124/71	126/71	128/72	129/72	128/71	128/70	128/74

+ 8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride

Continued

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Table no. (Cont'd.)

MEASUREMENTS OF BLOOD PRESSURES

2 A TREATMENT GROUP: Neosynephrine Elixir (10 mg phenylephrine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
7	125/70	130/65	125/65	120/70	130/65	125/80	120/80	120/80	125/80	120/80
15	130/65	135/70	140/70	125/70	130/70	135/60	125/65	130/70	125/70	130/75
18	130/70	115/70	120/75	115/75	120/70	130/70	115/70	120/70	120/70	120/70
19	130/70	125/70	130/70	125/80	130/75	125/70	130/65	125/70	130/70	125/70
37	115/70	120/70	135/80	140/80	135/70	125/70	130/75	115/70	120/70	115/75
40	130/75	125/75	130/70	125/80	120/70	125/80	130/70	120/70	125/80	130/70
42	120/70	115/70	125/80	120/80	130/70	120/70	115/65	120/75	115/80	120/70
46	125/80	130/70	135/70	140/70	135/70	120/70	125/80	130/70	125/70	130/70
MEANS	127/71	124/70	130/73	126/76	129/70	126/71	124/71	123/72	123/74	124/73

3 A TREATMENT GROUP: Propadrine Elixir (10 mg phenylpropanolamine hydrochloride)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
2	130/70	125/70	130/75	125/70	120/70	125/70	130/75	125/65	125/65	120/70
4	130/70	115/70	110/65	120/70	115/70	120/70	115/70	110/65	120/60	115/60
6	135/70	140/70	130/70	125/70	130/75	140/80	130/65	140/60	135/70	125/80
10	135/85	140/70	130/75	140/80	125/85	135/80	130/75	135/80	125/80	130/75
20	140/75	135/75	130/70	135/70	125/70	130/70	140/70	135/70	130/70	135/70
30	115/65	120/70	110/60	120/70	125/70	115/70	115/70	120/75	125/80	120/80
34	125/70	120/70	130/70	125/70	120/70	135/70	125/70	120/70	115/70	115/75
47	140/70	135/70	125/75	130/70	135/80	130/70	125/70	125/80	130/70	125/70
MEANS	129/72	129/71	124/70	128/71	124/74	129/74	126/71	126/71	126/72	123/73

4 A TREATMENT GROUP: Dimetane Elixir (8 mg brompheniramine maleate)

PAT. NO.	MINUTES AFTER DOSE 0	30	60	90	120	150	180	210	240	270
13	130/70	125/70	130/75	135/80	140/75	130/70	125/70	130/70	125/70	130/70
17	130/70	140/80	125/75	130/70	125/70	130/70	125/80	130/80	125/80	120/70
20	130/70	125/70	130/70	125/70	125/75	130/70	125/75	120/75	120/70	125/70
22	125/70	120/75	130/70	125/70	120/70	125/65	130/60	140/60	135/70	140/70
27	120/70	115/70	120/70	125/70	130/75	135/70	115/65	120/70	115/70	120/70
31	130/80	125/80	130/75	130/75	135/70	125/70	130/75	130/70	140/70	130/70
36	135/65	130/70	125/70	125/75	130/70	125/70	130/70	125/70	130/70	125/70
45	115/60	110/65	120/60	110/60	115/60	120/65	115/65	110/70	110/65	110/65
MEANS	127/69	124/73	126/71	126/71	128/71	128/69	124/70	126/71	125/71	125/69

4. STUDY PROTOCOL

4.1 PROTOCOL DESCRIPTION

4.1.1 Objective

To compare the effects of single doses of Dimetapp Elixir with each of its components on nasal airway resistance in patients with upper respiratory infections.

4.1.2 Study Design

This is a single investigator well controlled special study in which each of the patients with upper respiratory infections received a single dose of Dimetapp Elixir (24 patients) or one of its three components (8 patients/component) on a single test day; measurements of nasal airway resistance and subjective evaluations of nasal mucosa were made every 30 minutes after drug administration for 4.5 hours.

4.1.3 Patient Description

A. Selection Criteria

1. Treated Condition(s) and Diagnostic Criteria

   Nasal congestion due to upper respiratory infections whose duration was not less than 24 hours and not more than 72 hours at time of test day.

2. Prior Treatment Criteria

   48 hours off all drugs having the same general pharmacological actions as the study medication.

3. Safety Exclusion Criteria

   a. Chronic pulmonary disease

   ~~b. Allergic rhinitis~~

   c. Pregnancy

4. Miscellaneous Criteria

   a. Adults

   b. Males and females

   c. Outpatients (office)

   d. Willingness to participate in a one day study.

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B. The patients were numbered serially as they entered the study and were assigned to one of the study medications on the basis of a randomization schedule (see Appendix A4.3) prepared by the Biometry Unit, A. H. Robins Company.

4.1.4 Treatment Groups

A. Test Groups

1. Dimetapp Elixir containing 4 mg of brompheniramine maleate, 5 mg of phenylephrine hydrochloride, and 5 mg of phenylpropanolamine hydrochloride per 5 cc.

B. Control Groups

1. Dimetane Elixir containing 2 mg of brompheniramine maleate per 5 cc.

2. Neosynephrine Elixir containing 1 mg of phenylephrine hydrochloride per 1 cc.

3. Propadrine Elixir containing 4 mg of phenylpropanolamine hydrochloride per 1 cc.

C. Dosage Schedules

Using the Randomization Schedule in Appendix A4.3 each patient received single doses of test medication on the morning of the test day according to the following schedules:

Treatment Group 1: 10 cc of Dimetapp Elixir (8 mg brompheniramine maleate, 10 mg phenylephrine hydrochloride, 10 mg phenylpropanolamine hydrochloride).

Treatment Group 2: 20 cc of Dimetane Elixir (8 mg brompheniramine maleate).

Treatment Group 3: 10 cc of Neosynephrine Elixir (10 mg phenylephrine hydrochloride).

Treatment Group 4: 2.5 cc of Propadrine Elixir (10 mg phenylpropanolamine hydrochloride).

Since the test medications were not identical in appearance they were administered by a disinterested third party; hence, the investigator and the technician making the measurements and assessments were "blind" to the test medication received by each subject.

At four hours (240 minutes) after dosing, each patient received Afrin (oxymetazoline hydrochloride) nasal solution.

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C. Concomitant Treatments

1. Excluded

Nasal decongestants (oral and topical)

2. Included

Any medications and/or treatments needed for concurrent conditions were permitted but were to be recorded on data sheets.

4.1.5 Assessment of Special Findings

At "0 hour" and at 30, 60, 90, 120, 180, 240 and 270 minutes after test medication was administered, the following assessments were made:

A. Nasal Airway Resistance

Using the Respiron both nasal inspiratory and expiratory resistances were measured. The results were reported as pressure (cm H_2O) at 0.5 L/sec.

See Appendix A5.3 for the following reference on Respiron methodology.

Cohen, Burton M., "Nasal Airway Resistance and the Effects of Bronchodilator Drugs in Expiratory Airflow Disorders." *Respiration* 26:35-46, 1969.

B. Characteristics of Nasal Mucosa

Subjective evaluations were made of the following:

1. Nasal mucosal congestion

2. Nasal mucosal hyperemia

3. Nasal secretion

4. Ease of nasal breathing

Items 1-3 above were rated on a 5-point scale as follows:

0 = absent
1 = mild
2 = moderate
3 = severe
4 = very severe

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Item 4 above was rated on a 5-point scale as follows:

0 = normal
1 = only mildly impaired
2 = moderately impaired
3 = severely impaired
4 = total obstruction

[It should again be noted that Afrin (oxymetazoline hydrochloride) nasal solution was administered immediately after the above measurements were made at 240 minutes.]

4.1.6 Effectiveness Assessment: None

4.1.7 Safety Assessment

The investigator observed particularly for the following adverse effects: nervousness, headache, nausea, dizziness or light-headed, drowsiness, dry mouth, urticaria, palpitation, and blurred vision.

Blood pressures (right arm, sitting three minutes) and pulse rates (sitting three minutes) were measured pre-drug and post drug according to the following schedule:

"0 hour"	120 minutes
30 minutes	180 minutes
60 minutes	240 minutes
90 minutes	270 minutes

4.1.8 Data Management and Analysis

After initial medical screening by the Data Monitor (M.D.), primarily from a safety viewpoint, the data sheets were carefully monitored by a research physician in order to ascertain if they met the selection and treatment criteria of the protocol (see 4.1.3 and 4.1.4). Standard statistical methods were used to analyze the special ~~findings (see Section 5).~~

4.1.9 Summary of "Bias Minimization" Aspects

1. Assignment of patients to treatment groups by a pre-determined randomization schedules.

2. Drug administration of the differing test medications by a disinterested third party (i.e. the investigator and technician were "blind" to the medication each patient received).

3. Careful and independent medical auditing of the data sheets for "acceptability" (e.g. with respect to patient selection criteria, etc.) prior to biometric evaluation of the special findings.

AHP4-REG-310-0104267

4.2 PROTOCOL DEVIATIONS: None

4.3 INVESTIGATOR INFORMATION

One clinician supplied the data on the 48 patients participating in this study. The name and address of the investigator is shown in A4.4. Also included are the *curriculum vitae* of the investigator and pertinent information about the investigation.

AHP4-REG-310-0104268

INVESTIGATOR

Investigator:	Cohen, Burton Marcus, M.D.
Address:	230 W. Jersey Street Elizabeth, New Jersey 07202
Academic Affiliation:	Associate Clinical Professor of Medicine The New Jersey College of Medicine
Type of Practice:	Internal Medicine
Study Number:	0101
Date Initiated:	05/69
Study Status:	Complete
Status Date:	02/71
Patients Reported:	48

AHP4-REG-310-0104269

AHP4-REG-310-0104270

NASAL AIRWAY RESISTANCE-INSPIRATION: MEANS (a), RANKS AND DIFFERENCES

(Protocol C1-A-01)

TIMES (Min)	TREATMENT GROUP MEAN AND RANKS			
	10 mg Phenylephrine (8)+	10 mg Phenylpropanolamine (8)+	8 mg Brompheniramine (8)+	Combination (24)+
0	3.93	3.92	4.01	4.07
30	3.80 (3)	3.82 (4)	3.71 (1)	3.78 (2)
60	3.36 (2.5)	3.42 (4)	3.35 (2.5)	3.15 (1)
90	3.07 (3.5)	3.07 (3.5)	2.98 (2)	2.65 (1)
120	3.09 (4)	2.73 (2)	2.92 (3)	2.51 (1)
150	3.31 (4)	2.92 (3)	2.87 (2)	2.42 (1)
180	3.69 (4)	3.14 (3)	3.05 (2)	2.70 (1)
210	3.66 (4)	3.41 (3)	3.21 (2)	3.10 (1)
240	3.79 (4)	3.50 (3)	3.38 (1.5)	3.38 (1.5)
Overall Means (b)				
Resistance	3.471	3.251	3.186	2.967
Ranks	(3.6)	(3.2)	(2.0)	(1.2)

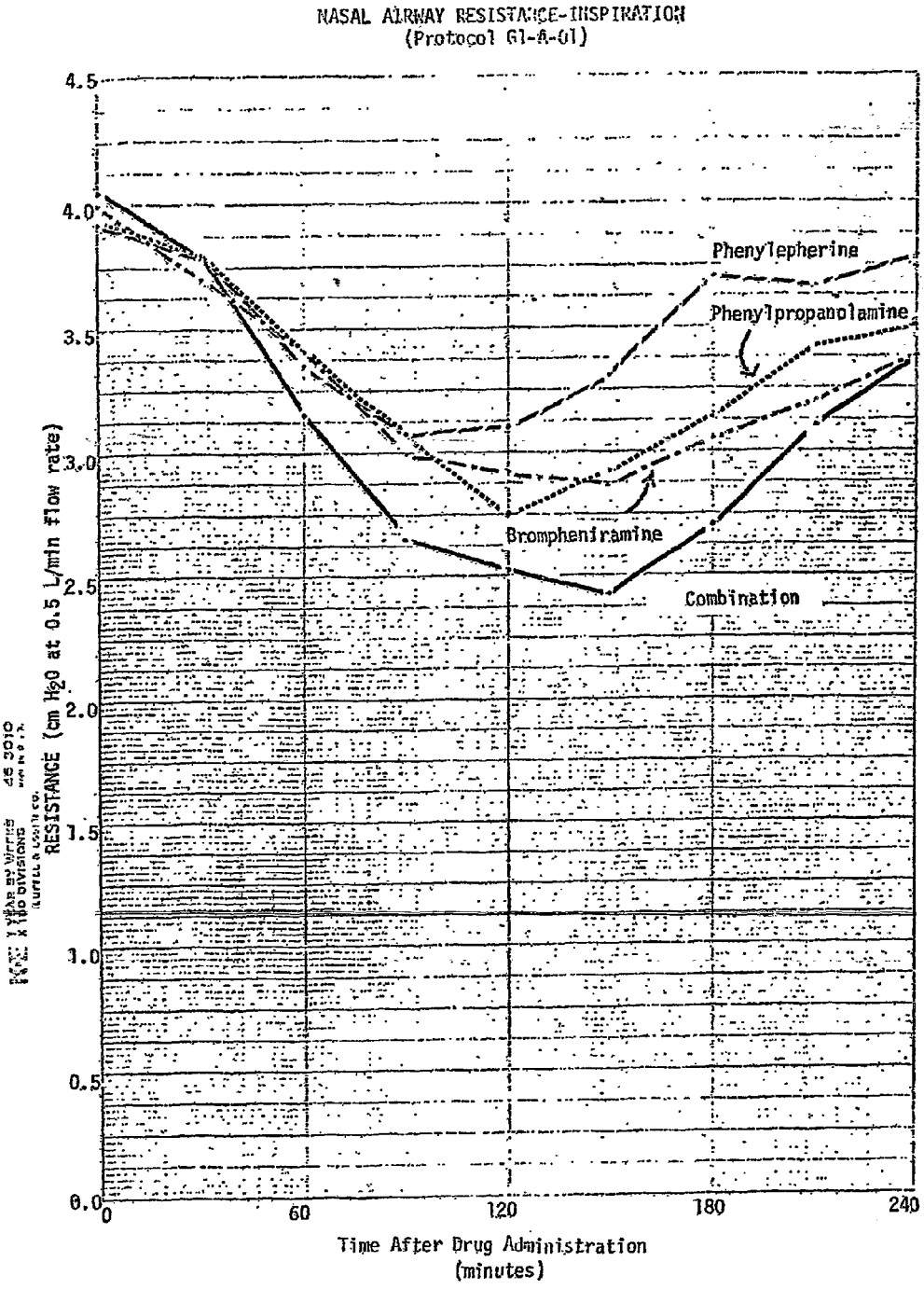
DIFFERENCES BETWEEN COMBINATION AND INDICATED COMPONENTS (+ = lower resistance for combination)		
Phenylephrine	Phenylpropanolamine	Brompheniramine
---	---	---
+0.019	+0.038	-0.069
+0.202	+0.264	+0.208
+0.421*	+0.421*	+0.327
+0.588***	+0.225	+0.412*
+0.862***	+0.475**	+0.425*
+0.983***	+0.433*	+0.345
+0.658**	+0.308	+0.102
+0.412*	+0.119	0.000

( )+ = Number of subjects

(a) cm H_2O at 0.5 L/min flow rate

(b) Means of 30 to 240 minutes, inclusive

* = Statistical Significant Difference at 10% level (t-test/two-tail)
** = Statistical Significant Difference at 5% level (t-test/two-tail)
*** = Statistical Significant Difference at 1% level (t-test/two-tail)



AHP4-REG-310-0104271

AHP4-REG-310-0104272

NASAL AIRWAY RESISTANCE - EXPIRATION: MEANS (a), RANKS AND DIFFERENCES
(Protocol 61-A-01)

TIMES (Min)	TREATMENT GROUP MEAN AND RANKS			
	10 mg Phenyl-epherine (8)+	10 mg Phenylpro panolamin (8)+	8 mg Bromphe-niramine (8)+	Combination (24)+
0	3.52	3.12	3.21	3.13
30	3.29 [4]	3.02 [2]	3.19 [3]	2.86 [1]
60	2.87 [3]	2.94 [4]	2.76 [2]	2.37 [1]
90	2.74 [4]	2.52 [3]	2.36 [2]	2.20 [1]
120	2.60 [4]	2.27 [3]	2.22 [2]	2.07 [1]
150	2.56 [4]	2.21 [2]	2.31 [3]	1.97 [1]
180	3.21 [4]	2.39 [2]	2.56 [3]	2.20 [1]
210	3.06 [4]	2.97 [3]	2.61 [2]	2.54 [1]
240	3.34 [4]	3.00 [3]	2.97 [2]	2.76 [1]
OVERALL MEANS (b)				
Resistance	2.959	2.665	2.622	2.371
Ranks	[3.9]	[2.8]	[2.4]	[1.0]

DIFFERENCES BETWEEN COMBINATION AND INDICATED COMPONENTS (+ = lower resistance for combination)		
Phenyl-epherine	Phenylpro-panolamine	Bromphe-niramine
---	---	---
+0.435**	+0.160	+0.335*
+0.496**	+0.565***	+0.390**
+0.535***	+0.323*	+0.154
+0.531***	+0.200	+0.156
+0.599**	+0.242	+0.342*
+0.998***	+0.183	+0.352*
+0.512***	+0.425	+0.069
+0.581***	+0.238	+0.212

( )+ = No. of subjects

(a) - cm H_2O at 0.5 L/min flow rate

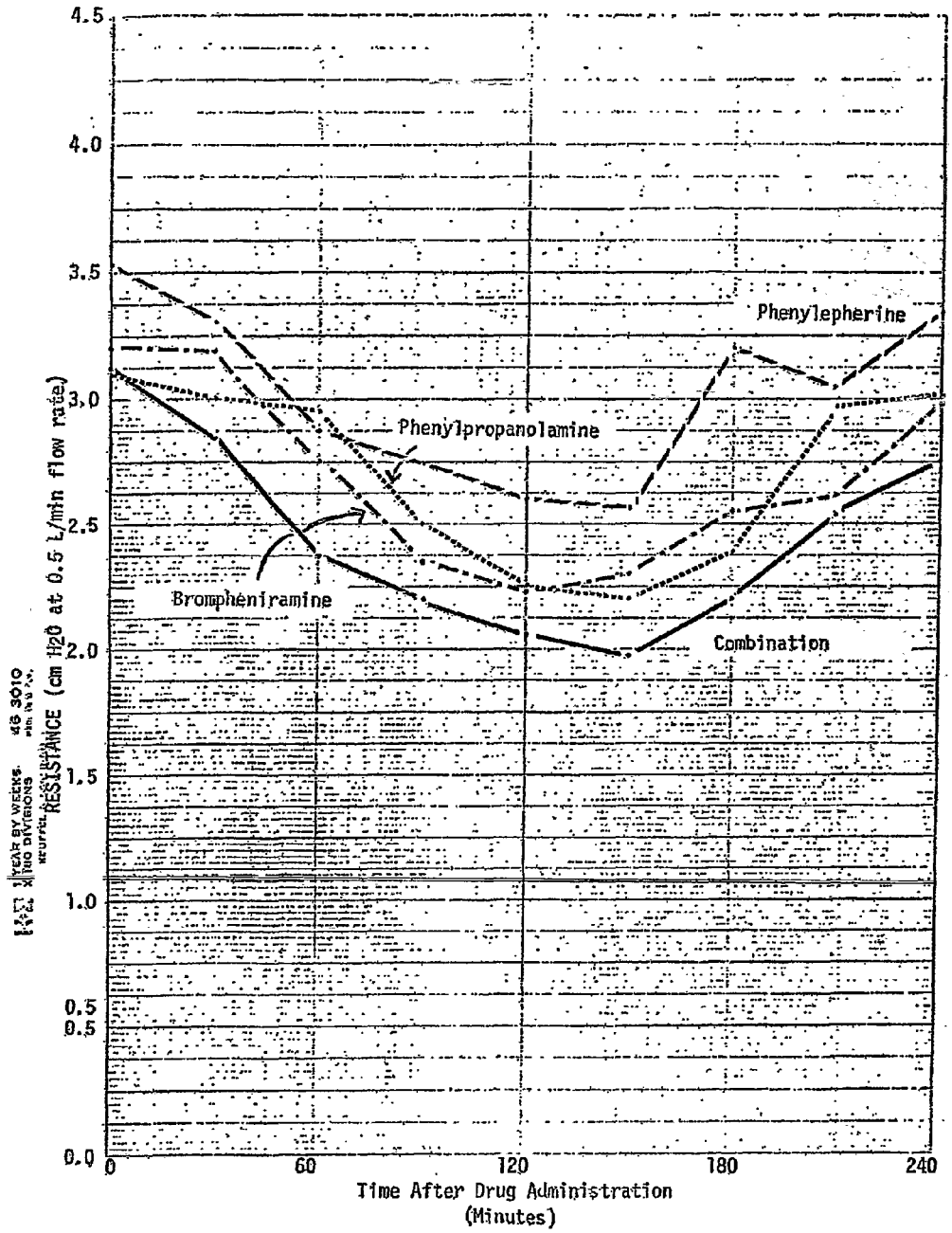
(b) - Means of 30 to 240 minutes, inclusive

* = Statistical significant difference at 10% level (t-test/two-tail)

** = Statistical significant difference at 5% level (t-test/two-tail)

*** = Statistical significant difference at 1% level (t-test/two-tail)

NASAL AIRWAY RESISTANCE-EXPIRATION
(Protocol 61-A-01)



AHP4-REG-310-0104273

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Final Clinical Study Report
Dimetapp
AHR-4010-3 Study 0401
Protocol 04

December 14, 1983

Report Prepared By: Carl E. Hyman

Approved By: P. M. Dietz, M.D.

Approved By: Robert E. Kaufman

Date: January 24, 1984

TABLE OF CONTENTS

ABSTRACT

A randomized, double-blind, placebo-controlled clinical trial was conducted to determine the relative efficacy and safety of proposed decongestant formulations. The study objective was to determine by subjective and objective methods if a two component decongestant formulation containing 12.5 mg phenylpropanolamine plus 5 mg phenylephrine/5 mL was at least equivalent, in terms of therapeutic effect, to either 10 mg phenylephrine/5 mL or 25 mg phenylpropanolamine/5 mL.

Adult patients with acute rhinitis due to upper respiratory infection were enrolled in a clinical trial of 3 days duration. Medication, other than the formulations under study, was prohibited during the trial. Forty eight patients entered the trial and were randomly assigned under double-blind conditions, to one of four parallel treatments; placebo (0 mg/5 mL), phenylpropanolamine (25 mg/5 mL), phenylephrine (10 mg/5 mL) or the combination (PPA 12.5 + PE 5/5 mL).

The evaluation of efficacy consisted of subjective and objective parameters. Subjectively, the patients rated symptoms of runny nose, stuffy nose, sneezing and headache throughout the study. At the end of the study both the investigator and the patient assessed symptom improvement and made a global evaluation. Objectively, nasal airway resistance was measured during a four-hour period immediately following the first dose of medication.

The results of the trial were analyzed in terms of symptom improvement for each symptom rated by the patient, overall symptom response as determined by the investigator and global evaluations recorded by both patients and the investigator. Nasal airway resistance was analyzed in terms of decrease and decrease from baseline.

The analysis of subjective symptom response for stuffy nose, runny nose and sneezing favored the combination in direct comparisons. All three active treatments resulted in improvement which was greater than placebo. A high degree of statistical significance was achieved for many comparisons in the analysis. The overall ratings by the investigator and the patients also yielded statistically greater improvement associated with the combination. Headache symptom improvement results were not analyzed due to a very low incidence rate.

Analysis of nasal airway resistance measurements clearly indicated a greater decrease among patients receiving the combination of decongestants. In the direct comparisons, the combination therapy resulted in a significantly greater decrease than phenylpropanolamine at 60, 120 and 240 minutes. The decrease resulting from combination therapy was also significantly greater than that observed with phenylephrine at 60 and 240 minutes.

No adverse reactions of a serious nature were reported throughout the study. Minor adverse reactions were reported most often among patients receiving placebo.

Keywords

Decongestant
Phenylpropanolamine
Phenylephrine
Nasal Airway Resistance
Human

I. INTRODUCTION

The purpose of this clinical study was to determine if a combination of decongestants at one half of the proposed OTC monograph dose (each), would have activity equal to either of the included components at full strength. The combination studied contained a direct acting decongestant, phenylephrine, and an indirect acting decongestant, phenylpropanolamine. The objective of the study was to make a comparative determination of the efficacy and safety of the combination, phenylpropanolamine 12.5 mg plus phenyl-ephrine 5 mg/5 mL to each of the single decongestants at full strength; phenylpropanolamine 25 mg/5 mL and phenylephrine 10 mg/5 mL. The comparison was made subjectively, in terms of symptom improvement and objectively in terms of nasal airway resistance. A placebo group was included as a negative control. A positive control was unnecessary since both decongestants at full strength are regarded as safe and effective. This clinical trial was part of a multicenter study conducted at 6 sites. It is reported as a separate study because a significant treatment by investigator interaction was found when data from all studies were pooled. Inquiries into the apparent difference led to findings indicating that this investigator used a more objective approach to making the evaluations described in the protocol. This was also the only investigator who contributed objective data in the form of nasal airway resistance measurements. A complete analysis of all 6 studies combined, this study alone and the remaining 5 pooled may be found in the attached statistical report.

II. METHODS

Study Design

The prospective design of this clinical study provided for random assignment of patients to each of four parallel treatment groups under double-blind conditions. A placebo group was included for control. The duration of the study was 3 days.

Patient Population

Patients eligible for this study were male and female outpatients over 18 years of age with acute rhinitis due to upper respiratory infection (U.R.I.) of 48 hours duration or less. To be included, the severity of illness had to be mild enough that medication other than nasal decongestants was not required. Patients demonstrated their willingness to participate in a controlled study of 3 days duration by voluntarily signing an informed consent describing the study and medications. Patients were excluded from study entry if they had; anatomical obstruction of the nasal airways, diabetes, thyroid, cardiovascular, renal, hepatic or respiratory disease other than URI. Females who were pregnant and any patients with known hypersensitivity to phenylpropanolamine, phenylephrine or chemically related drugs, were also excluded. Concomitant medications were not permitted during the study and MAO inhibitors, topical or oral decongestants, sympathomimetics and analgesics were specifically excluded.

Evaluations

Subjective assessment of efficacy was based upon patient and investigator rating of symptoms. The symptoms rated were; runny nose, stuffy nose, sneezing and headache. Patients rated themselves on a 4-point scale, where: not present = 0, mild = 1, moderate = 2 and marked = 3. These ratings were done at baseline and at 24, 48 and 72 hours post medication using a patient take home questionnaire. The investigator rated the same symptoms using the same rating scale, at baseline and 72 hours. An overall evaluation of therapeutic effect was made at 72 hours by both the patients and the investigator. A 4-point scale was used for this evaluation, where: marked benefit = 1, moderate benefit = 2, minimal benefit = 3 and no benefit = 4. The investigator global evaluation included an additional point on the scale, worse = 5. To aid him in making this subjective evaluation, the investigator examined the patients' nasal passages where degree of moisture, redness and swelling were considered as an indication of treatment benefit or lack thereof. This procedure provided an objective approach to this evaluation which may have made it more meaningful.

The objective evaluation of Total Nasal Airway Resistance was made by the investigator at baseline and at 15, 30, 45, 60, 120, 180 and 240 minutes after the first dose of medication. The measured factor, total nasal airway resistance (cm. H O/L/sec) was the sum of inspiratory and expiratory nasal airway resistance. The values were measured at a standard reference flow rate of 0.5 L per second. The value used was the mean of three successive readings taken with an electronic posterior rhinometry apparatus designed by the investigator.

Safety of treatment was evaluated using the incidence of solicited adverse effects reported at the final evaluation. In addition, pre- and post-study blood pressures and pulse rates were recorded.

Drug Supply and Schedule

Medication for 48 patients was provided to the investigator. The medication was prepackaged according to a randomization code which provided double-blind study conditions. Patients were assigned a sequential study number as they were entered. This provided an equal random distribution of 12 patients to each of the 4 treatment groups. The treatment groups were:

1. Placebo 0 mg/5 mL
2. Phenylpropanolamine 25 mg/5 mL
3. Phenylephrine 10 mg/5 mL
4. Phenylpropanolamine 12.5 mg plus phenylephrine 5 mg/5 mL

Each patient was provided a 90-mL bottle of study medication, with instructions to take 5 mL (1 teaspoon) every 4 hours for 3 days. The first dose was taken in the investigator's office prior to commencement of nasal airway resistance measurements. All 4 treatments were provided as a grape flavored elixir matched for color and taste.

A record of each patient's prescribed dosage and schedule was maintained on the case record forms.

III. RESULTS

Patient accountability and compliance was excellent for this clinical study. Forty-eight patients were entered into the trial. All patients completed the study without incident. No serious adverse reaction or deviation from protocol requirements was reported.

Random assignment of 12 patients to each of the 4 treatment groups resulted in groups which were essentially comparable for age, sex, duration of rhinitis and initial severity of symptoms. Demography and basaline severity ratings are displayed by treatment group in Table I.

The results of the subjective evaluation for symptom improvement favored the combination of phenylpropanolamine 12.5 mg plus phenylephrine 5 mg/5 mL in terms of numerical trend and statistical significance. Table II summarizes the results of the Statistical Analysis of symptom improvement for runny nose. Both the patients' evaluation for 24, 48 and 72 hours and the investigator final evaluation are shown. The combination resulted in symptom improvement which was statistically better than placebo or either of the single component preparations. At many points in the analysis high levels of significance were obtained.

The results from the patient's subjective evaluation of stuffy nose followed a similar pattern. Significant improvement was noted among patients receiving the combination when compared to placebo. This was evident at all time intervals. The comparison between the combination and the single entity preparations also indicated significance favoring the combination at 48 and 72 hours when compared to phenylpropanolamine alone and at 48 hours when compared to phenylephrine alone. Analysis of the investigator end of study evaluations indicated results consistent with the patients' evaluations. These were also found to be statistically significant. A summary of this analysis is presented in Table III.

A summary of the statistical analysis of the patient and investigator ratings of symptom improvement for sneezing is presented in Table IV. The combination resulted in greater improvement and these results were statistically significant in the comparison of the combination to placebo at 48 hours and to placebo or either single entity medication at 72 hours. The Investigator 72-hour evaluation resulted in statistical superiority of the combination when compared to placebo or phenylpropanolamine alone.

Evaluation of symptom improvement for headache was not attempted due to the low incidence of patients presenting with this symptom.

The results of the subjective global evaluations are found in Table V and are presented graphically in Figure 1. The scale used by the patients was a 4-point scale where 4 was no effect and 1 was marked effect. The investigator scale was similar but included a 5 = worse, rating. Despite the use of a different scale, the outcome was nearly identical. All patients in the group receiving the combination rated the treatment as having marked effect. The investigator also evaluated all patients on combination therapy as having marked therapeutic effect. This resulted in a high degree of statistical significance favoring the combination over placebo or either single entity preparation.

TABLE I

Comparability of Treatment Groups

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
1. Age (years)				
Mean	41.67	50.00	41.00	58.17
SD	17.23	17.07	18.30	9.52
N	12	12	12	12
2. Weight (lbs)				
Mean	166.31	162.94	141.79	162.52
SD	24.71	29.96	20.13	22.38
N	12	12	12	12
3. Sex				
Female	5	7	8	7
Male	7	5	4	5
4. Duration (hrs) of Rhinitis				
Mean	34.33	34.33	30.75	33.75
SD	5.43	6.26	5.74	6.08
N	12	12	12	12
5. Investigator's Baseline Rating of Runny Nose				
None	0	0	0	0
Mild	0	1	2	2
Moderate	10	9	8	9
Severe	2	2	2	1
6. Investigator's Baseline Rating of Stuffy Nose				
None	0	0	0	0
Mild	0	0	0	0
Moderate	5	6	5	5
Severe	7	6	7	7
7. Investigator's Baseline Rating of Sneezing				
None	0	0	0	0
Mild	3	5	4	3
Moderate	7	7	8	8
Severe	2	0	0	1

TABLE II

Comparisons of Treatment Group Mean[a] Scores of Patient's and Investigator's Subjective Evaluations[b] of Runny Nose

	Mean Patient's Evaluation of Runny Nose			Mean Investigator's Evaluation of Runny Nose
	24 Hours	48 Hours	72 Hours	72 Hours
Placebo [12][c]	2.03	1.93	1.41	1.34
Phenylpropanolamine [12]	1.87	1.98	1.25	1.18
Phenylephrine [12]	1.86	1.65	1.20	1.28
Combination [12]	1.53	1.34	0.49	0.64
Treatment Comparisons	P-Value[d]			
Combination vs Placebo	.0040	.0024	.0001	.0010
Phenylephrine vs Placebo	.1763	.0894	.1856	.3912
Phenylpropanolamine vs Placebo	.2020	.3823	.2481	.2311
Combination vs Phenylephrine	.0398	.0621	.0015	.0018
Combination vs Phenylpropanolamine	.0322	.0011	.0008	.0062
Phenylephrine vs Phenylpropanolamine	.9220	.1034	.8280	.6479

[a]Treatment group means are "Least Square Means" from the SAS GLM computer procedure.

[b]Code for evaluation of runny nose;
0 = not present, 1 = mild, 2 = moderate, 3 = severe.

[c]Numbers within brackets indicate sample size.

[d]Unless noted otherwise, P-values are one-tailed.

[e]Two-tailed P-values.

TABLE III

Comparisons of Treatment Group Mean[a] Scores of Patient's and Investigator's Subjective Evaluations[b] of Stuffy Nose

	Mean Patient's Evaluation of Stuffy Nose			Mean Investigator's Evaluation of Stuffy Nose
	24 Hours	48 Hours	72 Hours	72 Hours
Placebo [12][c]	2.32	2.05	1.81	1.91
Phenylpropanolamine [12]	2.12	1.74	1.60	1.67
Phenylephrine [12]	2.15	1.97	1.06	1.66
Combination [12]	1.95	1.16	0.94	0.91
Treatment Comparisons	P-Value[d]			
Combination vs Placebo	.0203	.0001	.0001	.0001
Phenylephrine vs Placebo	.1687	.3477	.0003	.0936
Phenylpropanolamine vs Placebo	.1285	.0071	.1569	.1035
Combination vs Phenylephrine	.1285	.0003	.2720	.0001
Combination vs Phenylpropanolamine	.1687	.0043	.0010	.0001
Phenylephrine vs Phenylpropanolamine[e]	.8531	.2953	.0112	.9549

[a] Treatment group means are "Least Square Means" from the SAS GLM computer procedure.

[b] Code for evaluation of runny nose;
0 = not present, 1 = mild, 2 = moderate, 3 = severe.

[c] Numbers within brackets indicate sample size.

[d] Unless noted otherwise, P-values are one-tailed.

[e] Two-tailed P-values.

TABLE IV

Comparisons of Treatment Group Mean[a] Scores of Patient's and Investigator's Subjective Evaluations of Sneezing[b] for Study 0401

	Mean Patient's Evaluation of Sneezing			Mean Investigator's Evaluation of Sneezing
	24 Hours	48 Hours	72 Hours	72 Hours
Placebo [12][c]	1.92	1.63	1.27	1.08
Phenylpropanolamine [12]	1.87	1.45	1.41	0.88
Phenylephrine [12]	1.60	1.23	1.21	0.70
Combination [12]	1.67	0.71	0.35	0.42
Treatment Comparisons	P-Value[d]			
Combination vs Placebo	.0905	.0003	.0002	.0038
Phenylephrine vs Placebo	.0466	.0588	.4100	.0594
Phenylpropanolamine vs Placebo	.3872	.2334	.2715	.2093
Combination vs Phenylephrine	.3480	.0212	.0005	.1223
Combination vs Phenylpropanolamine	.1524	.0025	.0001	.0283
Phenylephrine vs Phenylpropanolamine[e]	.1511	.3812	.3947	.4305

[a]Treatment group means are "Least Square Means" from the SAS GLM computer procedure.

[b]Code for evaluation of runny nose;
0 = not present, 1 = mild, 2 = moderate, 3 = severe.

[c]Numbers within brackets indicate sample size.

[d]Unless noted otherwise, P-values are one-tailed.

[e]Two-tailed P-values.

FIGURE 1

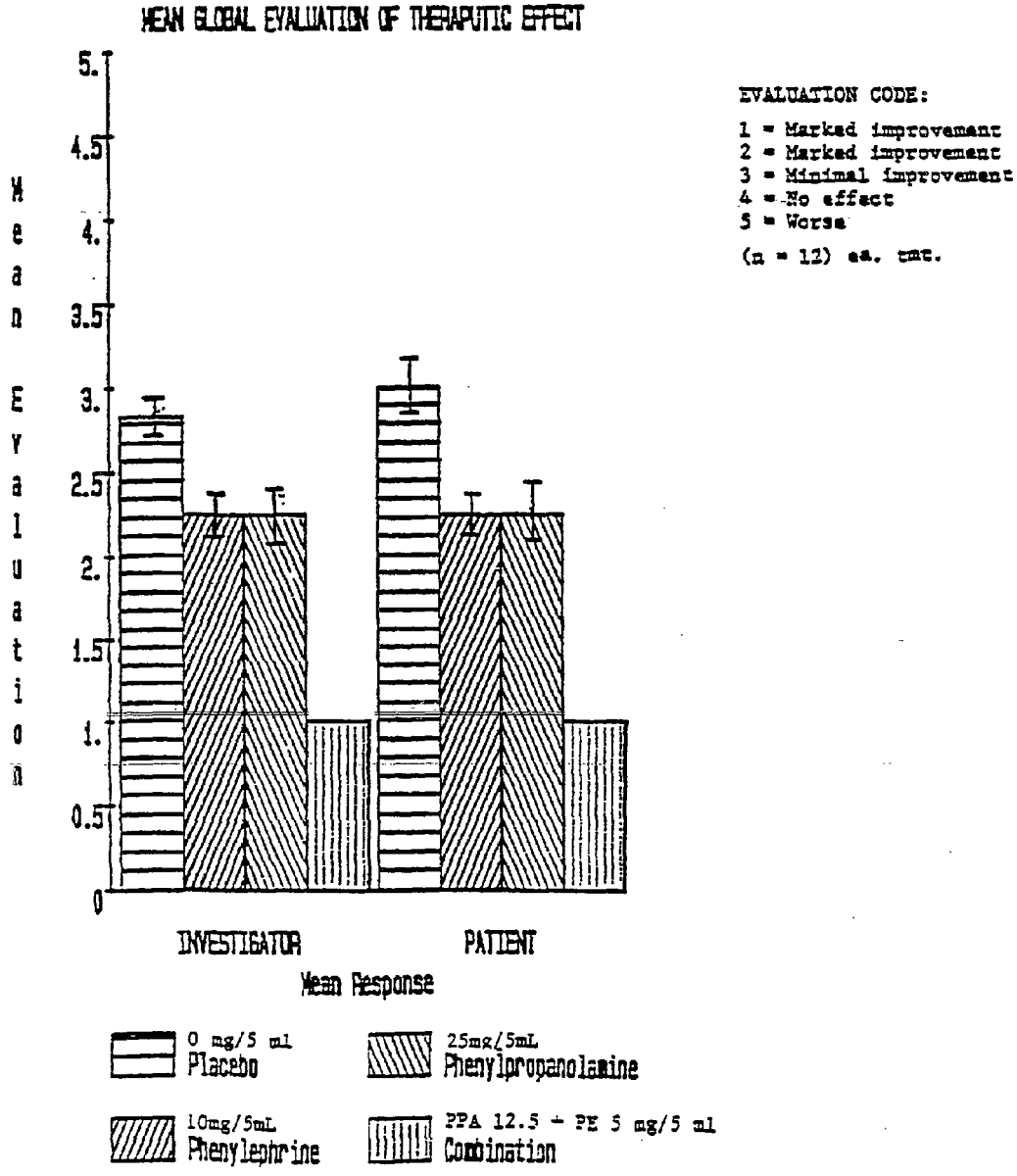

MEAN GLOBAL EVALUATION OF THERAPUTIC EFFECT
Mean Evaluation
5.
4.5
4.
3.5
3.
2.5
2.
1.5
1.
0.5
0
INVESTIGATOR
PATIENT
Mean Response
EVALUATION CODE:
1 = Marked improvement
2 = Marked improvement
3 = Minimal improvement
4 = No effect
5 = Worse
(n = 12) ea. tmt.
0 mg/5 ml Placebo
25mg/5mL Phenylpropanolamine
10mg/5mL Phenylephrine
PPA 12.5 + PE 5 mg/5 ml Combination

TABLE V

Summary of Investigators' 72-Hour Global Evaluations of Therapeutic Effect[a]

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
Mean	2.83	2.25	2.25	1.00
S.E.M.	0.11	0.13	0.18	0.00
n	12	12	12	12

[a]Code for scale: 1 = marked, 2 = moderate, 3 = minimum, 4 = unchanged, 5 = worse.

Summary of Patients' 72-Hour Evaluations of Overall Therapeutic Effect[a]

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
Study 0401				
Mean	3.00	2.25	2.25	1.00
S.E.M.	0.17	0.13	0.18	0.00
n	12	12	12	11

[a]~~Code for scale: 1 = marked, 2 = moderate, 3 = minimum, and 4 = none.~~

Results of the objective measurement, total nasal airway resistance, were also significantly favorable for the group treated with the combination of decongestants (phenylpropanolamine 12.5 mg plus phenylephrine 5 mg/5 mL). These measurements, the sum of inspiratory and expiratory nasal airway resistance, were taken at time of medication and at 15, 30, 45, 60, 120, 180 and 240 minutes post medication. An analysis was performed evaluating the decrease from baseline at each of the post treatment intervals. This was calculated as an analysis of covariance with the baseline measurements as the covariable. The results of nasal airway resistance measurements are presented graphically in Figure 2. The combination had the lowest mean NAR curve across the entire evaluation period and was the only mean NAR below baseline values at 240 minutes. The mean NAR values for phenylephrine and phenylpropanolamine were lower than the placebo group but higher than the

TABLE VI

Summary of Statistical Analysis for Decrease in total Nasal Airway Resistance in cm $H_2O/l/sec$

	Mean[a] Decrease in NAR at Evaluation Times (minutes) Following Initial Dose						
	15	30	45	60	120	180	240
Placebo [12][b]	0.186	0.412	0.181	0.323	0.084	-0.101	-0.132
Phenylpropanolamine [12]	0.403	0.939	1.358	1.010	0.790	0.353	-0.186
P-Ephrine [12]	0.535	0.841	1.211	1.019	0.862	0.514	-0.241
Combination [12]	0.491	1.183	1.450	1.522	1.376	0.784	0.426
Treatment Comparisons	P-Value[c]						
Combination vs Placebo	.0785	.0001	.0001	.0001	.0001	.0010	.0033
Phenylephrine vs Placebo	.0554	.0115	.0001	.0002	.0006	.0132	.2883
Phenylpropanolamine vs Placebo	.1606	.0031	.0001	.0002	.0015	.0494	.3911
Combination vs Phenylephrine	.4265	.0333	.0444	.0031	.0132	.1588	.0007
Combination vs Phenylpropanolamine	.3344	.0939	.2524	.0028	.0061	.0573	.0016
Phenylephrine vs Phenylpropanolamine[d]	.5416	.5927	.2937	.9585	.7490	.5519	.7800

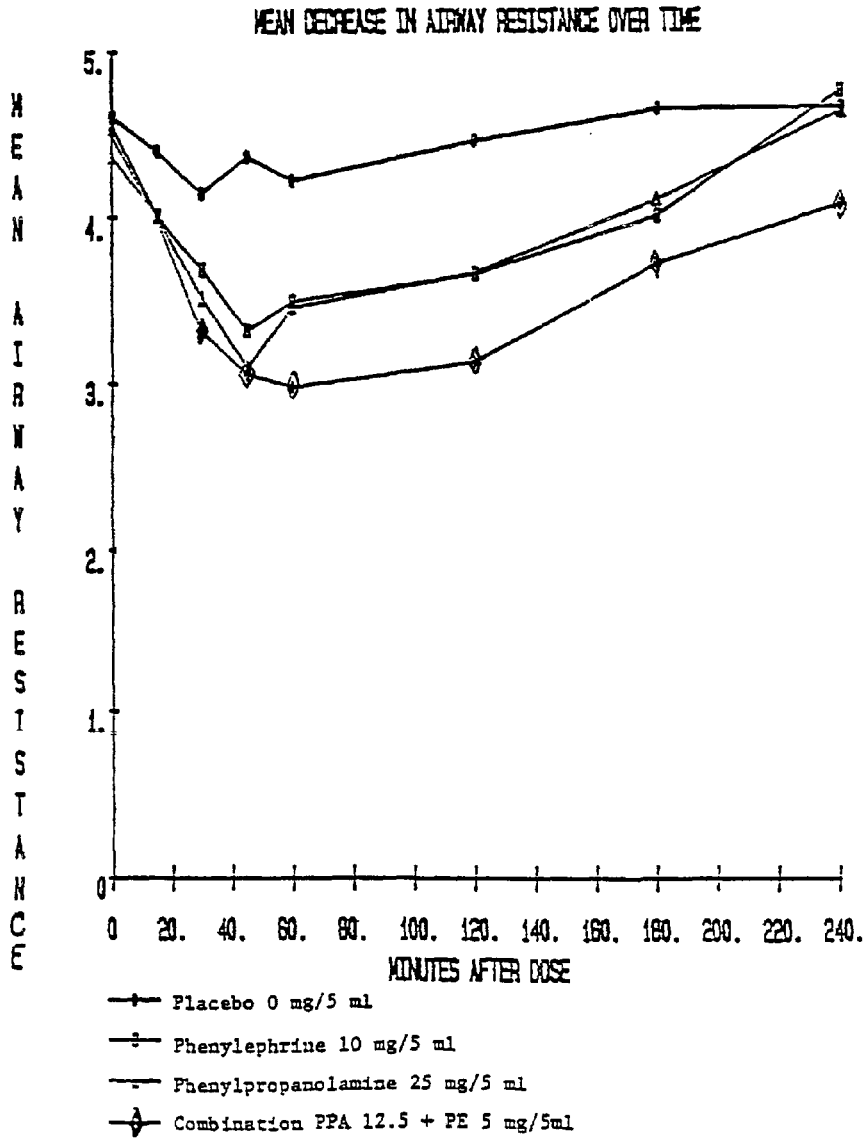
[a] Treatment group means are the adjusted means from Analysis of Covariance.

[b] Numbers within brackets indicate sample size.

[c] Unless noted otherwise, P-values are one-tailed.

[d] Two-tailed P-values.

FIGURE 2


MEAN DECREASE IN AIRWAY RESISTANCE OVER TIME
MEAN AIRWAY RESISTANCE
5.
4.
3.
2.
1.
0
0 20. 40. 60. 80. 100. 120. 140. 160. 180. 200. 220. 240.
MINUTES AFTER DOSE
Placebo 0 mg/5 ml
Phenylephrine 10 mg/5 ml
Phenylpropanolamine 25 mg/5 ml
Combination PPA 12.5 + PE 5 mg/5ml

placebo group but higher than the combination. Results of the statistical analysis of these measurements is presented in Table VI. The means shown are the "adjusted means" from the analysis of covariance. The mean decrease from baseline for the combination was significantly greater than placebo at 30, 45, 60, 120, 180 and 240 minutes. The decrease for the combination was significantly greater than the decrease observed for phenylpropanolamine at 60, 120 and 240 minutes and phenylephrine at 30, 45, 60, 120 and 240 minutes ($p \leq .05$). Both phenylephrine and phenylpropanolamine alone were responsible for significant decreases compared to placebo values at many intervals, but neither resulted in more significant decreases than the combination, nor did their effect appear to be as long lasting.

Results of the statistical evaluation of the summary measure for NAR, the area between the NAR curve and baseline values (NARAREA) are similar to those found for reduction from baseline. These summary values as "adjusted treatment" means and the appropriate statistical comparisons are presented in Table VII. This analysis demonstrates the superior treatment performance of the combination compared to phenylephrine ($p \leq .0027$) and to phenylpropanolamine ($p \leq .0011$). By this analysis all active treatments resulted in statistically greater reduction in NARAREA than placebo.

Results of the safety evaluations indicated a high level of tolerance to all treatments. A summary of all adverse effects reported during this study is presented in Table VIII. Examination and analysis of blood pressure and pulse rate recordings done pre and post study resulted in no meaningful changes. These values are presented in Table IX.

DISCUSSION

The most meaningful factor in this study is the correlation of subjective and objective results. In the results of both types of evaluation a clear superiority of the response to treatment with the combination of decongestants is apparent. Since no real differences were detected between the groups at baseline, the results of this evaluation are considered valid. The investigator is experienced in clinical evaluation of this nature and has conducted many similar trials in the past. His expertise and ability to instruct patients to record subjective responses must be considered as well as the objective approach he used in making the investigator evaluations.

Safety of treatment is not a question since as many adverse reactions were reported by placebo patients as by all treated patients. The ratio in this comparison should have been on the order of 1:3. No changes in cardiovascular signs were observed.

TABLE VII

Summary of Statistical Analysis for the Summary Measure for NAR, NARAREA, Area [cm H_2O/l/sec) x min] Between the Total Airway Resistance Curve and Baseline

	Mean NARAREA[a]
Placebo [12][b]	18.84
Phenylpropanolamine [12]	141.40
Phenylephrine [12]	152.39
Combination [12]	246.34
Treatment Comparison	**P-Value[c]**
Combination vs Placebo	.0001
Phenylephrine vs Placebo	.0001
Phenylpropanolamine vs Placebo	.0002
Combination vs Phenylephrine	.0027
Combination vs Phenylpropanolamine	.0011
Phenylephrine vs Phenylpropanolamine[d]	.7342

[a] Treatment group mean areas are the adjusted means from Analysis of Covariance.

[b] Numbers within brackets indicate sample size.

[c] Unless noted otherwise, P-values are one-tailed.

[d] Two-tailed P-values.

TABLE VIII

Summary Listing of Adverse Effects

Patient	Adverse Effect (AE)	Drug*	No. Days Duration	Maximum Intensity	Action Taken	Serious AE	Test Drug Cause AE	Patient Outcome
12	Lightheadedness	PE	1	Mild	None	No	Probably	Recovered
22	Lightheadedness	P	1	Mild	None	No	Possibly	Recovered
23	Very dry throat	C	2	Mild	None	No	Probably	Recovered
33	Dizziness	PP	2	Mild	None	No	Possibly	Recovered
36	Eructation	P	1	Mild	None	No	Probably	Recovered
46	Gaseousness	P	2	Mild	None	No	Possibly	Recovered

* PE = Phenylephrine
PP = Phenylpropanolamine
C = Combination
P = Placebo

V. CONCLUSION

The study objective was to compare the efficacy and safety of decongestant treatment consisting of two half-strength decongestants in combination, phenylpropanolamine 12.5 mg plus phenylephrine 5 mg/5 mL to treatment with each decongestant at full strength phenylpropanolamine 25 mg/5 mL and phenylephrine 10 mg/5 mL. The results clearly suggest that there may be a synergistic effect of the two decongestant entities in combination, which may provide more effective improvement of symptoms and airway function. Of apparent certainty is the fact that there is no more risk to the patients treated with the combination of decongestants.

APPENDIX A

References

1. Cohen, B.M. 1975. Physiologic/clinical comparisons of a sustained release decongestant combination, its components and placebo in patients with allergic rhinitis. J. Asthma Res. 13:7-13.

2. Cohen, B.M. 1977. Physiologic and subjective comparisons of two oral sustained release nasal decongestant combinations and placebo in patients with common colds. Current Ther. Res. 22:522-528 (Oct.).

CLINICAL STUDY PROTOCOL

A. H. ROBINS COMPANY
1407 Cummings Drive
Richmond, Virginia 23220

AHR No. (4010-3)

Dimetapp Elixir

Protocol # 04

Study # 01

Final Copy: 1/31/78

Signature of Medical Monitor — Date 2/27/78

Signature of Principal Investigator — Date 2/24/78

TABLE OF CONTENTS PAGE

A. H. ROBINS COMPANY
1407 Cummings Drive
Richmond, Virginia 23220

Synopsis of Protocol No. 04

IND # -

NDA # - 13-087

Phase (IV) Study

1. Drug Identification:

   AHR Drug No.: 4010-3

   Trade: Dimetapp Elixir (decongestants only)

   Generic: Phenylephrine; phenylpropanolamine

2. Pharmacologic Category: decongestant

3. Therapeutic Indication for this Study: Acute rhinitis due to URI, duration of 48 hours or less.

4. Objective of Study: Clinical trial to assess subjective toleration and efficacy of phenylephrine 10 mg versus phenylpropanolamine, 25 mg versus phenylephrine, 5.0 mg plus phenylpropanolamine, 12.5 versus placebo in adult patients with acute rhinitis due to URI.

5. Study Design: Double-blind, randomized, placebo control.

6. Clinical Monitor and Clinical Investigator:

   Clinical Monitor (AHR) Emily M. Morley, M.D.
   ~~Clinical Investigator~~

7. General description, source and number of patients to be entered: 288 patients; age 18 years and older with acute rhinitis due to URI of 48 hours duration or less. Office of Investigator; males and females (non-pregnant).

8. Treatment groups and dosage: Patients will be randomly assigned to one of 4 study groups: Phenylephrine (10 mg) - 5 ml every 4 hrs (6 doses/24 hrs) for 3 days. Phenylpropanolamine (25 mg) - 5 ml every 4 hrs (6 doses/24 hrs) for 3 days. Phenylephrine (5 mg) + Phenylpropanolamine (12.5 mg) - 5 ml every 4 hrs (6 doses/24 hrs) for 3 days. Placebo - 5 ml every 4 hrs (6 doses/24 hrs) for 3 days.

9. Greatest duration of drug exposure for any individual patient: 3 days

10. Exclusions:

    1. Pregnant females

    2. Allergy to phenylephrine, phenylpropanolamine

    3. History of allergy to chemically related drugs

    4. Patients with cardiovascular, renal, thyroid, diabetes or other systemic disease which may contraindicate therapy with study medication or confuse study results.

    5. Use of monoamine oxidase inhibitors, antihistamines, bronchodilators, nasal decongestants (local or parenteral) or antibiotics within 24 hrs of enrollment or during course of study. Analgesics are not permitted during the study period or for at least 12 hours prior to entry into the study.

    6. Evidence of anatomic obstruction of nasal airways, or chronic nasal disease.

11. Observations:

    a. Efficacy: Subjective parameters - stuffy nose, runny nose, sneezing, headache.
    b. Safety: B.P., pulse rate.

12. Estimated date of initiation:

    March, 1978.

13. Comments:

I. Background:

F.R. Notice of 7/27/72 declared Elixir as "probably effective" under the DESI Review Program. Extentab was declared "possibly effective" but on 4/25/77 was downgraded to "ineffective as a fixed dose combination." Subsequently, FDA advised Robins that a proposed reformulation of Dimetapp Extentabs to a brompheniramine and a single sympathomimetic combination would be an acceptable response to the Notice of Opportunity for Hearing on FDA's proposal to withdraw the NDA. Conferences were held with FDA personnel regarding the nature of the reformulation; AHR initially (9/73) proposed a reformulation containing brompheniramine and phenylpropanolamine and later (7/77) a reformulation containing brompheniramine and phenylephrine. However, FDA had indicated that it would not take final action on NDA amendments until such time as the OTC Cough/Cold Monograph was finalized (proposed monograph published 9/9/76, with the final monograph expected in mid-or-late-1978).

Robins prefers to maintain the current two-sympathomimetic product and made this proposal to FDA 5/76. The proposed OTC Monograph (September, 1976) lists phenylephrine at 10 mg and phenylpropanolamine at 25 mg single doses in immediate release form as Category I. A combination of two half-strength Category I agents would be acceptable as Category I if it can be shown that the clinical efficacy and toleration is equivalent to a single entity Category I agent.

II. Objective:

To obtain clinical pharmacological documentation by subjective parameters that a combination of 5 mg phenylephrine and 12.5 mg phenylpropanolamine/5 ml is at least equivalent in effect on subjective parameters to either 10 mg phenylephrine or 25 mg phenylpropanolamine.

III. Investigators:

A. Number of investigators scheduled to participate in studies using this protocol: 6

B. Investigator information for each separate study under this protocol: See Appendices.

IV. Experimental Plans:

A. Patients

1. Number - Scheduled to participate in this protocol: 288

2. Description

a.	Age:	18 years and older
b.	Sex and pregnancy potential:	Male and female (non-pregnant)
c.	Race:	N.A.
d.	Diagnosis (or description of symptoms):	Acute rhinitis due to URI of 48 hrs. duration or less.

e. Hospital status: Outpatient

3. Source private office practice. Office of investigator.

4. Criteria for inclusion

a. Acute rhinitis (nasal congestion) due to URI.

b. Required duration of condition: 48 hours or less.

c. Required severity of condition: Patient should not be sick enough to require medication other than nasal decongestants.

d. Willingness to participate in this study as demonstrated by providing voluntary written informed consent.

e. Ability to follow directions of the investigator or his staff to include the following:

(1) Appear for return visits at stated intervals for stated duration of study.

(2) Take study drug medication as scheduled.

(3) Avoid self-medication with either non-prescription or prescription drugs during course of study.

5. Criteria for exclusion:

a. Presence of concurrent disease: Diabetes; thyroid; cardiovascular, renal, or hepatic disease, other respiratory disease or other systemic disease which may contraindicate therapy with study medication or confuse study results. Evidence of anatomical nasal airway obstruction.

b. Pregnancy: Not pregnant

c. Known hypersensitivity to: phenylephrine; phenylpropanolamine or chemically related drugs.

d. Specifically excluded recent medication: bronchodilators; MAO inhibitors; antihistamines; topical or parenteral nasal decongestants or antibiotics within 24 hrs of initiation of study or during study. Analgesics during study period or for at least 12 hours prior to entry into study.

B. Procedure

1. General description of study: Double-blind, parallel, randomized clinical trial of 3-day duration.

2. Study medication (test drugs to be physically indistinguishable)

   a. Identity of each treatment group (name, dose form, unit strength, manufacturing lot number):

   b. Packaging and Labeling (Protocol packaging lot #__): (e.g.)

      (1) Study medication will be supplied to the investigator in prepackaged, pre-labeled and pre-coded bottle of stated amount of liquid. One bottle of medication will be supplied for each patient.

      (2) The assignment of study medication will be made on the basis of a randomization schedule by patient number, which is sequentially assigned to patients being admitted to the study; i.e., medication labeled for Patient #1 will be given to the first patient entering the study, medication labeled for Patient #2 will be given to the second patient, etc.

      Each 5 ml of study medication contains:

1.	Phenylephrine HCl	10 mg
or 2.	Phenylpropanolamine HCl	25 mg
or 3.	Phenylephrine HCl	5 mg
	plus phenylpropanolamine HCl	12.5 mg
or 4.	Matching placebo	

      (3) One bottle will be dispensed to each patient on Study Day 1.

      At the time of dispensing, the investigator will remove the tear-off portion of the two-part label (without opening) and staple it to the Case Report Form. The patient number on the bottle label must be the same as the patient number on the Case Report Form. At each visit a tablet count and any change in dosage schedule will be noted on the Case Report Form.

      (4) In the case of emergency, the contents of any bottle may be determined by cutting open the tear-off portion of the bottle label.

      (5) The investigator will be supplied with labeled medication for extra patients, so as to provide for study dropouts, bottles broken in transit, etc. Selection of the appropriate replacement medication will be made by the AHR monitor so as to preserve the double-blind features of this study.

c. Dosage schedule (e.g.):

(1) Initial dosage schedule: 5 ml of study medication every 4 hrs (6 doses in 24 hrs) for 3 days (72 hrs).

(2) Increasing or decreasing dosage from the initial dose to a stated maximum or to a stated minimum is permitted at any time during the study on physician's order. Regulation of dosage should be based on the patient's individual response and adverse effects. Any patient for whom any other dosage is required will be dropped from the study. Each patient should be cautioned to maintain the dosage schedule prescribed for him unless a change is prescribed by the physician.

Permissible dosage schedules: Maximum dosage permissible is 6 doses/24 hrs - 30 ml. A minimum of 4 doses/24 hrs (20 ml) is permissible, e.g., 8:00 am; noon; 4:00 pm; and 8:00 pm.

(3) Careful records of dosage schedules and changes must be kept on the CRF.

3. Concurrent management

a. Permitted:

(1) Diet: As desired.

(2) Temporary restructuring of activities and/or environment: None indicated.

b. Excluded: All other medications unless taken regularly pre-study and not included in the exclusion criteria.

4. Treatment plan (Evaluation for all patients within a study should be made by the same physician.)

~~a. Screening and admission period~~ (e.g.)

(1) Screening: Brief history, review of symptoms and respiratory system physical examination.

(2) Admission to study

Upon meeting the exclusion and inclusion criteria, including execution of written informed consent, a patient may be admitted to the study and given a sequentially assigned patient number.

Complete Study Admission Form.

All patients screened but not entered into the actual study will have a Case Report Form partially completed and submitted to the Sponsor.

(3) Study drug

Dispense one bottle of the correct study medication (check patient sequence number).

Instruct patient as to intended dosage schedule. 5 ml every 4 hrs for at least 4 doses up to a maximum of 6 doses/24 hrs.

(4) Instructions to patient

(a) Instruct patient on diet, activities, excluded medications.

(b) Instruct patient to note adverse effects and to notify the investigator if effects become severe or unremitting.

(c) Inform the patient that a telephone contact may be made at any time during the study period in the event of persistent and bothersome side effects or increasing symptomatology. At this time an adjustment in the dosage schedule may be made if indicated.

(d) Instruct patient to return to office at stated time and bring the unused medication.

(e) Each patient should rate his pre-drug symptoms i.e., nasal and other "target" symptoms in the presence of the investigator. Patients are to be specifically instructed to complete the questionnaire at end of 24, 48, and 72 hrs after starting the study.

b. Return visits: On day 3 of the study (72 hrs) the patient should return for the Final Visit.

(1) Observations:

(a) History: Brief review of symptoms.
(b) Physical exam: Examination of nasal passages and brief examination of respiratory system.

(2) Review of Patient Take-Home Questionnaire.

(3) Physicians assessment of patient's symptoms.

c. Interim (unscheduled) visits

At any time during a patient's participation in this study, either the patient or the investigator may initiate a clinic visit or other investigator-patient contact to evaluate his physical status.

5. Adverse effects - to be noted at least at each visit.

a. Identification

Spontaneous response to question "Any problems?"

b. Reporting

(1) All adverse reactions or experiences, both volunteered and solicited, will be appropriately entered on the Adverse Effects Report Form.

(2) Unanticipated or life-threatening adverse reactions to the investigational drug will be reported immediately to the sponsor by telephone.

c. Possible action

Depending on the nature and severity of the adverse effect, the investigator may institute any of the following:

(1) Continue patient on same dosage schedule until next visit to determine if effect is transient.

(2) Adjust schedule to omit one or more daily doses.

(3) Termination of the patient from the study, with initiation of appropriate follow-up.

6. Indications and procedures for removing a patient from study; complicating events

a. Situations where patient's participation in study may temporarily be interrupted and resumed:

b. The occurrence of any of the following will require permanent removal of the patient from the study:

(1) Refusal of patient to continue therapy with assigned drug.

(2) Failure of patient to follow investigator's directions, especially with respect to return visits, and avoiding prescribed medications.

(3) Unacceptable adverse effects which persist despite adjustment of dosage of study drug.

(4) Appearance of a complication that would have led to exclusion of the patient, if present at the time of admission to the study.

(5) Failure of patient's symptoms to improve within stated number of days of entering study.

c. The reason for any patient's removal from the study will be described on the appropriate Case Report Form.

d. Complicating events will be handled in a manner consistent with good medical practice, including institution of appropriate therapy and follow-up.

e. Study dropouts

For any patient removed from this study the following sequence will be indicated:

(1) Discontinue study medication
(2) Initiate indicated therapy
(3) Keep record of any follow-up
(4) Include patient in final evaluation

V. Monitoring

A. Monitors

1. Principal monitor: Emily M. Morley, M.D.
2. Research Associates:

B. Statistician: Roger Flora, Ph.D.

C. Execution

1. Anticipated duration of total study (all patients): 3 months

2. Controls and checks on study progress and data collection (e.g.):

Each investigator will be visited before or at the time of receipt of study drug supplies for the purpose of re-reviewing the protocol and the case report forms with involved personnel, and to observe area for drug storage and pattern of dispensing. Each investigator will be contacted at least bimonthly thereafter by phone or visit, or both, to assess progress and to review problems. Case Report forms, reflecting all available experience in the study, including reports on patients screened but not actually entered into the study (and the reasons therefor), will be reviewed at on-site visits and efforts made to achieve completeness of entries.

Completed forms, upon termination of drug administration to those patients, will be forwarded to the AHR medical monitor for review; existing questions will be referred back to the principal investigator. Completed forms bearing initials of the medical monitor as indicative of review for safety questions, general efficacy and completeness will then be transmitted for data processing procedures.

3. Procedures for terminating, extending, or modifying this study

   a. This study may be terminated at any time by either the sponsor or the investigator.

   b. By mutual agreement of the sponsor and the investigator, any aspect of this protocol may be amended.

   c. Upon completion or termination of total study, all unused study drugs will be returned to the drug sponsor.

VI. Data Management and Statistical Analysis

A. Data Management Procedures

Prior to receiving completed Case Report Forms (CRF's) from the Medical Monitor, procedures will be developed for transcribing data into a computerized data base for subsequent summarization and analysis. A Data Document Inventory Form will also be prepared for recording receival date and number of data sheets returned for each subject.

As CRF's are "logged in" they will undergo a review for completeness and clarity. Data which are incomplete or require clarification will be returned to the Medical Monitor. Following resolution of these items, data will be keypunched and verified directly from the CRF's. The data base will then undergo a final editing procedure designed to detect spurious values, perform tallay checks, etc., and make corrections where indicated.

Finally, a 10% random sample of data records will be selected from the edited data and checked against the CRF's to provide an estimate of the accuracy of the established data base. The data will then be referred to the statistician for analysis.

B. Statistical Design and Sample Size Considerations

The design of the study includes four parallel treatment groups with treatments administered in a randomized, double-blind fashion as described in IV above. The comparisons of primary interest are: phenylephrine (10 mg) vs. the combination [phenylephrine (5 mg) plus phenylpropanolamine (12.5 mg)], and phenylpropanolamine (25 mg) vs. the combination [phenylephrine (5 mg) plus phenylpropanolamine (12.5 mg)]. Placebo comparisons, however, are necessary in order to verify that a treatment effect can be shown by the methodology employed in the population under study.

The major purpose of the study is to demonstrate that the combination of the two decongestants at half strength is at least as good as either of the two at full strength. Thus, it is especially important that the sample size be large enough to provide a high probability of detecting any meaningful difference. Since the primary efficacy assessments are ordered categorical responses, e.g., physicians and patients global assessments, it is anticipated that pairwise comparisons among treatment groups using ridit analysis as described by Fleiss will provide appropriate comparisons. This procedure tests the null hypothesis that if a person is selected at random from each of two treatment groups (or the populations represented by each group) the probability is 0.50 that the individual from a specified group will show greater improvement (be in a higher category). Based on the normal approximation test given by Fleiss, the sample size of 72 per treatment group will provide a power of greater than 0.90 of detecting at the .05 level of significance, a departure of as much as 0.10 from the 0.50 probability. This assumes the use of a one-sided test and that pooling over investigators will be permissable. The latter assumption will, of course, be investigated before pooling as described below.

C. Statistical Analysis

Although it is likely that data from a single investigator will be insufficient to perform statistical analyses of desired sensitivity, tabulations and summarizations will be obtained by investigator. These summaries will be carefully inspected for trends and any evidence of possible treatment by investigator interactions. However, it is anticipated that analyses for detecting treatment differences will be across investigators.

Baseline comparability of treatment groups will first be examined including consideration of age, sex, race, and pre-study symptom assessments. Efficacy assessments will be compared for each of the three days on which evaluations are made as well as comparison of overall global assessments by patients and by physicians on the final day of the study. Since efficacy assessments are ordered categorical responses, comparisons will be made using ridit analysis as described by Fleiss. Frequency and intensity of adverse effects will be compared by means of chi-square or ridit analysis as appropriate.

Reference: Fleiss, Joseph L. Statistical Methods for Rates and Proportions, John Wiley and Sons, Inc. New York (1973).

VII. Appendices

A. General

1. Blank specimen of Case Report Form.

B. Specific to each study under this protocol

1. Identity and qualifications of principal investigator and key staff.

2. Location and nature of clinical facility to be utilized.

3. Location and nature of laboratory facility to be utilized, including normal test values for laboratory.

4. Blank specimen of informed consent form.

ADDENDUM TO PROTOCOL

A. H. ROBINS COMPANY
Medical Research Department
1407 Cummings Drive
Richmond, Virginia 23220

Name Burton Cohen

AHR Drug Number 4010-3 Drug Name Dimetapp Elixir

Study Number 0401 Protocol Number 04

PROTOCOL TO BE AMENDED AS FOLLOWS:

Prior to administration of the test drug nasal airway flow/resistance (Rn) will be measured for baseline values. Following these measurements 5 ml of one of 4 test formulations will be administered to the patient according to the randomization schedule. Nasal airway flow/resistance will be measured according to a predetermined schedule for a period of 4 hours. The results will be recorded on data sheets provided by the investigator.

Date _____ Investigator _____

Date _____ Study Monitor _____

A. H. ROBINS COMPANY
1211 Sherwood Avenue
Richmond, Virginia 23220

Report No.

DIMETAPP ELIXIR (AHR-4010-3)

PROTOCOL 04

STATISTICAL REPORT

Report Prepared By: Charles W. Kish Jr. — Charles W. Kish, Jr., M.S. — 7/28/81 Date

Report Approved By: Roger E. Flora — Roger E. Flora, Ph.D. Manager, Data Management and Analysis Group — 7/28/81 Date

AHP1-REG-048-0015109

Report Number
81-0552

A·H·ROBINS

RESEARCH REPORT

Dimetapp Elixir (AHR-4010-3)

Protocol 04

Statistical Report

BY
Charles W. Kish Jr.

7/28/81

A. H. Robins Company
Research & Development Division
1211 Sherwood Avenue
Richmond, Virginia 23220

AHP1-REG-048-0015110

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AHP1-REG-048-0015111

jective of this randomized, double-blind, placebo-controlled, clinical
of 3-days duration with adult patients with acute rhinitis due to
espiratory infection (URI) was to assess the efficacy and safety of
lowing treatments:

acebo, q4h,
enylpropanolamine, 25 g/5 ml, q4h,
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gestant effect in the nasal pasages through direct and indirect
f action, respectively.

emphasis was placed on determining whether the combination of de-
ants is at least equivalent in therapeutic effect to either decon-
alone. Six investigators enrolled 274 patients and collected data
n evaluation of runny nose, stuffy nose, sneezing, headache, and
therapeutic effect. Data from 1 investigator, Dr. Burton M. Cohen,
alyzed separately since treatment groups from his study did not
in the same manner as those from the other 5 investigators and
r. Cohen was the only investigator who also measured nasal airway
nce. Efficacy data from the other 5 investigators were pooled for
s.

s of the pooled data from the 5 investigators other than Dr. Cohen
d no significant difference among the treatment groups for any of
jective efficacy variables. Moreover, no consistent numerical
istinguishing between placebo and the other 3 treatments could be
d in these data.

rast to the other 5 investigators, Dr. Cohen was able to distin-
etween placebo and the 3 "active" treatments and among the 3
" treatments. Analysis of Dr. Cohen's data revealed the combina-
be statistically significantly superior ($P \leq .05$) to phenylpro-
ine, phenylephrine, and placebo for all of the efficacy variables:
ose, stuffy nose, sneezing, and nasal airway resistance.

effects across all 6 studies were minimal with respect to severity
quency. Fifty-three percent (10/19) of the patients who reported
effects were on placebo, and these patients accounted for 12 out
23 reported adverse effects.

und

spects of the protocol that are pertinent to statistical analysis
are reviewed in this section. A copy of the protocol is included
chment A for completeness.

AHP1-REG-048-0015112

Table I

Summary of Patients Lost to Efficacy Analyses

Study No.	Patient No.	Treatment Group	Time of Exclusion	Protocol Violation
0402	13	Phenylpropanolamine	48 hours	Administrative
	21	Phenylephrine	48 hours	Broke bottle*
0403	2	Placebo	48 hours	Took excluded medication
	15	Combination	24 hours	Medication not taken correctly
	31	Placebo	48 hours	Took excluded medication
0405	1	Combination	24 hours	Medication not taken correctly
	2	Placebo	24 hours	Medication not taken correctly
	13	Placebo	72 hours	Took excluded medication
	18	Phenylephrine	48 hours	Adverse effect
	20	Phenylephrine	24 hours	Medication not taken correctly
	42	Combination	24 hours	Broke bottle
0406	23	Combination	48 hours	Developed bronchitis and placed on other medication

*Dropped from study.

AHP1-REG-048-0015113

corrections and/or clarification were returned to the Medical Monitor. These problem data item requests and the dates resolved were documented. Following the resolution of problem data items, the data were keypunched directly from the CRFs. Keypunch errors were corrected at time of verification. Further confirmation of data item completeness and accuracy was achieved by computer aided editing procedures. A 10% random sample of data records was then selected for estimation of the data base accuracy. Each card in the 10% sample was checked against the CRF. No keypunch errors were found. The data was then turned over to the statistician for analysis.

III. Results

A. Patient Accountability

Patient accountability for this clinical trial was very good. According to the protocol, 6 investigators were to enroll 12 patients in each of 4 treatment groups for a total of 288 patients. Two hundred seventy-four patients were actually enrolled into the study, and 5 investigators enrolled at least 12 patients per treatment group. At the end of the 72-hour study period, only 12 patients had been lost to efficacy analyses (Table I). These 12 patients were included in efficacy analyses up to the point of their protocol violation. Table I summarizes the times and reasons for the exclusion from efficacy analyses for the patients. Tables which summarize accountability for all patients are included in Attachment E.

B. Treatment Group Comparability

Randomization of patients within each study resulted in treatment groups which were essentially comparable with respect to demographic characteristics, smoking habits, and baseline severity of disease. There were substantial differences with respect to average age seen by investigators, but treatment groups were reasonably well balanced within each study. A wide majority of the patients enrolled by each investigator did not smoke. Overall, 73.4% of the patients in the clinical trial were nonsmokers. Attachment F contains tables which show treatment group comparability for relevant variables. Attachment I contains enrollment raw data listings for each patient in each treatment group for each investigator.

C. Efficacy

Subjective parameters of major interest were evaluations of runny nose, stuffy nose, sneezing, and headache by patients at baseline, 24, 48 and 72 hours and by investigators at baseline and 72 hours. The following 4-point rating scale was used as a basis for the evaluation: not present (0), mild (1), moderate (2), and marked (3). In addition, subjective global evaluations of response to therapy were made at 72 hours by patients and investigators. Patients evaluated the benefit derived from therapy according to the following 4-point scale: marked benefit (1), moderate benefit (2), minimal benefit (3), and no benefit (4). Responses from investigators' evaluations of overall therapeutic effect of study medication were based

AHP1-REG-048-0015114

I. SUMMARY

The objective of this randomized, double-blind, placebo-controlled, clinical trial of 3-days duration with adult patients with acute rhinitis due to upper respiratory infection (URI) was to assess the efficacy and safety of the following treatments:

1. Placebo, q4h,
2. Phenylpropanolamine, 25 g/5 ml, q4h,
3. Phenylephrine, 10 mg/5 ml, q4h, and
4. Combination (phenylpropanolamine, 12.5 mg, plus phenylephrine, 5 mg) 5 ml, q4h.

Phenylephrine and phenylpropanolamine are vasoconstrictors which produce a decongestant effect in the nasal pasages through direct and indirect modes of action, respectively.

Primary emphasis was placed on determining whether the combination of decongestants is at least equivalent in therapeutic effect to either decongestant alone. Six investigators enrolled 274 patients and collected data based on evaluation of runny nose, stuffy nose, sneezing, headache, and overall therapeutic effect. Data from 1 investigator, Dr. Burton M. Cohen, were analyzed separately since treatment groups from his study did not respond in the same manner as those from the other 5 investigators and since Dr. Cohen was the only investigator who also measured nasal airway resistance. Efficacy data from the other 5 investigators were pooled for analysis.

Analyses of the pooled data from the 5 investigators other than Dr. Cohen revealed no significant difference among the treatment groups for any of the subjective efficacy variables. Moreover, no consistent numerical trend distinguishing between placebo and the other 3 treatments could be detected in these data.

In contrast to the other 5 investigators, Dr. Cohen was able to distinguish between placebo and the 3 "active" treatments and among the 3 "active" treatments. Analysis of Dr. Cohen's data revealed the combination to be statistically significantly superior ($P \leq .05$) to phenylpropanolamine, phenylephrine, and placebo for all of the efficacy variables: runny nose, stuffy nose, sneezing, and nasal airway resistance.

Adverse effects across all 6 studies were minimal with respect to severity and frequency. Fifty-three percent (10/19) of the patients who reported adverse effects were on placebo, and these patients accounted for 12 out of the 23 reported adverse effects.

II. Background

Those aspects of the protocol that are pertinent to statistical analysis of data are reviewed in this section. A copy of the protocol is included in Attachment A for completeness.

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on the following 5-point scale: marked (1), moderate (2), minimal (3), unchanged (4), and worse (5). One investigator, Dr. Burton M. Cohen (study 0401), also measured an objective parameter, nasal airway resistance over the 4-hour period following administration of the initial dose of study medication.

Attachment J contains raw data listings for all subjective efficacy parameters for individual patients in each treatment group for each investigator.

In the following discussion the terms pooled data and combined studies refer to the 5 investigators excluding Dr. Cohen. The results of primary interest are those for Dr. Cohen's study and for the combined studies. However, for the sake of completeness, results have also been included in Attachment G for each study separately and for all 6 pooled studies.

1. Investigators' and Patients' Subjective Global Evaluations of Therapeutic Effect

   Investigators' 72-hour evaluations of overall therapeutic effect are summarized in Table II and Figure 1. Table II lists means, standard errors of the mean (S.E.M.), and the number of observations (n) for each treatment group within each investigator. These statistics are graphically depicted in Figure 1. As can be seen in Figure 1, there was an apparent treatment by investigator interaction in that treatment responses in Dr. Cohen's study (0401) did not follow the same pattern as for the other studies. Only in Dr. Cohen's study was the mean score for the combination group markedly lower than those of the other 3 treatment groups with the mean scores for phenylpropanolamine and phenylephrine substantially lower than that of placebo. A statistically significant treatment by investigator interaction was found by analysis of variance when data from all studies were pooled ($P \leq .0300$) but not when study 0401 was excluded ($P \leq .9200$). Therefore data from Dr. Cohen's study were analyzed separately, and the data from the other 5 studies were pooled for analysis. Analysis of the investigator's global evaluation in study 0401 was carried out by the use of Analysis of Variance and the Kruskal-Wallis Rank Sum test followed by Dunn's multiple comparison procedure. The nonparametric procedures (Kruskal-Wallis and Dunn) were performed on these data because of the apparent departure from the assumption of homogeneity of variance in that all of the scores for the combination group were the same, i.e., marked improvement. Comparisons based on ANOVA and Dunn's procedure both found highly significant differences in favor of the combination when compared to phenylpropanolamine ($P \leq .0001$), phenylephrine ($P \leq .0001$), and placebo ($P \leq .0001$). In addition the results from the ANOVA showed phenylephrine ($P \leq .0009$) and phenylpropanolamine ($P \leq .0009$) to be statistically significantly superior to placebo. Dunn's procedure showed these to be significant at a slightly lower level. Phenylephrine and phenylpropanolamine were virtually identical.

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Table II

Summary of Investigators' 72-Hour Global Evaluations of Therapeutic Effect[a]

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
Study 0401				
Mean	2.83	2.25	2.25	1.00
S.E.M.	0.11	0.13	0.18	0.00
n	12	12	12	12
Study 0402				
Mean	2.50	2.00	1.80	3.00
S.E.M.	0.22	0.77	0.58	0.63
n	6	5	5	5
Study 0403				
Mean	2.50	2.08	2.25	2.00
S.E.M.	0.43	0.38	0.46	0.23
n	10	12	12	11
Study 0404				
Mean	3.00	2.42	2.92	3.00
S.E.M.	0.46	0.36	0.35	0.25
n	12	12	13	13
Study 0405				
Mean	2.17	2.23	2.17	2.50
S.E.M.	0.27	0.32	0.24	0.34
n	12	13	12	10
Study 0406				
Mean	2.46	2.36	2.58	3.00
S.E.M.	0.14	0.31	0.26	0.28
n	13	14	12	12
All Except 0401				
Mean	2.53	2.25	2.43	2.69
S.E.M.	0.15	0.16	0.16	0.14
n	53	56	54	51
All Studies Combined				
Mean	2.58	2.25	2.39	2.37
S.E.M.	0.13	0.14	0.14	0.14
n	65	68	66	63

[a]Code for scale: 1 = marked, 2 = moderate, 3 = minimal, 4 = unchanged, 5 = worse.

AHP1-REG-048-0015117

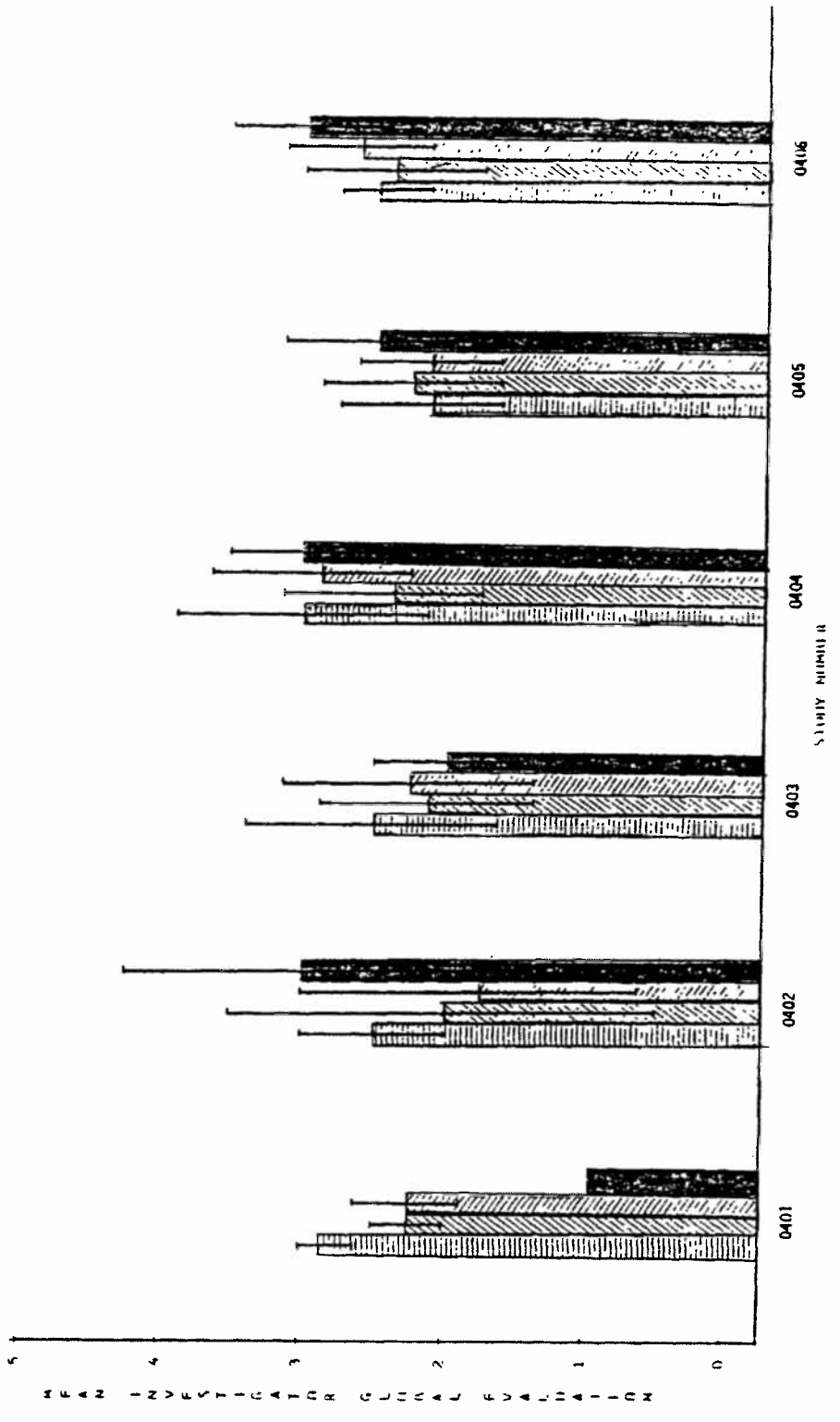
FIGURE 1

AHR-4010-3 DIMETAPP PRINCIPAL 04

GRAPH OF MEAN GLOBAL EVALUATION SCORES FOR EACH STUDY AND TREATMENT GROUP

VERTICAL LINES REPRESENT INTERVALS (IF PLUS AND MINUS TWO STANDARD ERRORS OF THE MEAN
EVALUATION CODE FOR THERAPEUTIC EFFECT 1=MARKED 2=MODERATE 3=MINIMAL 4=NO EFFECT 5=WORSE

PLACEBO = PHENYLPROPANOLAMINE = PHENYLEPHRINE = COMBINATION =



AHP1-REG-048-0015118

Table III

Summary of Analysis for Investigator's Evaluation of Overall Therapeutic Effect[a] at the End of 72 Hours for Study 0401

		Parametric Techniques	Nonparametric Techniques
1.	Test For Any Difference Among Treatment Groups	ANOVA	Kruskal-Wallis ANOVA By Ranks
		F-value = 38.61 df = (3,44) P-value = .0001	χ^2 = 31.08 df = 3 P-value = .0001
2.	Summary Measures	Mean Scores	Mean Rank Scores
	Placebo	2.83	37.58
	Phenylpropanolamine	2.25	27.38
	Phenylephrine	2.25	26.54
	Combination	1.00	6.50
3.	Treatment Comparisons	P-value[d]	P-value[e]
	Combination vs Placebo[b]	.0001	.0001
	Phenylephrine vs Placebo[b]	.0009	.0195
	Phenylpropanolamine vs Placebo[b]	.0009	.0282
	Combination vs Phenylephrine[b]	.0001	.0001
	Combination vs Phenylpropanolamine[b]	.0001	.0001
	Phenylephrine vs Phenylpropanolamine[c]	1.0000	.8762

[a] Code for Investigator's Global Evaluation of Therapeutic Effect: 1 = marked, 2 = moderate, 3 = minimal, 4 = unchanged, and 5 = worse.
[b] One-tailed P-values.
[c] Two-tailed P-values.
[d] P-values on contrasts obtained from ANOVA.
[e] P-values on Dunn's (1964) multiple comparison procedure using rank sums.

AHP1-REG-048-0015119

Analysis of variance of the pooled data (Attachment G) from the other 5 investigators revealed no statistically significant difference ($P \leq .1930$) among the treatment groups.

Data from patients' 72-hour evaluations of overall benefit of therapy are summarized in Table IV and Figure 2. These data parallel those from the investigators' global evaluations in every regard. In addition to the patients listed in Table I who were ineligible for analyses at 72 hours, patient number 11 in study 0401 and patient number 44 in study 0405 were not included in the analysis due to missing data. As shown in Attachment G, a statistically significant ($P<.0100$) treatment by investigator interaction was again found when data from all 6 investigators were pooled. This interaction was highly insignificant ($P \leq .5500$) for the pooled data from the 5 investigators with Dr. Cohen's data excluded. Hence, comparisons among treatment groups were done separately for Dr. Cohen's data.

As was the case for the investigator's global evaluation in study 0401, all of the patients on the combination reported having received the maximum benefit from therapy. Therefore, the nonparametric analog to ANOVA was also performed. Table V shows that both methods of analysis revealed the combination to be statistically superior ($P \leq .0002$) to phenylpropanolamine, phenylephrine, and placebo. In addition, the differences between phenylephrine and placebo and phenylpropanolamine and placebo were found to be highly significant by the parametric technique ($P \leq .0003$) and marginally statistically significant by the nonparametric technique ($P \leq .0200$).

For the pooled data from studies 0402-0406, no statistically significant difference among treatments ($P = .1000$) was found Attachment G.

2. Patients' and Investigators' Ratings of Symptoms of Acute Rhinitis

Because of the strong treatment by investigator interaction encountered in the global evaluation of therapeutic effect (Dr. Cohen's study differing from all others) and since this trend continued for other efficacy parameters, Dr. Cohen's study was again analyzed separately with data from all other investigators being pooled for analysis.

a. Runny Nose

Patients' and investigator's ratings of runny nose in Dr. Cohen's study are summarized in Tables VI and VII, respectively. The numerical superiority of the combination group throughout the 3-day study is graphically displayed in Figure 3. Table VIII summarizes the results from the statistical analysis for study 0401. Treatment

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Table IV

Summary of Patients' 72-Hour Evaluations of Overall Therapeutic Effect[a]

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
Study 0401				
Mean	3.00	2.25	2.25	1.00
S.E.M.	0.17	0.13	0.18	0.00
n	12	12	12	11
Study 0402				
Mean	2.25	1.80	2.00	3.00
S.E.M.	0.22	0.58	0.55	0.63
n	6	5	5	5
Study 0403				
Mean	2.90	2.33	2.08	2.18
S.E.M.	0.28	0.28	0.29	0.26
n	10	12	12	11
Study 0404				
Mean	2.75	2.33	2.69	2.92
S.E.M.	0.37	0.33	0.29	0.21
n	12	12	13	13
Study 0405				
Mean	2.33	2.46	2.42	2.33
S.E.M.	0.28	0.24	0.29	0.37
n	12	13	12	9
Study 0406				
Mean	2.38	2.21	2.50	2.92
S.E.M.	0.14	0.24	0.23	0.23
n	13	14	12	12
All Except 0401				
Mean	2.57	2.29	2.39	2.66
S.E.M.	0.12	0.13	0.13	0.14
n	53	56	54	50
All Studies Combined				
Mean	2.65	2.28	2.36	2.36
S.E.M.	0.11	0.11	0.11	0.14
n	65	68	66	61

[a]Code for scale: 1 = marked, 2 = moderate, 3 = minimal, and 4 = none.

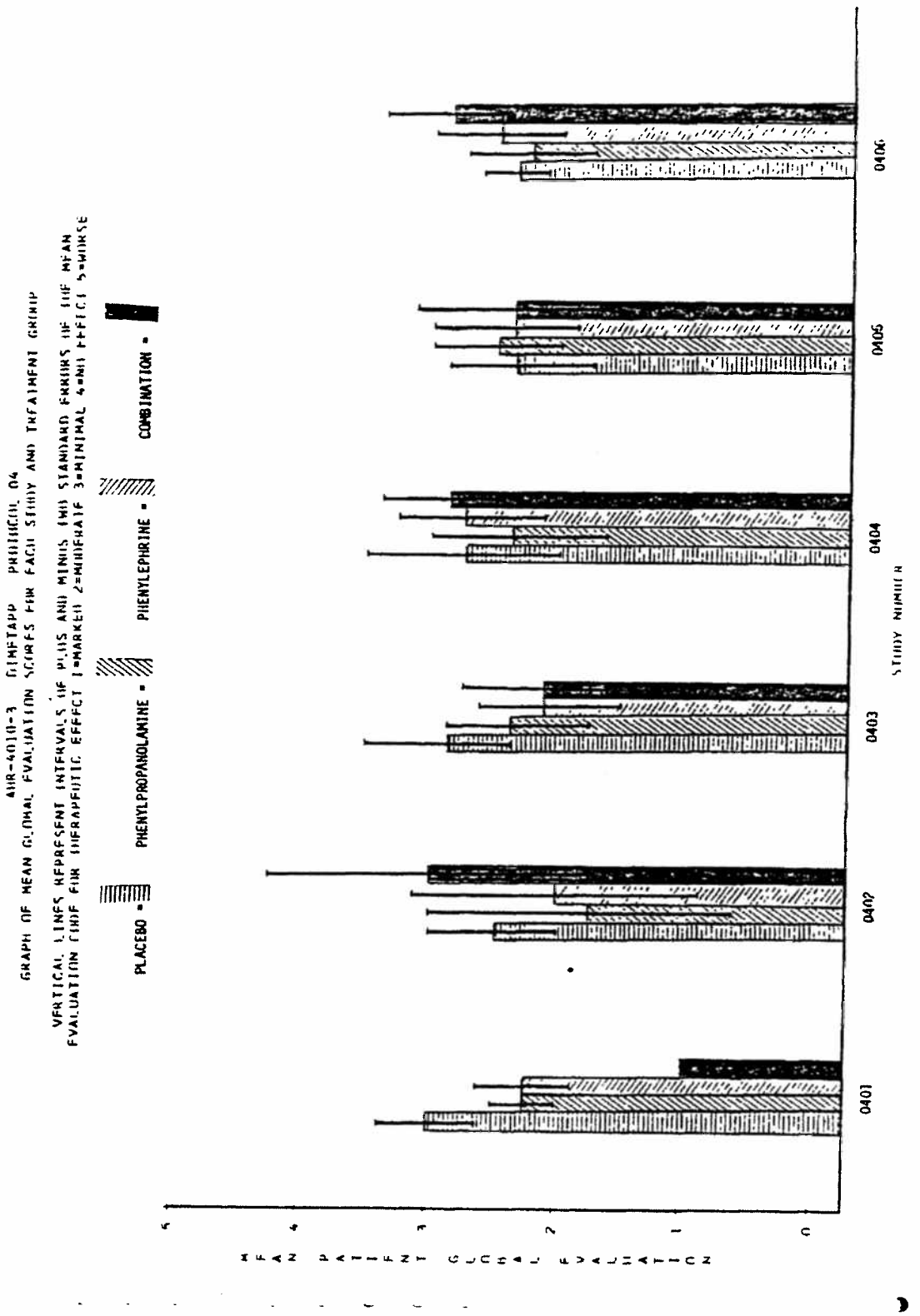
AHP1-REG-048-0015121

FIGURE 2

AHR-6010-3 CIMETAPP PHYSICIAN 04

GRAPH OF MEAN GLOBAL EVALUATION SCORES FOR EACH STUDY AND TREATMENT GROUP

VERTICAL LINES REPRESENT INTERVALS OF PLUS AND MINUS ONE STANDARD ERRORS OF THE MEAN
EVALUATION CODE FOR THERAPEUTIC EFFECT 1=MARKED 2=MODERATE 3=MINIMAL 4=NO EFFECT 5=WORSE



AHP1-REG-048-0015122

Table V

Summary of Analysis for Patients' Evaluations of Overall Therapeutic Effect[a] at the End of 72 Hours for Study 0401

		Parametric Techniques	Nonparametric Techniques
1.	Test For Any Difference Among Treatment Groups	ANOVA	Kruskal-Wallis ANOVA By Ranks
		F-value = 32.02 df = (3,43) P-value = .0001	χ^2 = 30.15 df = 3 P-value = .0001
2.	Summary Measures	Mean Scores	Mean Rank Scores
	Placebo	3.00	37.00
	Phenylpropanolamine	2.25	26.13
	Phenylephrine	2.25	25.38
	Combination	1.00	6.00
3.	Treatment Comparisons	P-value[d]	P-value[e]
	Combination vs Placebo[b]	.0001	.0001
	Phenylephrine vs Placebo[b]	.0003	.0135
	Phenylpropanolamine vs Placebo[b]	.0003	.0193
	Combination vs Phenylephrine[b]	.0001	.0002
	Combination vs Phenylpropanolamine[b]	.0001	.0001
	Phenylephrine vs Phenylpropanolamine[c]	1.0000	.8865

[a] Code for Patients' Global Evaluation of Therapeutic Effect: 1 = marked, 2 = moderate, 3 = minimal, and 4 = none.
[b] One-tailed P-values.
[c] Two-tailed P-values.
[d] P-values based on contrasts obtained from ANOVA.
[e] P-values based on Dunn's (1964) multiple comparison procedure using rank sums.

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comparisons for patients' rating at 72 hr revealed statistically significant differences in favor of the combination when compared to phenylpropanolamine ($P \leq .0008$), phenylephrine ($P \leq .0015$), and placebo ($P \leq .0001$). Phenylephrine and phenylpropanolamine did not exhibit a significantly lower severity of runny nose at 72 hours when compared with placebo. The results based on the investigator's rating at 72 hr were practically identical to those for the patients' rating. As shown in Table VIII the mean severity of runny nose for the combination was statistically significantly lower than that for phenylpropanolamine ($P \leq .0062$), phenylephrine ($P \leq .0018$), and placebo ($P \leq .0001$). Phenylpropanolamine and phenylephrine were again not significantly different from placebo. The data for patients' and investigator's ratings of runny nose pooled from studies 0402-0406 are summarized in Tables VI and VII, respectively. Treatment group mean scores for runny nose data pooled from the other 5 investigators are plotted across the 3-day treatment period in Figure 4. The graph of these data does not display trends or differences among treatments as data for Dr. Cohen (Figure 3). Results from Analysis of Variance for the pooled data (Attachment G) revealed no significant difference among the treatment groups for the 72 hr rating of runny nose by patients ($P \leq .5900$) or investigators ($P \leq .1900$).

b. Patients' and Investigators' Ratings for Stuffy Nose

Data for patients' and investigators' ratings of severity of stuffy nose are summarized in Tables IX and X respectively and are very similar to those obtained for runny nose.

Dr. Cohen's results for stuffy nose were very similar to those for runny nose. The numerical superiority of the combination group is again demonstrated throughout the 3-day period (especially at 48 hr) as displayed in Figure 5. Results from statistical analysis of patients' 72-hr data (Table XI) showed the combination to have statistically significant lower severity of stuffy nose than phenylpropanolamine ($P \leq .0010$) and placebo ($P \leq .0001$). The mean severity for phenylephrine was also significantly lower ($P \leq .0003$) than that of placebo, whereas that for phenylpropanolamine was not ($P \leq .1569$). Dr. Cohen's rating of stuffy nose at 72 hr revealed statistically significant differences in favor of the combination versus phenylpropanolamine ($P \leq .0001$), phenylephrine ($P \leq .0001$), and placebo ($P \leq .0001$). Strong trends ($P \leq .1000$) in favor of phenylephrine and phenylpropanolamine were also found when compared with placebo.

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TABLE VI

SUMMARY OF PATIENT RATING OF RUNNY NOSE
FOR ALL PATIENTS ELIGIBLE FOR EFFICACY ANALYSIS
PATIENT SCALE: 0=NONE 1=MILD 2=MODERATE 3=SEVERE

STUDY	TREATMENT GROUP	BASELINE MEAN	BASELINE STD ERR OF MEAN	BASELINE N	DAY 1 MEAN	DAY 1 STD ERR OF MEAN	DAY 1 N	DAY 2 MEAN	DAY 2 STD ERR OF MEAN	DAY 2 N	DAY 3 MEAN	DAY 3 STD ERR OF MEAN	DAY 3 N
401	PLACEBO	2.33	0.14	12	2.17	0.11	12	1.83	0.11	12	1.50	0.15	12
	PHENYLPROPANOLAMINE	2.33	0.19	12	2.00	0.12	12	1.92	0.08	12	1.33	0.14	12
	PHENYLEPHRINE	2.08	0.15	12	1.92	0.15	12	1.58	0.15	12	1.25	0.13	12
	COMBINATION	2.33	0.14	12	1.67	0.14	12	1.25	0.18	12	0.58	0.15	12
402	PLACEBO	1.33	0.42	6	1.33	0.42	6	0.83	0.31	6	0.67	0.21	6
	PHENYLPROPANOLAMINE	1.67	0.33	6	1.50	0.22	6	0.60	0.24	5	0.60	0.40	5
	PHENYLEPHRINE	2.33	0.33	6	2.00	0.26	6	0.80	0.37	5	0.40	0.24	5
	COMBINATION	1.20	0.58	5	1.00	0.45	5	1.00	0.63	5	1.00	0.45	5
403	PLACEBO	1.75	0.28	12	1.67	0.33	12	0.80	0.25	10	0.70	0.26	10
	PHENYLPROPANOLAMINE	1.25	0.25	12	0.83	0.21	12	0.92	0.23	12	0.67	0.22	12
	PHENYLEPHRINE	2.08	0.19	12	1.50	0.19	12	1.08	0.23	12	1.08	0.31	12
	COMBINATION	1.83	0.27	12	1.45	0.25	11	0.73	0.27	11	0.45	0.21	11
404	PLACEBO	3.00	0.00	12	2.58	0.19	12	2.08	0.29	12	2.08	0.29	12
	PHENYLPROPANOLAMINE	3.00	0.00	12	2.25	0.22	12	1.75	0.28	12	1.33	0.33	12
	PHENYLEPHRINE	2.85	0.10	13	2.69	0.13	13	2.23	0.26	13	1.92	0.31	13
	COMBINATION	3.00	0.00	13	2.77	0.12	13	2.31	0.24	13	2.00	0.25	13
405	PLACEBO	2.00	0.00	14	1.15	0.25	13	1.38	0.29	13	0.75	0.28	12
	PHENYLPROPANOLAMINE	2.23	0.20	13	1.00	0.23	13	0.92	0.24	13	0.77	0.23	13
	PHENYLEPHRINE	2.21	0.11	14	1.77	0.20	13	1.50	0.23	12	1.17	0.27	12
	COMBINATION	2.09	0.09	11	0.90	0.28	10	1.10	0.31	10	0.80	0.25	10
406	PLACEBO	1.77	0.20	13	1.38	0.21	13	1.08	0.21	13	0.77	0.17	13
	PHENYLPROPANOLAMINE	1.93	0.13	14	1.50	0.20	14	1.21	0.19	14	0.71	0.13	14
	PHENYLEPHRINE	2.00	0.12	12	1.50	0.19	12	1.17	0.21	12	0.75	0.22	12
	COMBINATION	1.85	0.15	13	1.69	0.24	13	1.42	0.26	12	0.83	0.27	12
ALL EXCEPT 401	PLACEBO	2.04	0.11	57	1.64	0.14	56	1.30	0.13	54	1.04	0.13	53
	PHENYLPROPANOLAMINE	2.05	0.11	57	1.40	0.12	57	1.14	0.12	56	0.86	0.11	56
	PHENYLEPHRINE	2.30	0.08	57	1.89	0.10	56	1.44	0.13	54	1.17	0.14	54
	COMBINATION	2.11	0.11	54	1.69	0.14	52	1.39	0.15	51	1.06	0.14	51
ALL COMBINED	PLACEBO	2.09	0.09	69	1.74	0.12	68	1.39	0.11	66	1.12	0.11	65
	PHENYLPROPANOLAMINE	2.10	0.10	69	1.51	0.10	69	1.28	0.10	68	0.93	0.10	68
	PHENYLEPHRINE	2.26	0.07	69	1.98	0.09	68	1.47	0.11	66	1.18	0.12	66
	COMBINATION	2.15	0.10	66	1.69	0.12	64	1.37	0.13	63	0.97	0.12	63

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CONFIDENTIAL

TABLE VII

SUMMARY OF INVESTIGATOR RATING OF RUNNY NOSE
FOR ALL PATIENTS ELIGIBLE FOR EFFICACY ANALYSIS
RATING SCALE: 0=NONE 1=MILD 2=MODERATE 3=SEVERE

STUDY	TREATMENT CODE	BASELINE MEAN	BASELINE STD ERR OF MEAN	BASELINE N	DAY 3 MEAN	DAY 3 STD ERR OF MEAN	DAY 3 N
601	PLACEBO	2.17	0.11	12	1.33	0.14	12
	PHENYLPROPANOLAMINE	2.08	0.15	12	1.17	0.17	12
	PHENYLEPHRINE	2.00	0.17	12	1.25	0.13	12
	COMBINATION	1.92	0.15	12	0.58	0.15	12
602	PLACEBO	1.33	0.42	6	0.67	0.21	6
	PHENYLPROPANOLAMINE	1.50	0.34	6	0.60	0.40	5
	PHENYLEPHRINE	2.17	0.33	6	0.60	0.24	5
	COMBINATION	1.20	0.58	5	1.00	0.45	6
603	PLACEBO	1.75	0.30	12	0.75	0.25	12
	PHENYLPROPANOLAMINE	1.75	0.25	12	0.42	0.15	12
	PHENYLEPHRINE	2.08	0.19	12	1.08	0.31	12
	COMBINATION	1.83	0.27	12	0.36	0.15	11
604	PLACEBO	2.92	0.08	12	2.08	0.26	12
	PHENYLPROPANOLAMINE	3.00	0.00	12	1.33	0.33	12
	PHENYLEPHRINE	2.92	0.08	13	1.62	0.31	13
	COMBINATION	3.00	0.00	11	2.00	0.25	11
605	PLACEBO	2.86	0.07	14	0.11	0.20	13
	PHENYLPROPANOLAMINE	2.15	0.22	11	0.73	0.17	11
	PHENYLEPHRINE	2.21	0.11	14	0.92	0.26	13
	COMBINATION	2.08	0.08	11	0.60	0.22	10
606	PLACEBO	1.77	0.20	11	0.77	0.20	11
	PHENYLPROPANOLAMINE	1.93	0.13	14	0.79	0.19	14
	PHENYLEPHRINE	2.00	0.12	12	0.65	0.22	12
	COMBINATION	1.85	0.15	11	0.75	0.22	12
ALL EXCEPT 604	PLACEBO	2.06	0.11	51	1.04	0.11	56
	PHENYLPROPANOLAMINE	1.92	0.12	57	0.60	0.12	56
	PHENYLEPHRINE	1.93	0.08	57	1.01	0.14	56
	COMBINATION	2.11	0.11	55	0.90	0.14	51
ALL COMBINED	PLACEBO	2.06	0.09	68	1.09	0.11	68
	PHENYLPROPANOLAMINE	2.03	0.10	69	0.77	0.10	[illegible]
	PHENYLEPHRINE	[illegible]	0.07	69	1.31	0.12	77
	COMBINATION	2.07	0.10	61	0.90	0.11	63

AHP1-REG-048-0015126

FIGURE 3

AHR-4010-3 DIMETAPP PROTOCOL 04
GRAPH OF MEAN SYMPTOM SCORE PLOTTED ACROSS TIME
RATING SCALE 0=NONE 1=MILD 2=MODERATE 3=SEVERE

AHP1-REG-048-0015127

FIGURE 4

AHR-4010-3 DIMETAPP PROTOCOL 04
GRAPH OF MEAN SYMPTOM SCORE PLOTTED ACROSS TIME
RATING SCALE 0=NONE 1=MILD 2=MODERATE 3=SEVERE

- ..... =PLACEBO
- - - - - - =PHENYLPROPANOLAMINE
- . - . - . =PHENYLEPHRINE
- ——— =COMBINATION

GROUP=ALL STUDIES EXCEPT 0401

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Table VIII

Comparisons of Treatment Group Mean[a] Scores for Patient's and Investigator's Subjective Evaluations[b] of Runny Nose for Study 0401

	Mean Patient's Evaluation of Runny Nose			Mean Investigator's Evaluation of Runny Nose
	24 Hours	48 Hours	72 Hours	72 Hours
Placebo [12][c]	2.03	1.93	1.41	1.34
Phenylpropanolamine [12]	1.87	1.98	1.25	1.18
Phenylephrine [12]	1.86	1.65	1.20	1.28
Combination [12]	1.53	1.34	0.49	0.64
Treatment Comparisons	P-Value[d]			
Combination vs Placebo	.0040	.0024	.0001	.0010
Phenylephrine vs Placebo	.1763	.0894	.1856	.3912
Phenylpropanolamine vs Placebo	.2020	.3823	.2481	.2311
Combination vs Phenylephrine	.0398	.0621	.0015	.0018
Combination vs Phenylpropanolamine	.0322	.0011	.0008	.0062
Phenylephrine vs Phenylpropanolamine	.9220	.1034	.8280	.6479

[a] Treatment group means are "Least Squares Means" from the SAS GLM computer procedure.
[b] Code for evaluation of runny nose;
[c] 0 = not present, 1 = mild, 2 = moderate, 3 = severe.
[d] Numbers within brackets indicate sample size.
[e] Unless noted otherwise, P-values are one-tailed.
Two-tailed P-values

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TABLE IX

SUMMARY OF PATIENT RATING OF STUFFY NOSE
FOR ALL PATIENTS ELIGIBLE FOR EFFICACY ANALYSIS
RATING SCALE: 0=NONE 1=MILD 2=MODERATE 3=SEVERE

		BASELINE			DAY 1			DAY 2			DAY 3		
STUDY	TREATMENT GROUP	MEAN	STD ERR OF MEAN	N	MEAN	STD ERR OF MEAN	N	MEAN	STD ERR OF MEAN	N	MEAN	STD ERR OF MEAN	N
401	PLACEBO	2.58	0.15	12	2.33	0.14	12	2.08	0.19	12	1.83	0.11	12
	PHENYLPROPANOLAMINE	2.75	0.13	12	2.17	0.11	12	1.83	0.17	12	1.67	0.14	12
	PHENYLEPHRINE	2.58	0.15	12	2.17	0.11	12	2.00	0.12	12	1.08	0.19	12
	COMBINATION	2.75	0.13	12	2.00	0.12	12	1.25	0.13	12	1.00	0.12	12
402	PLACEBO	2.17	0.17	6	1.67	0.33	6	1.17	0.31	6	0.83	0.31	6
	PHENYLPROPANOLAMINE	2.17	0.31	6	1.50	0.22	6	1.20	0.20	5	0.60	0.40	5
	PHENYLEPHRINE	1.83	0.17	6	1.67	0.33	6	0.60	0.40	5	0.40	0.24	5
	COMBINATION	1.80	0.20	5	1.40	0.40	5	1.20	0.37	5	1.00	0.45	5
403	PLACEBO	2.17	0.24	12	2.33	0.22	12	1.70	0.26	10	1.30	0.21	10
	PHENYLPROPANOLAMINE	1.83	0.17	12	1.50	0.19	12	1.17	0.11	12	0.58	0.19	12
	PHENYLEPHRINE	2.17	0.21	12	1.58	0.23	12	1.00	0.25	12	1.00	0.30	12
	COMBINATION	1.67	0.28	12	1.27	0.30	11	1.09	0.25	11	0.82	0.23	11
404	PLACEBO	3.00	0.00	12	2.58	0.19	12	2.17	0.30	12	2.08	0.29	12
	PHENYLPROPANOLAMINE	3.00	0.00	12	2.50	0.19	12	2.17	0.27	12	1.83	0.30	12
	PHENYLEPHRINE	3.00	0.00	13	2.77	0.12	13	2.38	0.21	13	2.15	0.27	13
	COMBINATION	3.00	0.00	13	3.00	0.00	13	2.69	0.13	13	2.31	0.21	13
405	PLACEBO	2.36	0.13	14	1.62	0.24	13	1.46	0.29	13	1.33	0.28	12
	PHENYLPROPANOLAMINE	2.38	0.14	13	1.31	0.21	13	1.15	0.22	13	1.15	0.30	13
	PHENYLEPHRINE	2.50	0.14	14	2.08	0.18	13	1.92	0.19	12	1.58	0.26	12
	COMBINATION	2.27	0.14	11	2.00	0.21	10	1.70	0.30	10	1.50	0.27	10
406	PLACEBO	1.85	0.15	13	1.46	0.18	13	1.08	0.21	13	0.77	0.17	13
	PHENYLPROPANOLAMINE	2.00	0.10	14	1.50	0.17	14	1.21	0.15	14	0.57	0.17	14
	PHENYLEPHRINE	1.58	0.15	12	1.42	0.15	12	1.25	0.13	12	0.83	0.17	12
	COMBINATION	1.77	0.20	13	1.77	0.20	13	1.33	0.22	12	1.17	0.27	12
ALL EXCEPT 401	PLACEBO	2.32	0.09	57	1.95	0.12	56	1.54	0.13	54	1.30	0.13	53
	PHENYLPROPANOLAMINE	2.28	0.08	57	1.67	0.10	57	1.39	0.10	56	0.98	0.13	56
	PHENYLEPHRINE	2.28	0.09	57	1.95	0.11	56	1.56	0.13	54	1.31	0.14	54
	COMBINATION	2.15	0.11	54	1.98	0.13	52	1.69	0.14	51	1.43	0.14	51
ALL COMBINED	PLACEBO	2.36	0.08	69	2.01	0.10	68	1.64	0.12	66	1.40	0.11	65
	PHENYLPROPANOLAMINE	2.36	0.07	69	1.75	0.09	69	1.47	0.09	68	1.10	0.12	68
	PHENYLEPHRINE	2.33	0.08	69	1.99	0.09	68	1.64	0.11	66	1.27	0.12	66
	COMBINATION	2.26	0.10	66	1.98	0.11	64	1.60	0.11	63	1.35	0.12	63

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TABLE X

SUMMARY OF INVESTIGATOR RATING OF STUFFY NOSE
FOR ALL PATIENTS ELIGIBLE FOR EFFICACY ANALYSIS
RATING SCALES: 0=NONE 1=MILD 2=MODERATE 3=SEVERE

STUDY	TREATMENT GROUP	BASELINE MEAN	BASELINE STD ERR OF MEAN	BASELINE N	DAY 1 MEAN	DAY 1 STD ERR OF MEAN	DAY 1 N
[illegible]	[illegible]	2.58	0.15	12	1.92	0.08	12
	[illegible]	2.50	0.15	12	1.67	0.14	12
	[illegible]	2.58	0.15	12	1.67	0.19	12
	[illegible]	2.50	0.15	12	0.92	0.08	12
[illegible]	[illegible]	2.17	0.17	6	0.83	0.31	6
	[illegible]	2.17	0.31	6	0.50	0.50	6
	[illegible]	1.83	0.11	6	0.50	0.34	6
	[illegible]	1.80	0.20	5	0.80	0.49	5
[illegible]	[illegible]	2.17	0.24	12	1.33	0.26	12
	[illegible]	1.83	0.17	12	0.50	0.19	12
	[illegible]	2.17	0.21	12	0.42	0.31	12
	[illegible]	1.58	0.26	12	0.33	0.19	12
[illegible]	[illegible]	3.00	0.00	12	2.00	0.20	12
	[illegible]	3.00	0.00	12	1.42	0.26	12
	[illegible]	3.00	0.00	13	2.15	0.27	13
	[illegible]	3.00	0.00	11	2.41	0.21	13
[illegible]	[illegible]	2.46	0.14	14	1.29	0.28	14
	[illegible]	2.50	0.14	14	0.85	0.27	13
	[illegible]	2.50	0.14	14	1.15	0.32	13
	[illegible]	2.25	0.13	12	1.00	0.00	10
[illegible]	[illegible]	1.85	0.15	14	0.85	0.10	14
	[illegible]	2.00	0.10	14	0.21	0.14	14
	[illegible]	1.50	0.15	12	1.00	0.25	12
	[illegible]	1.77	0.20	13	1.25	0.25	12
All [illegible]	[illegible]	2.10	0.05	57	1.40	0.14	56
	[illegible]	1.98	0.08	57	0.75	0.13	56
	[illegible]	2.08	0.05	57	1.16	0.14	56
	[illegible]	2.04	0.11	55	1.07	0.14	54
All [illegible]	[illegible]	2.07	0.08	60	1.41	0.11	58
	[illegible]	2.12	0.07	60	1.03	0.11	57
	[illegible]	2.11	0.08	60	1.18	0.11	57
	[illegible]	2.01	0.08	57	1.09	0.10	54

FIGURE 5

AHH-4010-3 DIMETAPP PROTOCOL 04
GRAPH OF MEAN SYMPTOM SCORE PLOTTED ACROSS TIME
RATING SCALE 0=NONE 1=MILD 2=MODERATE 3=SEVERE

- PLACEBO
- PHENYLPROPANOLAMINE
- PHENYLEPHRINE
- COMBINATION

GROUP=STUDY 0401

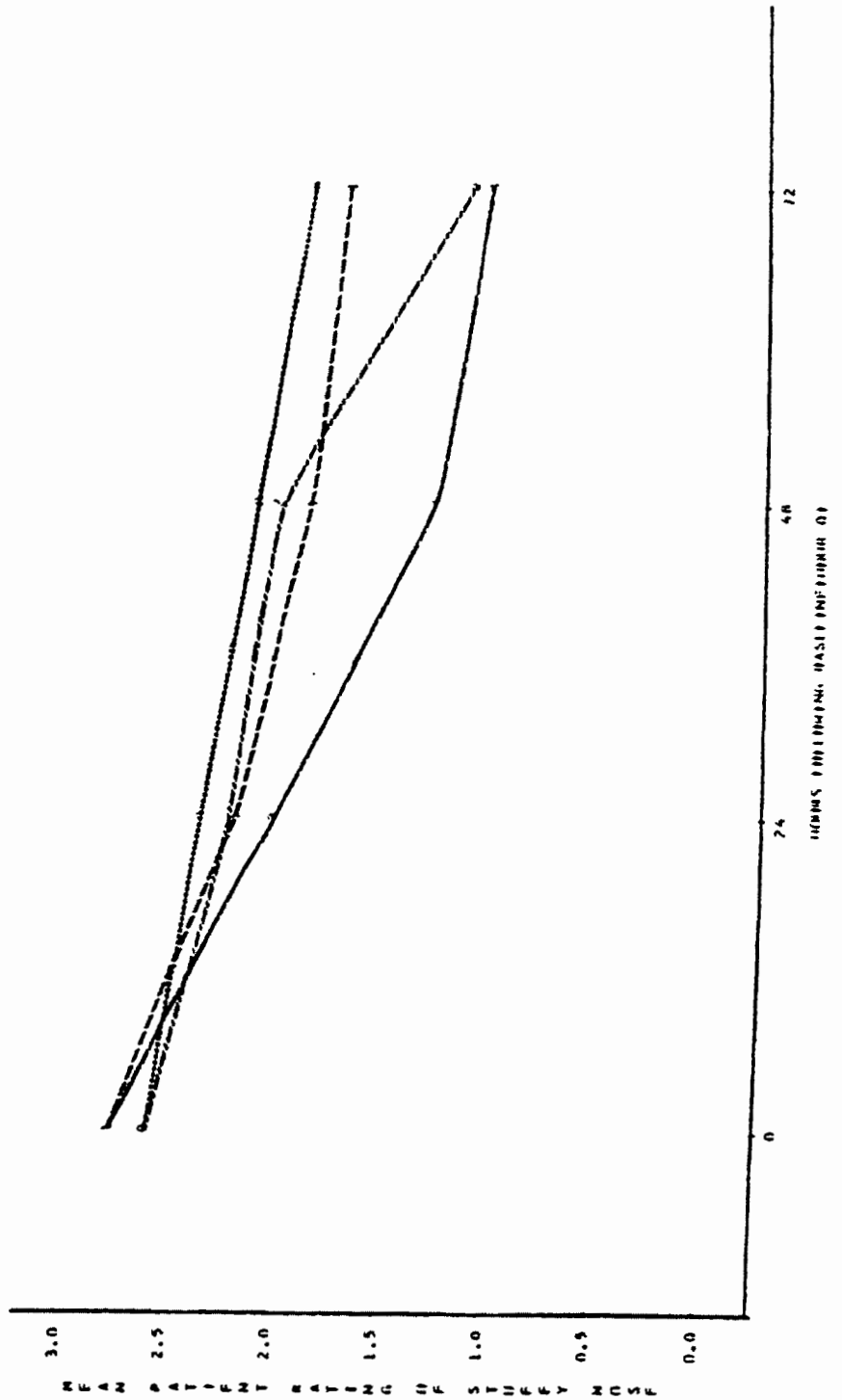

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FIGURE 6

AHR-4010-3 DIMETAPP PROTOCOL 04
GRAPH OF MEAN SYMPTOM SCORE PLOTTED ACROSS TIME
RATING SCALE 0=NONE 1=MILD 2=MODERATE 3=SEVERE
.....=PLACEBO
- - - - - =PHENYLPROPANOLAMINE
-.-.-.-.-=PHENYLEPHRINE
——.——=COMBINATION

GROUP=ALL STUDIES EXCEPT 0401

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Table XI

Comparisons of Treatment Group Mean[a] Scores for Patient's and Investigator's Subjective Evaluations[b] of Stuffy Nose for Study 0401.

	Mean Patient's Evaluation of Stuffy Nose			Mean Investigator's Evaluation of Stuffy Nose
	24 Hours	48 Hours	92 Hours	72 Hours
Placebo [12][c]	2.32	2.05	1.81	1.91
Phenylpropanolamine [12]	2.12	1.74	1.60	1.67
Phenylephrine [12]	2.15	1.97	1.06	1.66
Combination [12]	1.95	1.16	0.94	0.91
Treatment Comparisons	P-Values[d]			
Combination vs Placebo	.0203	.0001	.0001	.0001
Phenylephrine vs Placebo	.1687	.3477	.0003	.0936
Phenylpropanolamine vs Placebo	.1285	.0771	.1569	.1035
Combination vs Phenylephrine	.1285	.0003	.2720	.0001
Combination vs Phenylpropanolamine	.1687	.0043	.0010	.0001
Phenylephrine vs Phenylpropanolamine[e]	.8531	.2953	.0112	.9549

[a] Treatment group means are "Least Squares Means" from the SAS GLM computer procedure.
[b] Code for evaluation of stuffy nose;
0 = none, 1 = mild, 2 = moderate, 3 = severe.
[c] Numbers within brackets indicate sample size.
[d] Unless noted otherwise, P-values are one-tailed.
[e] Two-tailed P-values

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Stuffy nose data from the other 5 investigators are summarized in Table IX and Figure 6 for patients' evaluations and Table X for investigators' evaluations. As Figure 6 shows, there is a slight trend in favor of phenylpropanolamine for patients' evaluations of stuffy nose. However, no statistically significant ($P \leq .0500$) difference among treatment groups could be detected for the data pooled across studies 0402-0406.

c. Subjective Patients' and Investigators' Ratings of Sneezing

Data for patients' and investigators' ratings of sneezing are summarized at each evaluation time in Tables XII and XIII respectively. Plots of mean patients' ratings are shown in Figures 7 and 8 for Dr. Cohen's study and for the other studies combined respectively.

Dr. Cohen's data for patients' ratings of sneezing again exhibited trends demonstrating the superiority of the combination with placebo exhibiting the worst response (Figure 7). Statistical analysis of patients' 72-hr ratings of sneezing, Table XIV, showed the combination to have statistically significantly lower severity of sneezing than phenylpropanolamine ($P \leq .0001$), phenylephrine ($P \leq .0005$), and placebo ($P \leq .0002$). No statistically significant difference between phenylephrine or phenylpropanolamine and placebo were found. The numerical superiority of the combination is also reflected in the investigator's evaluation of sneezing. The mean sneezing score for the combination was again significantly lower than that of placebo ($P \leq .0038$) and marginally significantly lower than phenylpropanolamine ($P \leq .0283$). Phenylephrine was marginally significantly lower then placebo ($P \leq .0594$) where as no significant difference between phenylpropanolamine and placebo was detected.

Summarizations for sneezing data from the other 5 investigators are presented in Table XII and Figure 8 for patients' evaluations and in Table XIII for investigators' ratings. As shown in these data summaries and in the analysis of variance tables in Attachment G, treatment differences were not detected for either patients' or investigators' evaluations at the $\alpha = .05$ level of significance.

d. Patients' and Investigators' Subjective Ratings of Headaches

Summary tables for subjective ratings of headache by patients' and investigators' are presented in Tables XV and XVI respectively. Formal statistical analysis of these data were not performed due to the very mild severity of headache at baseline.

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TABLE XII

SUMMARY OF PATIENT RATING OF SNEEZING
FOR ALL PATIENTS ELIGIBLE FOR EFFICACY ANALYSIS
RATING SCALE: 0=NONE 1=MILD 2=MODERATE 3=SEVERE

STUDY	TREATMENT GROUP	BASELINE MEAN	BASELINE STD ERR OF MEAN	BASELINE N	DAY 1 MEAN	DAY 1 STD ERR OF MEAN	DAY 1 N	DAY 2 MEAN	DAY 2 STD ERR OF MEAN	DAY 2 N	DAY 3 MEAN	DAY 3 STD ERR OF MEAN	DAY 3 N
401	PLACEBO	2.08	0.15	12	2.00	0.21	12	1.75	0.13	12	1.33	0.22	12
	PHENYLPROPANOLAMINE	1.92	0.08	12	1.83	0.11	12	1.58	0.19	12	1.42	0.15	12
	PHENYLEPHRINE	1.83	0.11	12	1.50	0.15	12	1.33	0.22	12	1.17	0.17	12
	COMBINATION	2.08	0.15	12	1.75	0.13	12	0.83	0.11	12	0.42	0.15	12
402	PLACEBO	0.83	0.31	6	0.33	0.21	6	0.17	0.17	6	0.17	0.17	6
	PHENYLPROPANOLAMINE	2.33	0.33	6	1.33	0.33	6	1.00	0.32	5	0.60	0.40	5
	PHENYLEPHRINE	1.33	0.42	6	1.33	0.49	6	0.40	0.24	5	0.20	0.20	5
	COMBINATION	0.80	0.37	5	0.60	0.24	5	0.80	0.49	5	0.40	0.24	5
403	PLACEBO	1.08	0.23	12	0.92	0.19	12	0.40	0.16	10	0.40	0.22	10
	PHENYLPROPANOLAMINE	0.50	0.19	12	0.25	0.13	12	0.25	0.18	12	0.08	0.08	12
	PHENYLEPHRINE	1.50	0.29	12	0.75	0.25	12	0.67	0.24	12	0.75	0.30	12
	COMBINATION	1.08	0.29	12	0.82	0.26	11	0.36	0.20	11	0.09	0.09	11
404	PLACEBO	2.50	0.15	12	2.00	0.21	12	1.58	0.34	12	1.42	0.36	12
	PHENYLPROPANOLAMINE	2.33	0.14	12	1.67	0.19	12	1.33	0.26	12	0.92	0.31	12
	PHENYLEPHRINE	2.46	0.14	13	1.92	0.26	13	1.46	0.27	13	1.31	0.31	13
	COMBINATION	2.54	0.14	13	2.08	0.18	13	1.77	0.26	13	1.46	0.33	13
405	PLACEBO	2.00	0.15	14	0.85	0.22	13	0.92	0.29	13	0.42	0.19	12
	PHENYLPROPANOLAMINE	1.92	0.26	13	0.69	0.24	13	0.92	0.31	13	0.85	0.27	13
	PHENYLEPHRINE	1.86	0.14	14	1.15	0.25	13	1.00	0.21	12	0.58	0.19	12
	COMBINATION	1.82	0.23	11	1.20	0.36	10	0.90	0.31	10	0.70	0.26	10
406	PLACEBO	1.00	0.11	14	0.62	0.14	13	0.46	0.18	13	0.15	0.10	13
	PHENYLPROPANOLAMINE	0.86	0.10	14	0.57	0.17	14	0.21	0.11	14	0.00	0.00	14
	PHENYLEPHRINE	1.33	0.22	12	0.58	0.26	12	0.50	0.19	12	0.33	0.14	12
	COMBINATION	0.92	0.21	13	1.00	0.23	13	0.50	0.23	12	0.42	0.26	12
ALL EXCEPT 401	PLACEBO	1.56	0.11	57	1.00	0.11	56	0.78	0.13	54	0.55	0.12	53
	PHENYLPROPANOLAMINE	1.49	0.13	57	0.84	0.11	57	0.70	0.12	56	0.46	0.11	56
	PHENYLEPHRINE	1.75	0.11	57	1.14	0.14	56	0.87	0.12	54	0.70	0.12	54
	COMBINATION	1.52	0.14	54	1.23	0.13	52	0.90	0.14	51	0.67	0.14	51
ALL COMBINED	PLACEBO	1.65	0.10	69	1.18	0.11	68	0.95	0.12	66	0.69	0.11	65
	PHENYLPROPANOLAMINE	1.57	0.11	69	1.01	0.10	69	0.85	0.11	68	0.63	0.10	68
	PHENYLEPHRINE	1.77	0.09	69	1.21	0.12	68	0.95	0.11	66	0.79	0.11	66
	COMBINATION	1.62	0.12	66	1.33	0.11	64	0.89	0.12	63	0.62	0.11	63

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TABLE XIII

SUMMARY OF INVESTIGATOR RATING OF SNEEZING
FOR ALL PATIENTS ELIGIBLE FOR EFFICACY ANALYSIS
RATING SCALE: 0=NONE 1=MILD 2=MODERATE 3=SEVERE

STUDY	TREATMENT	BASELINE (DAY 0)			DAY 1		
		MEAN	STD DEV OF MEAN	N	MEAN	STD DEV OF MEAN	N
[illegible]	[illegible]	1.92	0.15	12	1.08	0.14	12
	PSEUDOEPHEDRINE AMINE	1.58	0.15	12	0.83	0.17	12
	PSEUDOEPHEDRINE	1.67	0.14	12	0.67	0.14	12
	COMBINATION	1.83	0.17	12	0.92	0.15	12
[illegible]	PLACEBO	0.83	0.31	6	0.17	0.17	6
	PSEUDOEPHEDRINE AMINE	2.33	0.33	6	0.50	0.50	6
	PSEUDOEPHEDRINE	1.33	0.42	6	0.20	0.20	5
	COMBINATION	0.60	0.24	5	0.40	0.24	5
[illegible]	PLACEBO	1.08	0.23	12	0.13	0.13	12
	PSEUDOEPHEDRINE AMINE	0.50	0.19	12	0.08	0.08	12
	PSEUDOEPHEDRINE	1.50	0.29	12	0.25	0.18	12
	COMBINATION	1.00	0.28	12	0.09	0.09	11
[illegible]	PLACEBO	2.25	0.13	12	1.42	0.46	12
	PSEUDOEPHEDRINE AMINE	2.41	0.14	12	0.92	0.11	12
	PSEUDOEPHEDRINE	2.41	0.11	11	1.18	0.41	11
	COMBINATION	2.54	0.14	11	1.45	0.41	11
[illegible]	PLACEBO	2.07	0.16	14	0.42	0.21	14
	PSEUDOEPHEDRINE AMINE	1.92	0.26	11	0.36	0.21	11
	PSEUDOEPHEDRINE	1.96	0.14	14	0.42	0.24	14
	COMBINATION	1.81	0.21	12	0.50	0.22	10
[illegible]	PLACEBO	1.00	0.11	14	0.21	0.12	14
	PSEUDOEPHEDRINE AMINE	0.86	0.10	14	0.00	0.00	14
	PSEUDOEPHEDRINE	1.14	0.22	14	0.29	0.14	14
	COMBINATION	0.92	0.21	14	0.17	0.11	12
ALL EVALUABLE [illegible]	PLACEBO	1.51	0.11	57	0.59	0.12	56
	PSEUDOEPHEDRINE AMINE	1.40	0.11	57	0.37	0.11	56
	PSEUDOEPHEDRINE	1.42	0.11	54	0.41	0.13	55
	COMBINATION	1.40	0.11	50	0.50	0.11	51
ALL [illegible]	PLACEBO	1.50	0.10	60	0.60	0.11	60
	PSEUDOEPHEDRINE AMINE	1.41	0.11	60	0.34	0.09	60
	PSEUDOEPHEDRINE	1.41	0.09	60	0.38	0.11	60
	COMBINATION	1.45	0.11	57	0.44	0.11	57

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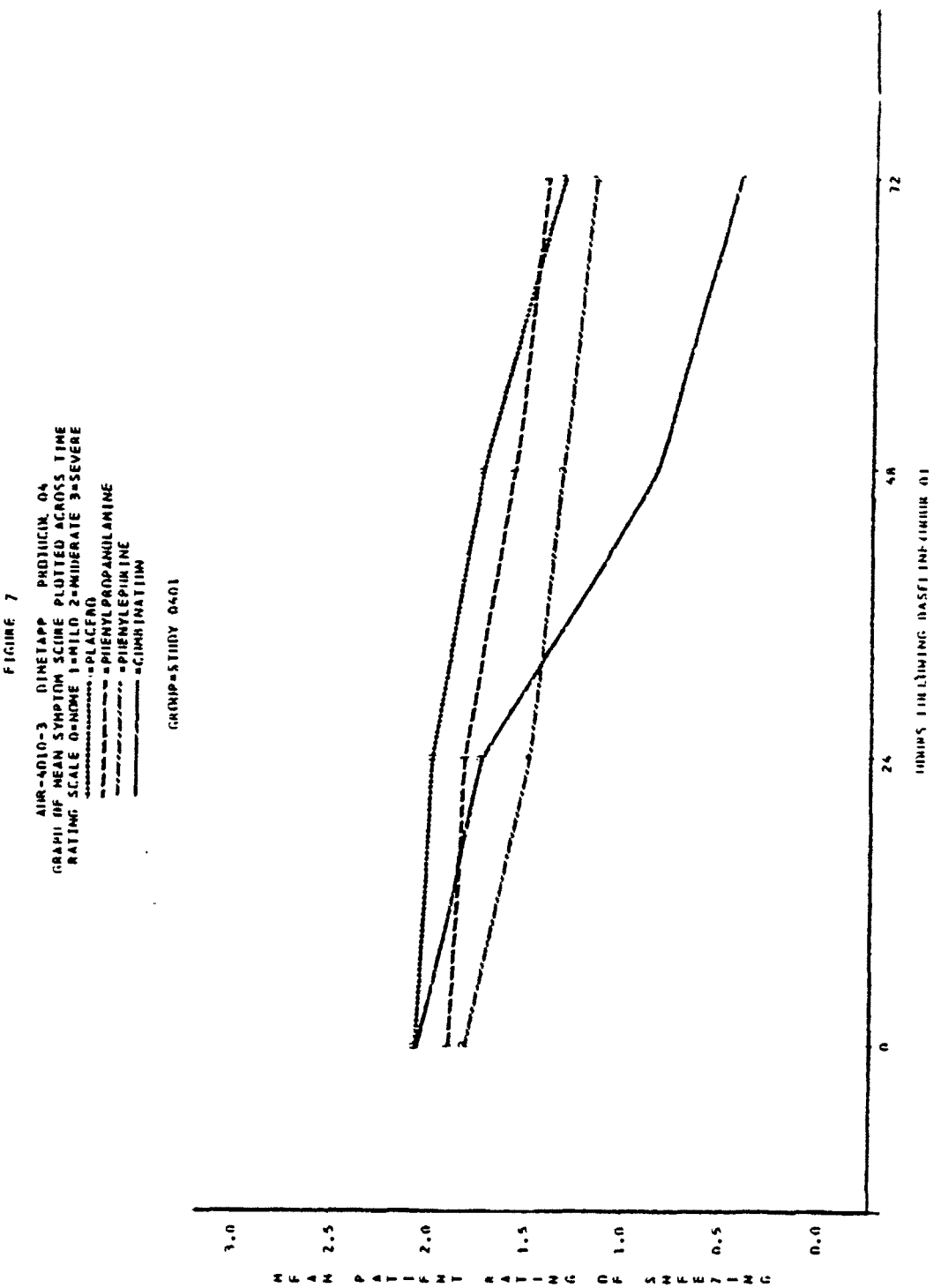

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FIGURE 8

AHR-4010-3 DIMETAPP PROTOCOL 04
GRAPH OF MEAN SYMPTOM SCORE PLOTTED ACROSS TIME
RATING SCALE 0=NONE 1=MILD 2=MODERATE 3=SEVERE

PLACEBO
PHENYLPROPANOLAMINE
PHENYLEPHRINE
COMBINATION

GRIMP=ALL STUDIES EXCEPT 0401

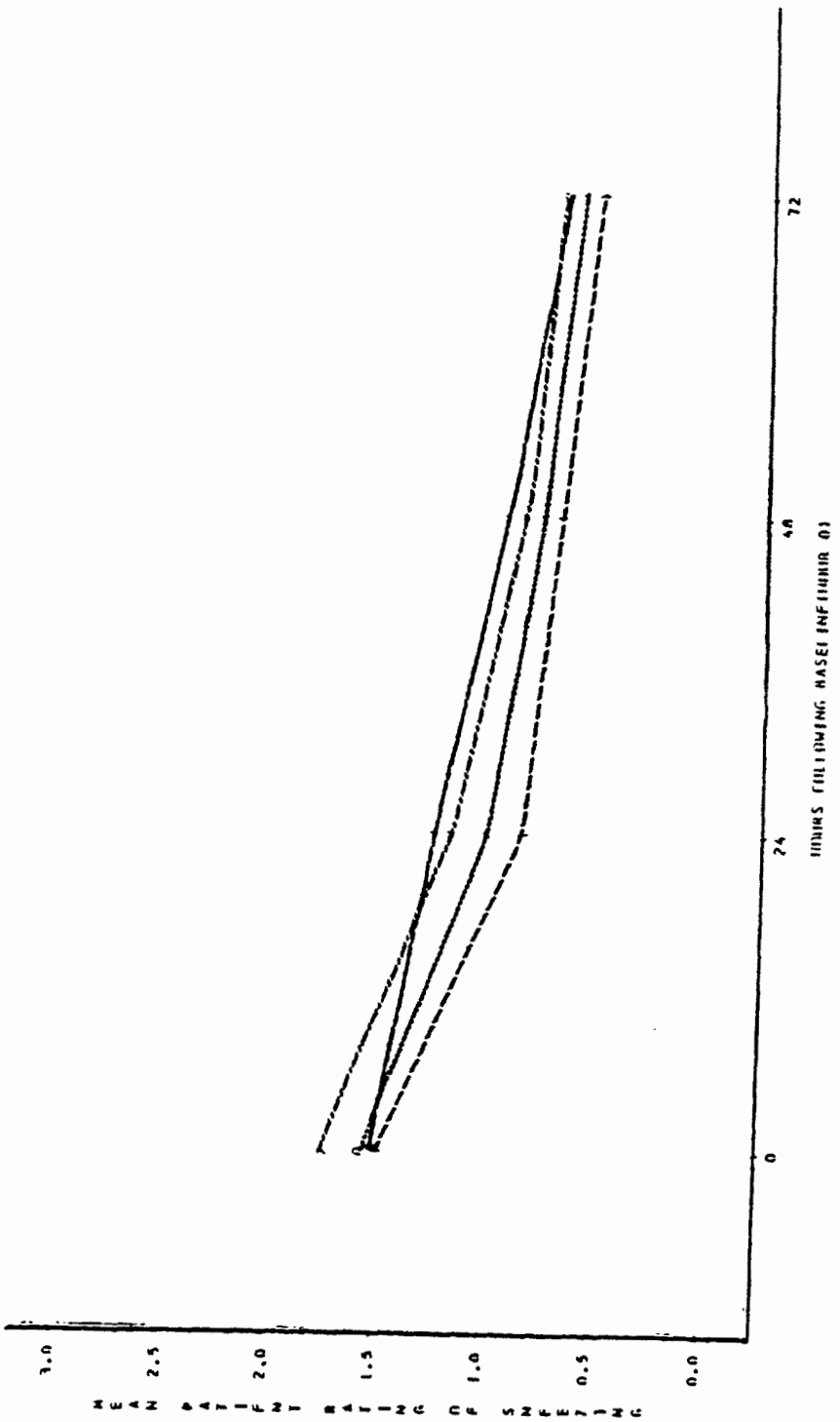

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Table XIV

Comparisons of Treatment Group Mean[a] Scores for Patient's[b] and Investigator's Subjective Evaluations of Sneezing for Study 0401

	Mean Patient's Evaluation of Sneezing			Mean Investigator's Evaluation of Sneezing
	24 Hours	48 Hours	72 Hours	72 Hours
Placebo [12][c]	1.92	1.63	1.27	1.08
Phenylpropanolamine [12]	1.87	1.45	1.41	0.88
Phenylephrine [12]	1.60	1.23	1.21	0.70
Combination [12]	1.67	0.71	0.35	0.42
Treatment Comparisons	P-Values[d]			
Combination vs Placebo	.0905	.0003	.0002	.0038
Phenylephrine vs Placebo	.0466	.0588	.4100	.0594
Phenylpropanolamine vs Placebo	.3872	.2334	.2715	.2093
Combination vs Phenylephrine	.3480	.0212	.0005	.1223
Combination vs Phenylpropanolamine	.1524	.0025	.0001	.0283
Phenylephrine vs Phenylpropanolamine[e]	.1511	.3812	.3947	.4305

[a] Treatment group means are "Least Squares Means" from the SAS GLM computer procedure.
[b] Code for evaluation of sneezing;
0 = none, 1 = mild, 2 = moderate, 3 = severe.
[c] Numbers within brackets indicate sample size.
[d] Unless noted otherwise, P-values are one-tailed.
[e] Two-tailed P-values

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TABLE XV

SUMMARY OF PATIENT PAIN OF DURATION
FOR ALL PATIENTS ELIGIBLE FOR EFFICACY ANALYSIS
PAIN SCALE: ZERO=0 TWELVE=12 HOURS=1 ASSESS

STUDY	TREATMENT GROUP	BASELINE MEAN	BASELINE STD ERR OF MEAN	BASELINE N	DAY 1 MEAN	DAY 1 STD ERR OF MEAN	DAY 1 N	DAY 2 MEAN	DAY 2 STD ERR OF MEAN	DAY 2 N	DAY 3 MEAN	DAY 3 STD ERR OF MEAN	DAY 3 N
401	PLACEBO	0.33	0.14	12	0.25	0.13	12	0.00	0.00	12	0.00	0.00	12
	PHENYLPROPANOLAMINE	0.33	0.14	12	0.17	0.11	12	0.00	0.00	12	0.00	0.00	12
	PHENYLEPHRINE	0.17	0.11	12	0.17	0.11	12	0.25	0.18	12	0.00	0.00	12
	COMBINATION	0.42	0.15	12	0.25	0.13	12	0.08	0.08	12	0.08	0.08	12
402	PLACEBO	1.17	0.48	6	1.00	0.45	6	0.17	0.17	6	0.17	0.17	6
	PHENYLPROPANOLAMINE	1.17	0.31	6	0.67	0.33	6	0.20	0.20	5	0.20	0.20	5
	PHENYLEPHRINE	0.50	0.34	6	0.50	0.34	6	0.40	0.24	5	0.00	0.00	5
	COMBINATION	0.00	0.00	5	0.00	0.00	5	0.00	0.00	5	0.20	0.20	5
403	PLACEBO	0.83	0.21	12	0.92	0.26	12	0.40	0.16	10	0.30	0.15	10
	PHENYLPROPANOLAMINE	0.92	0.23	12	0.67	0.22	12	0.50	0.19	12	0.42	0.19	12
	PHENYLEPHRINE	0.42	0.19	12	0.33	0.22	12	0.08	0.08	12	0.08	0.08	12
	COMBINATION	0.75	0.30	12	0.45	0.16	11	0.55	0.21	11	0.27	0.14	11
404	PLACEBO	2.17	0.24	12	1.58	0.29	12	1.17	0.34	12	1.08	0.44	12
	PHENYLPROPANOLAMINE	1.83	0.17	12	1.17	0.27	12	0.50	0.23	12	0.50	0.23	12
	PHENYLEPHRINE	1.69	0.17	13	1.15	0.27	13	1.08	0.41	11	0.92	0.26	13
	COMBINATION	1.85	0.15	13	1.62	0.24	13	0.92	0.29	13	0.92	0.31	13
405	PLACEBO	1.07	0.27	14	1.00	0.36	14	0.85	0.46	13	0.42	0.19	12
	PHENYLPROPANOLAMINE	1.41	0.31	13	0.77	0.28	13	0.69	0.29	13	0.54	0.29	13
	PHENYLEPHRINE	1.01	0.20	14	0.92	0.26	13	0.67	0.28	12	0.58	0.29	12
	COMBINATION	1.09	0.41	11	0.90	0.38	10	0.40	0.41	10	0.50	0.27	10
406	PLACEBO	0.62	0.21	13	0.54	0.18	13	0.14	0.10	14	0.15	0.10	14
	PHENYLPROPANOLAMINE	0.64	0.17	14	0.50	0.20	14	0.14	0.10	14	0.14	0.10	14
	PHENYLEPHRINE	0.75	0.22	12	0.67	0.22	12	0.58	0.19	12	0.29	0.13	12
	COMBINATION	0.54	0.18	13	0.62	0.21	13	0.31	0.14	12	0.08	0.08	12
ALL EXCEPT 401	PLACEBO	1.16	0.13	57	1.00	0.14	56	0.50	0.14	54	0.45	0.11	53
	PHENYLPROPANOLAMINE	1.16	0.12	57	0.75	0.12	57	0.43	0.10	56	0.38	0.10	56
	PHENYLEPHRINE	0.95	0.12	57	0.75	0.12	56	0.59	0.12	54	0.43	0.10	54
	COMBINATION	0.96	0.14	56	0.83	0.14	52	0.51	0.12	51	0.41	0.11	51
ALL COMBINED	PLACEBO	1.01	0.12	69	0.87	0.12	68	0.48	0.11	66	0.37	0.09	65
	PHENYLPROPANOLAMINE	1.01	0.11	69	0.65	0.10	69	0.45	0.08	68	0.41	0.08	68
	PHENYLEPHRINE	0.83	0.11	69	0.65	0.10	68	0.54	0.10	66	0.45	0.09	66
	COMBINATION	0.86	0.12	66	0.72	0.12	64	0.44	0.10	64	0.37	0.09	64

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TABLE XVI

SUMMARY OF INVESTIGATOR RATINGS OF HEADACHE
FOR ALL PATIENTS ELIGIBLE FOR EFFICACY ANALYSIS
RATING SCALE: 0=NONE 1=MILD 2=MODERATE 3=SEVERE

TIMEPOINT	TREATMENT GROUP	BASELINE MEAN	BASELINE STD ERR OF MEAN	BASELINE N	DAY 1 MEAN	DAY 1 STD ERR OF MEAN	DAY 1 N
AM1	PLACEBO	0.42	0.15	12	0.00	0.00	12
	PHENYLPROPANOLAMINE	0.42	0.19	12	0.08	0.08	12
	PHENYLEPHRINE	0.08	0.08	12	0.00	0.00	12
	COMBINATION	0.13	0.14	12	0.00	0.00	12
AM2	PLACEBO	1.17	0.48	6	0.17	0.17	6
	PHENYLPROPANOLAMINE	1.17	0.31	6	0.20	0.20	5
	PHENYLEPHRINE	0.50	0.34	6	0.00	0.00	5
	COMBINATION	0.00	0.00	5	0.20	0.20	5
AM3	PLACEBO	0.84	0.24	12	0.25	0.14	12
	PHENYLPROPANOLAMINE	0.92	0.21	12	0.33	0.19	12
	PHENYLEPHRINE	0.42	0.19	12	0.00	0.00	12
	COMBINATION	0.25	0.18	12	0.27	0.14	11
AM4	PLACEBO	2.08	0.21	12	1.25	0.37	12
	PHENYLPROPANOLAMINE	1.75	0.13	12	0.67	0.31	12
	PHENYLEPHRINE	1.54	0.22	13	1.00	0.26	13
	COMBINATION	1.77	0.17	13	0.92	0.31	13
PM1	PLACEBO	1.07	0.27	14	0.62	0.21	13
	PHENYLPROPANOLAMINE	1.23	0.28	14	0.62	0.29	13
	PHENYLEPHRINE	1.07	0.29	14	0.54	0.31	13
	COMBINATION	1.08	0.32	12	0.38	0.21	13
PM2	PLACEBO	0.54	0.18	13	0.08	0.08	13
	PHENYLPROPANOLAMINE	0.64	0.17	14	0.07	0.07	14
	PHENYLEPHRINE	0.71	0.22	12	0.25	0.13	12
	COMBINATION	0.54	0.19	13	0.08	0.08	13
ALL TIMEPOINTS AVG	PLACEBO	1.11	0.14	54	0.50	0.12	50
	PHENYLPROPANOLAMINE	1.17	0.11	57	0.37	0.11	55
	PHENYLEPHRINE	0.64	0.10	57	0.45	0.11	55
	COMBINATION	0.73	0.15	55	0.37	0.11	54
ALL TIMEPOINTS	PLACEBO	0.90	0.11	66	0.41	0.10	62
	PHENYLPROPANOLAMINE	1.00	0.10	69	0.33	0.09	67
	PHENYLEPHRINE	0.77	0.11	69	0.33	0.09	67
	COMBINATION	0.91	0.12	67	0.33	0.09	67

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e. Objective Evaluation of Total Nasal Airway Resistance, NAR, in Study 0401.

In addition to the subjective evaluations of symptoms and overall therapeutic effect, Dr. Cohen measured total nasal airway resistance, NAR (sum of inspiratory and expiratory nasal airway resistance), following the initial dose of study medication. Measurements were taken at time of administration and at 15, 30, 45, 60, 120, 180, and 240 min following administration of medication. Analysis of covariance with the baseline measurement as a covariate was performed on the decrease from baseline in NAR at each of the post treatment evaluations and on a summary measure, the area between the NAR curve and the baseline NAR value.

NAR raw data listings for individual patients along with treatment group summary statistics are presented in Attachment K. Mean NAR is plotted across time for each of the treatment groups in Figure 9. As shown in the graph, the combination had the lowest mean NAR curve across the entire evaluation period and the only mean NAR below baseline at 240 min. The mean NAR's for phenylpropanolamine and phenylephrine were consistently higher than that for the combination, but lower than placebo.

Results from the statistical analyses for decrease in NAR are presented in Table XVII. The means shown in the table are the "adjusted means" from the analysis of covariance. The mean decrease from baseline in NAR for the combination was statistically significantly ($P \leq .0100$) greater than that for phenylpropanolamine at 60, 120, and 240 min. Compared to phenylephrine, the decrease in NAR for the combination was statistically significantly ($P \leq .100$) greater at 60 and 240 min and marginally significantly ($P \leq .0500$) greater at 30, 45, and 120 min. In addition, the mean decrease in NAR for the combination was statistically significantly greater than placebo at 30, 45, 60, 120, 180, and 240 min. Phenylpropanolamine exhibited significantly ($P \leq .0100$) greater reductions in NAR versus placebo at 30, 45, 60, and 120 min. Phenylephrine also exhibited statistically significant ($P \leq .0100$) reductions in NAR versus placebo at 45, 60, and 120 min with marginal significance ($P \leq .0500$) attained at 30 and 180 min.

Results from statistical analysis of the summary measure for NAR, the area between the NAR curve and baseline (NARAREA), are vertually identical as those found for reduction from baseline in NAR. The treatment comparisons and "adjusted treatment" means are summarized in Table XVIII. The combination exhibited a statistically significantly greater NARAREA than phenylpropanolamine ($P \leq .0011$), phenylephrine ($P \leq .0027$) and placebo ($P \leq .0001$). Likewise, statistically significant NARAREA's were found in favor of phenylephrine ($P \leq .0001$) and phenylpropanolamine ($P \leq .0002$) when compared with that for placebo.

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FIGURE 9

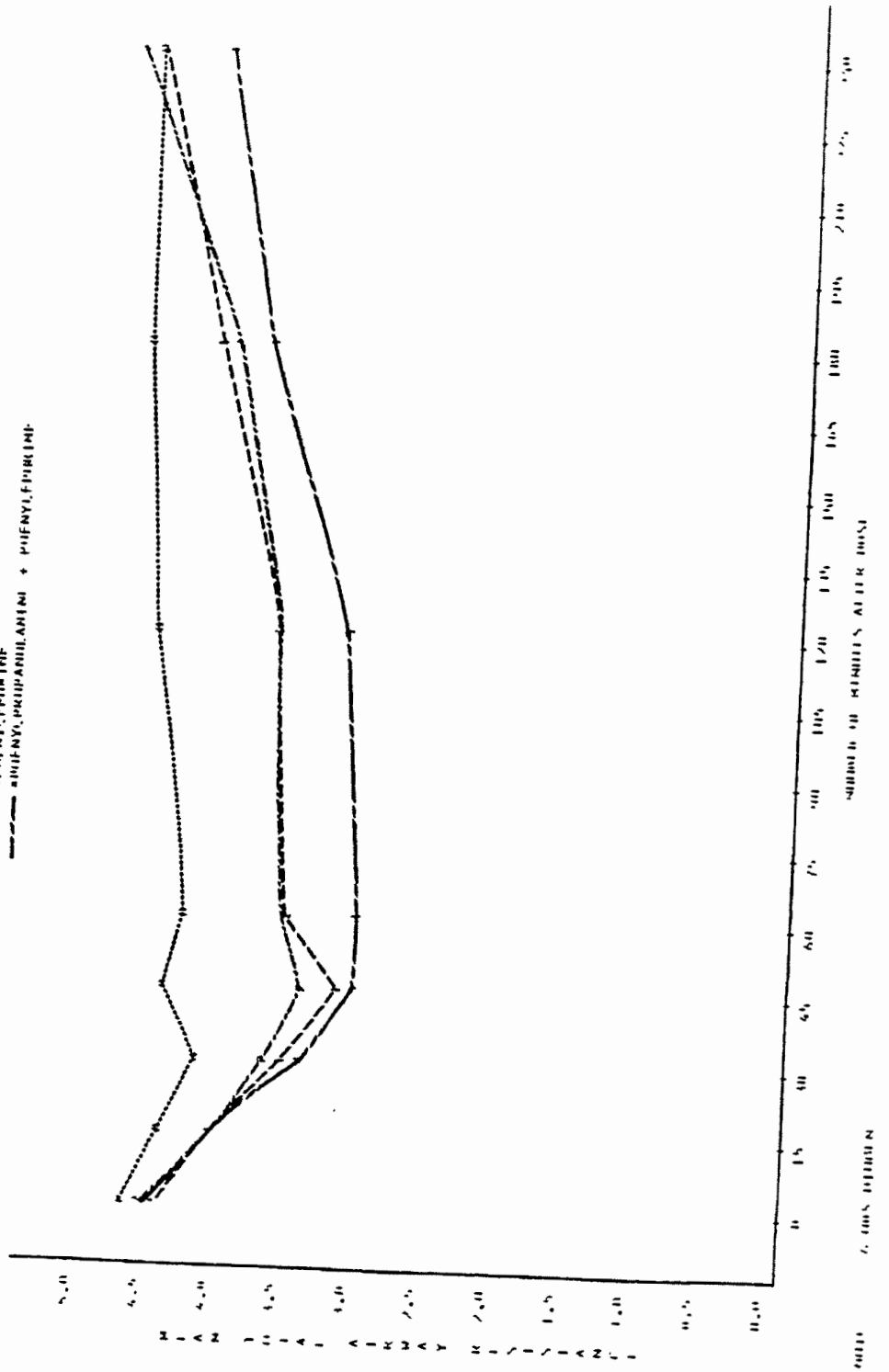

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Table XVII

Summary of Statistical Analysis for Decrease in Total Nasal Airway Resistance in cm $H_2O/l/sec$

	Mean[a] Decrease in NAR at Evaluation Times (minutes) Following Initial Dose						
	15	30	45	60	120	180	240
Placebo [12][b]	0.186	0.412	0.181	0.323	0.084	-0.101	-0.132
P-Propanolamine [12]	0.403	0.939	1.358	1.010	0.790	0.353	-0.186
P-Ephrine [12]	0.535	0.841	1.211	1.019	0.862	0.514	-0.241
Combination [12]	0.491	1.183	1.450	1.522	1.376	0.784	0.426
Treatment Comparison	P-Value[c]						
Combination vs Placebo	.0785	.0001	.0001	.0001	.0001	.0010	.0033
Phenylephrine vs Placebo	.0554	.0115	.0001	.0002	.0006	.0132	.2883
Phenylpropanolamine vs Placebo	.1606	.0031	.0001	.0002	.0015	.0494	.3911
Combination vs Phenylephrine	.4265	.0333	.0444	.0031	.0132	.1588	.0007
Combination vs Phenylpro-panolamine	.3344	.0939	.2524	.0028	.0061	.0573	.0016
Phenylephrine vs Phenylpro-panolamine[d]	.5416	.5927	.2937	.9585	.7490	.5519	.7800

[a] Treatment group means are the adjusted means from Analysis of Covariance.
[b] Numbers within brackets indicate sample size.
[c] Unless noted otherwise, P-values are one-tailed
[d] Two-tailed P-values.

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Table XVIII

Summary of Statistical Analysis for the Summary Measure for NAR, NARAREA, Area [cm H_2O/l/sec) x min] Between the Total Airway Resistance Curve and Baseline

	Mean NARAREA[a]
Placebo [12][b]	18.84
Phenylpropanolamine [12]	141.40
Phenylephrine [12]	152.39
Combination [12]	246.37
Treatment Comparison	**P-Value[c]**
Combination vs Placebo	.0001
Phenylephrine vs Placebo	.0001
Phenylpropanolamine vs Placebo	.0002
Combination vs Phenylephrine	.0027
Combination vs Phenylpropanolamine	.0011
Phenylephrine vs Phenylpropanolamine[d]	.7342

[a]Treatment group mean areas are the adjusted means from Analysis of Covariance.
[b]Numbers within brackets indicate sample size.
[c]Unless noted otherwise, P-values are one-tailed.
[d]Two-tailed P-values.

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Table XIX
Summary Listing of Adverse Effects by Study

Study	Patient	Adverse Effect (AE)	Drug*	No. days Duration	Maximum Intensity	Action Taken	Serious AE	Test Drug Cause AE	Patient Outcome
0401	12	Lightheadedness	PE	1	Mild	None	No	Probably	Recovered
0401	22	Lightheadedness	P	1	Mild	None	No	Possibly	Recovered
0401	23	Very dry throat	C	2	Mild	None	No	Probably	Recovered
0401	33	Dizziness	PP	2	Mild	None	No	Possibly	Recovered
0401	36	Eructation	P	1	Mild	None	No	Probably	Recovered
0401	46	Gaseousness	P	2	Mild	None	No	Possibly	Recovered
0404	4	Sleepy	P	3	Moderate	Dosage Reduced	No	Definitely	Recovered
0404	6	Lightheadedness	P	2	Moderate	None	No	Probably	Recovered
0404	6	Sleepy	P	2	Moderate	None	No	Probably	Recovered
0404	7	Insomnia	P	2	Moderate	None	No	Probably	Recovered
0404	7	Palpitation	P	2	Moderate	None	No	Probably	Recovered
0404	18	Drowsy	P	2	Moderate	None	No	Def. Not	Recovered
0404	21	Drowsy	C	3	Moderate	None	No	Probably	Recovered
0404	22	Sleepy	C	2	Moderate	None	No	Probably	Recovered
0404	47	Sleepy	C	3	Moderate	None	No	Probably	AE still present - No treatment
0404	47	Tired	C	3	Moderate	None	No	Probably	AE still present - No treatment
0405	18	Dizziness	PE	2	Mild	Discontinued	No	Possibly	Recovered
0406	26	Piloerection	PP	2	Mild	None	No	Probably	AE still present - No treatment
0406	26	Constipation	PP	2	Moderate	None	Yes	Probably	AE still present - No treatment
0406	29	Headache	P	1	Mild	None	No	Probably Not	Recovered
0406	39	Nausea	P	1	Mild	None	No	Probably	Recovered
0406	43	Increased Sweating	PP	3	Mild	None	No	Probably Not	Recovered
0406	45	Lightheadedness	P	5	Mild	None	No	Probably	Recovered

PE = Phenylephrine
PP = Phenylpropanolamine
C = Combination of phenylephrine plus phenylpropanolamine
P = Placebo

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Table XX

Number of Adverse Effects Reported by Treatment Group

Adverse Effect	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination	Total
Lightheadedness	3	0	1	0	4
Dizziness	0	1	1	0	2
Headache	1	0	0	0	1
Sleepy	2	0	0	2	4
Drowsy	1	0	0	1	2
Tired	0	0	0	1	1
Insomnia	1	0	0	0	1
Palpitations	1	0	0	0	1
Eructation	1	0	0	0	1
Gaseousness	1	0	0	0	1
Nausea	1	0	0	0	1
Constipation	0	1	0	0	1
Piloerection	0	1	0	0	1
Increased Sweating	0	1	0	0	1
Dry Throat	0	0	0	1	1
Total	12	4	2	5	23

Table XXI

Number of Patients Reporting Adverse Experiences

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination	Total
Number of patients reporting adverse experiences	10	3	2	4	19

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Table XXII

Summary Statistics for Systolic Blood Pressure (*mmHg*)

Treatment Group		Enrollment Visit	Final Visit	Change from Baseline (Final-Enrollment)	P-value†
Placebo	Mean	121.90	121.17	- 0.72	.56
	S.E.M.	1.60	1.55	1.22	
	n	69	69	69	
Phenylpropanolamine	Mean	121.41	120.79	- 0.62	.48
	S.E.M.	1.35	1.40	0.87	
	n	68	68	68	
Phenylephrine	Mean	120.04	120.13	0.09	.95
	S.E.M.	1.26	1.51	1.28	
	n	68	68	68	
Combination	Mean	121.67	121.51	- 0.17	.89
	S.E.M.	1.57	1.21	1.19	
	n	65	65	65	

†P-values (two-tailed) obtained from a paired t-test.

Table XXIII

Summary Statistics for Diastolic Blood Pressure (mmHg)

Treatment Group		Enrollment Visit	Final Visit	Change from Baseline (Final-Enrollment)	P-value†
Placebo	Mean	75.84	74.61	- 1.23	.19
	S.E.M.	1.04	1.12	0.93	
	n	69	69	69	
Phenylpropanolamine	Mean	74.88	75.41	0.53	.53
	S.E.M.	1.18	1.08	0.84	
	n	68	68	68	
Phenylephrine	Mean	74.88	73.88	- 1.00	.24
	S.E.M.	1.12	1.24	0.85	
	n	68	68	68	
Combination	Mean	74.31	73.78	- 0.52	.53
	S.E.M.	1.11	1.05	0.83	
	n	65	65	65	

†P-values (two-tailed) obtained from a paired t-test.

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Table XXIV

Summary Statistics for Pulse Rate (Beats/Minute)

Treatment Group		Enrollment Visit	Final Visit	Change from Baseline (Final-Enrollment)	P-value[a]
Placebo	Mean	76.52	74.90	- 1.65	.13
	S.E.M.	1.23	1.04	1.08	
	n	69	69	69	
Phenylpropanolamine	Mean	75.96	74.54	- 1.41	.15
	S.E.M.	1.06	0.81	0.97	
	n	68	68	68	
Phenylephrine	Mean	75.03	75.12	0.09	.93
	S.E.M.	1.11	1.18	1.00	
	n	68	68	68	
Combination	Mean	75.26	74.26	- 1.00	.34
	S.E.M.	1.00	0.97	1.04	
	n	65	65	65	

[a]P-values (two-tailed) obtained from a paired t-test.

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Additional analysis of the NAR data were performed to investigate the possible effect of certain background variables on the NAR measurements in Dr. Cohen's study. Due to the substantial treatment group baseline differences with respect to age and weight and the obvious importance of duration of illness, the effect of these 3 variables on Dr. Cohen's NAR data was investigated. Results from analysis of covariance (Attachment G) demonstrated that none of three covariables (age, weight, and duration of allergic rhinitis) had a significant effect on NAR at the $\alpha = .05$ level.

E. Safety

All adverse effects are summarized in Tables XIX-XXI. Nineteen patients reported adverse effects with a majority of the patients belonging to the placebo group. None of the adverse effects were of a serious nature.

Raw data listings for baseline and final visit blood pressures and pulse rates are included in Attachment L. Summary statistics are presented in Tables XXII-XXIV. For each treatment group, a paired t-test was performed on the 72-hr change from baseline for systolic and diastolic blood pressure and pulse rate. As shown in Tables XXII-XXIV, no significant treatment group change from baseline was detected for any of the 3 safety variables. Two hundred seventy patients were included in the analyses. The following patients were excluded due to missing data at 72 hours: patient numbers 13 and 21 (Study #0402), 42 (Study #0405), and 23 (Study #0406).

IV. Discussion

Dr. Cohen's study (0401) was the only study in which the patient response to treatments consisting of 1 or more decongestants (especially the combination) was statistically superior to that of placebo. A meeting with Dr. Cohen was held to determine possible reasons for the treatment groups in his study responding in a different fashion than those from the other studies. Several possible explanations were set forth during the discussion. First, Dr. Cohen is very familiar with his patients, and the communication between patient and physician is very good. As a result, his patients may have had a superior understanding of their participation in the study. Second, Dr. Cohen made a conscious effort based on past experience to exclude from the study patients he felt to be "placebo responders." This may explain the particularly poor response to therapy by his placebo patients. Third, Dr. Cohen based his evaluation of overall therapeutic effect on examination of the nasal passages. He considered moisture, redness, and swelling as criteria for his evaluation. As a consequence, Dr. Cohen's evaluation may have been more "objective" than those from the other investigators.

V. Statistical Methods

In accordance with the objective of the study, the following one-directional treatment comparisons are of high interest--the combination, phenylephrine, and phenylpropanolamine versus placebo, and the combination each

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versus each of its components. The remaining possible pairwise contrast which is two-sided in nature, phenylephrine versus phenylpropanolamine, is of lesser interest and is reported for the purpose of internal review. In order to keep the experimentwise type I error rate for the 5 primary comparisons at the nominal .05 level, each comparison was tested at the $\alpha = .01$ level of significance.

Investigators' and patients' subjective global evaluations of response to therapy and subjective ratings of runny nose, stuffy nose, and sneezing were analyzed by standard Analysis of Variance (ANOVA) techniques (Neter and Wasserman, 1974). A two-factor analysis of variance in a completely randomized design was used for the data from the global evaluations. Terms included in the model were investigator, treatment, and treatment by investigator interaction. For the data from the subjective ratings of the nasal symptoms, a three-factor analysis of variance was utilized. Effects included in this model were, baseline symptom severity used as a block effect, investigator, treatment, treatment by investigator interaction. Stratifying by baseline severity removes possible effects due to baseline symptom severity from the treatment comparison and actually may be thought of as a function-free regression scheme (Winer, 1971).

Originally, analysis of subjective variables was planned for the data pooled across all 6 investigators. However, it was obvious that the treatment groups in study 0401 responded differently from those of the other 5 investigators. Significant ($P \leq .05$) investigator by treatment interactions found in analyses of data pooled from all 6 investigators were not found when analyses were repeated on data pooled from from studies 0402-0406. Therefore, analyses were performed on Dr. Cohen's data alone, the pooled data from the other 5 investigators, and on pooled data from all 6 investigators (these analyses are included in Attachment G only for completeness).

The rational for using analysis of variance methods for the data from the subjective rating scales is based on the applicability of central limit theory and on the following 2 characteristics of the data: the responses from the 4 and 5 point rating scales were reasonably spread over the range of the scales and the cell mean sample sizes were relatively large. Due to the importance of this clinical trial, the results based on ANOVA methods for the bulk of the efficacy data, patients' and investigators' evaluations of runny nose, stuffy nose, and sneezing, were confirmed by an additional statistical method of analysis. The Generalized Cochran-Mantel-Haenszel (GCMH) categorical data procedure for ordinal data (Case II of Landis et al., 1978) was also performed on the evaluation of symptoms for Dr. Cohen's study and for the other 5 investigators combined. The results from the ANOVA and GCMH procedures were vertually identical as shown in Attachment H.

Analysis of variance techniques adjusting for baseline were used for the total nasal airway resistance (NAR) data measured by Dr. Cohen. NAR was calculated as the raw sum of inspiratory and exspiratory nasal airway resistance. A two-factor analysis of covariance with baseline NAR as a covariable and treatment was performed on the change from baseline (NAR - baseline NAR) at each of the 7 post initial dosage evaluations and on a summary measure for NAR incorporating all 7 of the observations throughout

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the 4-hr observation period, the area between the total nasal airway resistance curve and baseline, NARAREA. The analysis of NARAREA was straightforward since all NAR data were non-missing. The estimate of NARAREA for patient k, $NARAREA_k$, was calculated according to the trapezoidal rule as:

$$NARAREA_k = .5 \sum_{i=1}^{7} [(NAR_k(t_0)-NAR_k(t_i))+ (NAR_k(t_0)-NAR_k(t_{i+1}))](t_{i+1}-t_i)$$

where

i = 1,2,..., 7

t_i = the number of minutes following administration of the initial dose of study medication corresponding to the ith NAR measurement; i.e., t_1, t_2, t_3, t_4, t_5, t_6 and t_7 are 15, 30, 45, 60, 120, 180, and 240 minutes following the initial dose, respectively, and t_0 (baseline) is the time just prior the administration of the initial dose.

$NAR_k(t_i)$ is the total nasal airway resistance for patient k at time t_i.

All analyses of data were performed on the Statistical Analysis System (SAS) version 79.3 (Barr, et al., 1980) on an IBM 4331 mainframe computer. The SAS GLM (General Linear Model) procedure was used to obtain all results based on analysis of variance methods. ANOVA tables from the analyses are included in Attachment G. The sums of squares in the ANOVA tables are SAS type IV sums of squares. See Hocking et al. (1976) for a complete discussion of the sums of squares utilized by SAS. SAS GLM "Least Squares Means" are used in the text of this report (Tables XVIII, XI, and XII) to help summarize the treatment comparisons based on analysis of variance. As Searle et al. (1980) have suggested, these means may be thought of as "estimated population marginal means" which simply put are estimates one would expect had equal cell sizes been obtained. For the NAR summaries (Tables XVII and XVIII), the estimated population marginal means are in fact the adjusted means obtained from Analysis of Covariance.

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ATTACHMENT A

Copy of Protocol

AHP1-REG-048-0015155

CLINICAL STUDY PROTOCOL

A. H. ROBINS COMPANY
1407 Cummings Drive
Richmond, Virginia 23220

AHR No. (4010-3)

Dimetapp Elixir

Protocol # 04

Study # _____

Final Copy: 1/31/78

_____ _____
Signature of Medical Monitor Date

_____ _____
Signature of Principal Investigator Date

AHP1-REG-048-0015156

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A. H. ROBINS COMPANY
1407 Cummings Drive
Richmond, Virginia 23220

Synopsis of Protocol No. 04

IND # -

NDA # - 13-087

Phase (IV) Study

1. Drug Identification:

   AHR Drug No.: 4010-3

   Trade: Dimetapp Elixir (decongestants only)

   Generic: Phenylephrine; phenylpropanolamine

2. Pharmacologic Category: decongestant

3. Therapeutic Indication for this Study: Acute rhinitis due to URI, duration of 48 hours or less.

4. Objective of Study: Clinical trial to assess subjective toleration and efficacy of phenylephrine 10 mg versus phenylpropanolamine, 25 mg versus phenylephrine, 5.0 mg plus phenylpropanolamine, 12.5 versus placebo in adult patients with acute rhinitis due to URI.

5. Study Design: Double-blind, randomized, placebo control.

6. Clinical Monitor and Clinical Investigator:

   Clinical Monitor (AHR) Emily M. Morley, M.D.
   Clinical Investigator

7. General description, source and number of patients to be entered: 288 patients; age 18 years and older with acute rhinitis due to URI of 48 hours duration or less. Office of Investigator; males and females (non-pregnant), 6 investigators (48 patients per investigator).

8. Treatment groups and dosage: Patients will be randomly assigned to one of 4 study groups: Phenylephrine (10 mg) - 5 ml every 4 hrs (6 doses/24 hrs) for 3 days. Phenylpropanolamine (25 mg) - 5 ml every 4 hrs (6 doses/24 hrs) for 3 days. Phenylephrine (5 mg) + Phenylpropanolamine (12.5 mg) - 5 ml every 4 hrs (6 doses/24 hrs) for 3 days. Placebo - 5 ml every 4 hrs (6 doses/24 hrs) for 3 days.

9. Greatest duration of drug exposure for any individual patient: 3 days

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10. Exclusions:

    1. Pregnant females

    2. Allergy to phenylephrine, phenylpropanolamine

    3. History of allergy to chemically related drugs

    4. Patients with cardiovascular, renal, thyroid, diabetes or other systemic disease which may contraindicate therapy with study medication or confuse study results.

    5. Use of monoamine oxidase inhibitors, antihistamines, bronchodilators, nasal decongestants (local or parenteral) or antibiotics within 24 hrs of enrollment or during course of study. Analgesics are not permitted during the study period or for at least 12 hours prior to entry into the study.

    6. Evidence of anatomic obstruction of nasal airways, or chronic nasal disease.

11. Observations:

    a. Efficacy: Subjective parameters - stuffy nose, runny nose, sneezing, headache.
    b. Safety: B.P., pulse rate.

12. Estimated date of initiation:

    March, 1978.

13. Comments:

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I. Background:

F.R. Notice of 7/27/72 declared Elixir as "probably effective" under the DESI Review Program. Extentab was declared "possibly effective" but on 4/25/77 was downgraded to "ineffective as a fixed dose combination." Subsequently, FDA advised Robins that a proposed reformulation of Dimetapp Extentabs to a brompheniramine and a single sympathomimetic combination would be an acceptable response to the Notice of Opportunity for Hearing on FDA's proposal to withdraw the NDA. Conferences were held with FDA personnel regarding the nature of the reformulation; AHR initially (9/73) proposed a reformulation containing brompheniramine and phenylpropanolamine and later (7/77) a reformulation containing brompheniramine and phenylephrine. However, FDA had indicated that it would not take final action on NDA amendments until such time as the OTC Cough/Cold Monograph was finalized (proposed monograph published 9/9/76, with the final monograph expected in mid-or-late-1978).

Robins prefers to maintain the current two-sympathomimetic product and made this proposal to FDA 5/76. The proposed OTC Monograph (September, 1976) lists phenylephrine at 10 mg and phenylpropanolamine at 25 mg single doses in immediate release form as Category I. A combination of two half-strength Category I agents would be acceptable as Category I if it can be shown that the clinical efficacy and toleration is equivalent to a single entity Category I agent.

II. Objective:

To obtain clinical pharmacological documentation by subjective parameters that a combination of 5 mg phenylephrine and 12.5 mg phenylpropanolamine/5 ml is at least equivalent in effect on subjective parameters to either 10 mg phenylephrine or 25 mg phenylpropanolamine.

III. Investigators:

A. Number of investigators scheduled to participate in studies using this protocol: 6

B. Investigator information for each separate study under this protocol: See Appendices.

IV. Experimental Plans:

A. Patients

1. Number - Scheduled to participate in this protocol: 288

2. Description

a.	Age:	18 years and older
b.	Sex and pregnancy potential:	Male and female (non-pregnant)
c.	Race:	N.A.
d.	Diagnosis (or description of symptoms):	Acute rhinitis due to URI of 48 hrs. duration or less.

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e. Hospital status: Outpatient

3. Source private office practice. Office of investigator.

4. Criteria for inclusion

a. Acute rhinitis (nasal congestion) due to URI.

b. Required duration of condition: 48 hours or less.

c. Required severity of condition: Patient should not be sick enough to require medication other than nasal decongestants.

d. Willingness to participate in this study as demonstrated by providing voluntary written informed consent.

e. Ability to follow directions of the investigator or his staff to include the following:

(1) Appear for return visits at stated intervals for stated duration of study.

(2) Take study drug medication as scheduled.

(3) Avoid self-medication with either non-prescription or prescription drugs during course of study.

5. Criteria for exclusion:

a. Presence of concurrent disease: Diabetes; thyroid; cardiovascular, renal, or hepatic disease, other respiratory disease or other systemic disease which may contraindicate therapy with study medication or confuse study results. Evidence of anatomical nasal airway obstruction.

b. Pregnancy: Not pregnant

c. Known hypersensitivity to: phenylephrine; phenylpropanolamine or chemically related drugs.

d. Specifically excluded recent medication: bronchodilators; MAO inhibitors; antihistamines; topical or parenteral nasal decongestants or antibiotics within 24 hrs of initiation of study or during study. Analgesics during study period or for at least 12 hours prior to entry into study.

B. Procedure

1. General description of study: Double-blind, parallel, randomized clinical trial of 3-day duration.

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2. Study medication (test drugs to be physically indistinguishable)

   a. Identity of each treatment group (name, dose form, unit strength, manufacturing lot number):

   b. Packaging and Labeling (Protocol packaging lot #__): (e.g.)

      (1) Study medication will be supplied to the investigator in prepackaged, pre-labeled and pre-coded bottle of stated amount of liquid. One bottle of medication will be supplied for each patient.

      (2) The assignment of study medication will be made on the basis of a randomization schedule by patient number, which is sequentially assigned to patients being admitted to the study; i.e., medication labeled for Patient #1 will be given to the first patient entering the study, medication labeled for Patient #2 will be given to the second patient, etc.

      Each 5 ml of study medication contains:

1.	Phenylephrine HCl	10 mg
or 2.	Phenylpropanolamine HCl	25 mg
or 3.	Phenylephrine HCl	5 mg
	plus phenylpropanolamine HCl	12.5 mg
or 4.	Matching placebo	

      (3) One bottle will be dispensed to each patient on Study Day 1.

      At the time of dispensing, the investigator will remove the tear-off portion of the two-part label (without opening) and staple it to the Case Report Form. The patient number on the bottle label must be the same as the patient number on the Case Report Form. At each visit a tablet count and any change in dosage schedule will be noted on the Case Report Form.

      (4) In the case of emergency, the contents of any bottle may be determined by cutting open the tear-off portion of the bottle label.

      (5) The investigator will be supplied with labeled medication for extra patients, so as to provide for study dropouts, bottles broken in transit, etc. Selection of the appropriate replacement medication will be made by the AHR monitor so as to preserve the double-blind features of this study.

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c. Dosage schedule (e.g.):

(1) Initial dosage schedule: 5 ml of study medication every 4 hrs (6 doses in 24 hrs) for 3 days (72 hrs).

(2) Increasing or decreasing dosage from the initial dose to a stated maximum or to a stated minimum is permitted at any time during the study on physician's order. Regulation of dosage should be based on the patient's individual response and adverse effects. Any patient for whom any other dosage is required will be dropped from the study. Each patient should be cautioned to maintain the dosage schedule prescribed for him unless a change is prescribed by the physician.

Permissible dosage schedules: Maximum dosage permissible is 6 doses/24 hrs - 30 ml. A minimum of 4 doses/24 hrs (20 ml) is permissible, e.g., 8:00 am; noon; 4:00 pm; and 8:00 pm.

(3) Careful records of dosage schedules and changes must be kept on the CRF.

3. Concurrent management

a. Permitted:

(1) Diet: As desired.

(2) Temporary restructuring of activities and/or environment: None indicated.

b. Excluded: All other medications unless taken regularly pre-study and not included in the exclusion criteria.

4. Treatment plan (Evaluation for all patients within a study should be made by the same physician.)

a. Screening and admission period (e.g.)

(1) Screening: Brief history, review of symptoms and respiratory system physical examination.

(2) Admission to study

Upon meeting the exclusion and inclusion criteria, including execution of written informed consent, a patient may be admitted to the study and given a sequentially assigned patient number.

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Complete Study Admission Form.

All patients screened but not entered into the actual study will have a Case Report Form partially completed and submitted to the Sponsor.

(3) Study drug

Dispense one bottle of the correct study medication (check patient sequence number).

Instruct patient as to intended dosage schedule. 5 ml every 4 hrs for at least 4 doses up to a maximum of 6 doses/24 hrs.

(4) Instructions to patient

(a) Instruct patient on diet, activities, excluded medications.

(b) Instruct patient to note adverse effects and to notify the investigator if effects become severe or unremitting.

(c) Inform the patient that a telephone contact may be made at any time during the study period in the event of persistent and bothersome side effects or increasing symptomatology. At this time an adjustment in the dosage schedule may be made if indicated.

(d) Instruct patient to return to office at stated time and bring the unused medication.

(e) Each patient should rate his pre-drug symptoms i.e., nasal and other "target" symptoms in the presence of the investigator. Patients are to be specifically instructed to complete the questionnaire at end of 24, 48, and 72 hrs after starting the study.

b. Return visits: On day 3 of the study (72 hrs) the patient should return for the Final Visit.

(1) Observations:

(a) History: Brief review of symptoms.
(b) Physical exam: Examination of nasal passages and brief examination of respiratory system.

(2) Review of Patient Take-Home Questionnaire.

(3) Physicians assessment of patient's symptoms.

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c. Interim (unscheduled) visits

At any time during a patient's participation in this study, either the patient or the investigator may initiate a clinic visit or other investigator-patient contact to evaluate his physical status.

5. Adverse effects - to be noted at least at each visit.

a. Identification

Spontaneous response to question "Any problems?"

b. Reporting

(1) All adverse reactions or experiences, both volunteered and solicited, will be appropriately entered on the Adverse Effects Report Form.

(2) Unanticipated or life-threatening adverse reactions to the investigational drug will be reported immediately to the sponsor by telephone.

c. Possible action

Depending on the nature and severity of the adverse effect, the investigator may institute any of the following:

(1) Continue patient on same dosage schedule until next visit to determine if effect is transient.

(2) Adjust schedule to omit one or more daily doses.

(3) Termination of the patient from the study, with initiation of appropriate follow-up.

6. Indications and procedures for removing a patient from study; complicating events

a. Situations where patient's participation in study may temporarily be interrupted and resumed:

b. The occurrence of any of the following will require permanent removal of the patient from the study:

(1) Refusal of patient to continue therapy with assigned drug.

(2) Failure of patient to follow investigator's directions, especially with respect to return visits, and avoiding prescribed medications.

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(3) Unacceptable adverse effects which persist despite adjustment of dosage of study drug.

(4) Appearance of a complication that would have led to exclusion of the patient, if present at the time of admission to the study.

(5) Failure of patient's symptoms to improve within stated number of days of entering study.

c. The reason for any patient's removal from the study will be described on the appropriate Case Report Form.

d. Complicating events will be handled in a manner consistent with good medical practice, including institution of appropriate therapy and follow-up.

e. Study dropouts

For any patient removed from this study the following sequence will be indicated:

(1) Discontinue study medication
(2) Initiate indicated therapy
(3) Keep record of any follow-up
(4) Include patient in final evaluation

V. Monitoring

A. Monitors

1. Principal monitor: Emily M. Morley, M.D.
2. Research Associates:

B. Statistician: Roger Flora, Ph.D.

C. Execution

1. Anticipated duration of total study (all patients): 3 months

2. Controls and checks on study progress and data collection (e.g.):

Each investigator will be visited before or at the time of receipt of study drug supplies for the purpose of re-reviewing the protocol and the case report forms with involved personnel, and to observe area for drug storage and pattern of dispensing. Each investigator will be contacted at least bimonthly thereafter by phone or visit, or both, to assess progress and to review problems. Case Report forms, reflecting all available experience in the study, including reports on patients screened but not actually entered into the study (and the reasons therefor), will be reviewed at on-site visits and efforts made to achieve completeness of entries.

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Completed forms, upon termination of drug administration to those patients, will be forwarded to the AHR medical monitor for review; existing questions will be referred back to the principal investigator. Completed forms bearing initials of the medical monitor as indicative of review for safety questions, general efficacy and completeness will then be transmitted for data processing procedures.

3. Procedures for terminating, extending, or modifying this study

   a. This study may be terminated at any time by either the sponsor or the investigator.

   b. By mutual agreement of the sponsor and the investigator, any aspect of this protocol may be amended.

   c. Upon completion or termination of total study, all unused study drugs will be returned to the drug sponsor.

VI. Data Management and Statistical Analysis

A. Data Management Procedures

Prior to receiving completed Case Report Forms (CRF's) from the Medical Monitor, procedures will be developed for transcribing data into a computerized data base for subsequent summarization and analysis. A Data Document Inventory Form will also be prepared for recording receival date and number of data sheets returned for each subject.

As CRF's are "logged in" they will undergo a review for completeness and clarity. Data which are incomplete or require clarification will be returned to the Medical Monitor. Following resolution of these items, data will be keypunched and verified directly from the CRF's. The data base will then undergo a final editing procedure designed to detect spurious values, perform talley checks, etc., and make corrections where indicated.

Finally, a 10% random sample of data records will be selected from the edited data and checked against the CRF's to provide an estimate of the accuracy of the established data base. The date will then be referred to the statistician for analysis.

B. Statistical Design and Sample Size Considerations

The design of the study includes four parallel treatment groups with treatments administered in a randomized, double-blind fashion as described in IV above. The comparisons of primary interest are: phenylephrine (10 mg) vs. the combination [phenylephrine (5 mg) plus phenylpropanolamine (12.5 mg)], and phenylpropanolamine (25 mg) vs. the combination [phenylephrine (5 mg) plus phenylpropanolamine (12.5 mg)]. Placebo comparisons, however, are necessary in order to verify that a treatment effect can be shown by the methodology employed in the population under study.

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The major purpose of the study is to demonstrate that the combination of the two decongestants at half strength is at least as good as either of the two at full strength. Thus, it is especially important that the sample size be large enough to provide a high probability of detecting any meaningful difference. Since the primary efficacy assessments are ordered categorical responses, e.g., physicians and patients global assessments, it is anticipated that pairwise comparisons among treatment groups using ridit analysis as described by Fleiss will provide appropriate comparisons. This procedure tests the null hypothesis that if a person is selected at random from each of two treatment groups (or the populations represented by each group) the probability is 0.50 that the individual from a specified group will show greater improvement (be in a higher category). Based on the normal approximation test given by Fleiss, the sample size of 72 per treatment group will provide a power of greater than 0.90 of detecting at the .05 level of significance, a departure of as much as 0.10 from the 0.50 probability. This assumes the use of a one-sided test and that pooling over investigators will be permissable. The latter assumption will, of course, be investigated before pooling as described below.

C. Statistical Analysis

Although it is likely that data from a single investigator will be insufficient to perform statistical analyses of desired sensitivity, tabulations and summarizations will be obtained by investigator. These summaries will be carefully inspected for trends and any evidence of possible treatment by investigator interactions. However, it is anticipated that analyses for detecting treatment differences will be across investigators.

Baseline comparability of treatment groups will first be examined including consideration of age, sex, race, and pre-study symptom assessments. Efficacy assessments will be compared for each of the three days on which evaluations are made as well as comparison of overall global assessments by patients and by physicians on the final day of the study. Since efficacy assessments are ordered categorical responses, comparisons will be made using ridit analysis as described by Fleiss. Frequency and intensity of adverse effects will be compared by means of chi-square or ridit analysis as appropriate.

Reference: Fleiss, Joseph L. Statistical Methods for Rates and Proportions, John Wiley and Sons, Inc. New York (1973).

VII. Appendices

A. General

1. Blank specimen of Case Report Form.

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B. Specific to each study under this protocol

1. Identity and qualifications of principal investigator and key staff.

2. Location and nature of clinical facility to be utilized.

3. Location and nature of laboratory facility to be utilized, including normal test values for laboratory (if indicated).

4. Blank specimen of informed consent form.

AHP1-REG-048-0015169

ATTACHMENT B

Randomization Schedules

AHP1-REG-048-0015170

ADUM TO PROTOCOL

A. H. ROBINS COMPANY
Medical Research Department
1407 Cummings Drive
Richmond, Virginia 23220

Name Burton Cohen

AHR Drug Number 4010-3 Drug Name Dimetapp Elixir

Study Number 0401 Protocol Number 04

PROTOCOL TO BE AMENDED AS FOLLOWS:

Prior to administration of the test drug nasal airway flow/resistance (Rn) will be measured for baseline values. Following these measurements 5 ml of one of 4 test formulations will be administered to the patient according to the randomization schedule. Nasal airway flow/resistance will be measured according to a predetermined schedule for a period of 4 hours. The results will be recorded on data sheets provided by the investigator.

Date _____ Investigator _____

Date _____ Study Monitor _____

AHP1-REG-048-0015171

RANDOMIZATION SCHEDULE

Investigator:_____ AHR-4010-3 (Dimetapp Elixir)

Study No.: 0401 Protocol 04

Patient No.	Treatment Group	Patient No.	Treatment Group
1	A	31	C
2	B	32	B
3	A	33	B
4	A	34	D
5	C	35	B
6	C	36	A
7	D	37	B
8	C	38	C
9	A	39	B
10	D	40	D
11	D	41	B
12	C	42	B
13	A	43	A
14	D	44	C
15	D	45	A
16	C	46	A
17	A	47	C
18	D	48	B
19	C	49	A
20	B	50	D
21	C	51	B
22	A	52	D
23	D	53	B
24	C	54	C
25	D	55	A
26	B	56	D
27	A	57	C
28	B	58	A
29	D	59	C
30	D	60	B

A - Placebo
B - Phenylpropanolamine
C - Phenylephrine
D - Phenylephrine + Phenylpropanolamine

02/09/78

AHP1-REG-048-0015172

RANDOMIZATION SCHEDULE

Investigator: _____ AHR-4010-3 (Dimetapp Elixir)

Study No.: 5402 Protocol 04

Patient No.	Treatment Group	Patient No.	Treatment Group
1	C	31	B
2	D	32	C
3	B	33	C
4	A	34	C
5	A	35	B
6	A	36	D
7	C	37	B
8	C	38	B
9	A	39	D
10	A	40	A
11	C	41	D
12	B	42	C
13	B	43	D
14	A	44	A
15	D	45	B
16	D	46	D
17	B	47	A
18	D	48	A
19	D	49	A
20	B	50	B
21	C	51	D
22	C	52	A
23	B	53	D
24	A	54	C
25	B	55	B
26	C	56	C
27	C	57	B
28	A	58	D
29	D	59	C
30	D	60	A

A - Placebo
B - Phenylpropanolamine
C - Phenylephrine
D - Phenylephrine + Phenylpropanolamine

02/09/78

AHP1-REG-048-0015173

RANDOMIZATION SCHEDULE

Investigator: _____

Study No.: 040j Protocol 04

Patient No.	Treatment Group	Patient No.	Treatment Group
1	D	31	A
2	A	32	B
3	D	33	A
4	A	34	D
5	C	35	C
6	C	36	A
7	A	37	D
8	B	38	C
9	A	39	A
10	C	40	C
11	B	41	D
12	B	42	A
13	B	43	D
14	C	44	D
15	D	45	C
16	A	46	C
17	D	47	B
18	D	48	B
19	B	49	D
20	C	50	B
21	C	51	A
22	C	52	B
23	B	53	A
24	B	54	B
25	B	55	C
26	D	56	C
27	A	57	D
28	B	58	A
29	A	59	D
30	D	60	C

A - Placebo
B - Phenylpropanolamine
C - Phenylephrine
D - Phenylephrine + Phenylpropanolamine

02/09/78

AHP1-REG-048-0015174

RANDOMIZATION SCHEDULE

[illegible] _____ AHR-[illegible] (Wyeth-Ayerst Division)

Study No.: 0404 Protocol 04

Patient No.	Treatment Group	Patient No.	Treatment Group
1	C	31	C
2	C	32	B
3	D	33	A
4	A	34	C
5	B	35	D
6	A	36	C
7	A	37	A
8	C	38	A
9	A	39	B
10	C	40	B
11	B	41	B
12	B	42	C
13	A	43	B
14	D	44	D
15	B	45	C
16	B	46	A
17	B	47	D
18	A	48	C
19	B	49	C
20	C	50	D
21	D	51	A
22	D	52	B
23	D	53	A
24	D	54	C
25	C	55	A
26	A	56	C
27	D	57	D
28	A	58	B
29	D	59	B
30	D	60	D

A - Placebo
B - Phenylpropanolamine
C - Phenylephrine
D - Phenylephrine + Phenylpropanolamine

02/09/78

AHP1-REG-048-0015175

RANDOMIZATION SCHEDULE

Investigator: _____ AHP-0[illegible] (Dimetapp Elixir)

Study No.: 0405 Protocol 04

Patient No.	Treatment Group	Patient No.	Treatment Group
1	D	31	A
2	A	32	D
3	A	33	D
4	A	34	C
5	B	35	C
6	D	36	A
7	C	37	B
8	B	38	D
9	D	39	D
10	B	40	B
11	D	41	A
12	A	42	D
13	A	43	B
14	C	44	D
15	B	45	C
16	A	46	A
17	B	47	B
18	C	48	C
19	C	49	C
20	C	50	A
21	A	51	C
22	C	52	A
23	B	53	B
24	B	54	D
25	C	55	B
26	D	56	D
27	B	57	A
28	C	58	C
29	D	59	B
30	A	60	D

A - Placebo
B - Phenylpropanolamine
C - Phenylephrine
D - Phenylephrine + Phenylpropanolamine

02/09/78

AHP1-REG-048-0015176

RANDOMIZATION SCHEDULE

Investigator: _____ AHP-4010-J (Dilation Study)

Study No.: 0406 Protocol 04

Patient No.	Treatment Group	Patient No.	Treatment Group
1	B	31	C
2	D	32	C
3	C	33	C
4	B	34	D
5	A	35	B
6	A	36	B
7	D	37	D
8	A	38	A
9	A	39	A
10	D	40	A
11	D	41	D
12	C	42	C
13	B	43	B
14	B	44	C
15	A	45	A
16	B	46	B
17	D	47	B
18	C	48	D
19	C	49	B
20	A	50	B
21	C	51	A
22	B	52	D
23	D	53	C
24	C	54	B
25	A	55	A
26	B	56	D
27	D	57	C
28	D	58	D
29	A	59	C
30	C	60	A

A - Placebo
B - Phenylpropanolamine
C - Phenylephrine
D - Phenylephrine + Phenylpropanolamine

02/09/78

AHP1-REG-048-0015177

ATTACHMENT C

List of Investigators

AHP1-REG-048-0015178

Principal Investigators

0401
Burton M. Cohen, M.D.
230 West Jersey Street
Elizabeth, New Jersey 07202

0402
William P. Coleman, M.D.
3100 Houma Boulevard
Metairie, Louisiana 70002

0403
John C. Esposito, M.D.
226 East Springfield Road
Springfield, Pennsylvania 19064

0404
Richard Snyder, M.D.
2632 East 21st Street
Brooklyn, New York 11235

0405
Jerome Miller, M.D.
191 Presidential Boulevard
Bala-Cynwyd, Pennsylvania 19004

0406
F. Birkam, M.D.
Ferris State College
Student Health Service
Big Rapids, Michigan 49307

AHP1-REG-048-0015179

ATTACHMENT D

Sample Case Report Form

AHP1-REG-048-0015180

M.D. Monitor	Date
Admin. Asst.	Date
[illegible]	Date
SID	

AHR-4010-3 PROTOCOL 04

CRF #01

SCREENING FORM

21-0552 4 4

Study No.	Patient No.	Patient Initials	Office (Clinic) No.	Screening Date Mo. Da. Yr.

FOR AHR USE ONLY

A. INCLUSION CRITERIA: [redacted] = Ineligible to be enrolled in study.

Yes	No		
☐	☐	1.	Acute rhinitis due to upper respiratory infection of 48 hrs duration or less. Absence of abnormal findings on auscultation of chest. Must have at least moderate rating for stuffy or runny nose at time of entry into study.
☐	☐	2.	Male or female (*not pregnant*) 18 years of age or older; willing to participate in a controlled study of widely used decongestants.
☐	☐	3.	Patient willing and able to accurately complete "Patient Take-Home Questionnaire", take medication as instructed, and return for final examination after 72 hours of treatment.

B. EXCLUSION CRITERIA: [redacted] = Ineligible to be enrolled in the study.

[redacted]	☐	1.	Is patient known to be pregnant?
[redacted]	☐	2.	Is patient known to be allergic to phenylephrine or phenylpropanolamine?
[redacted]	☐	3.	Is antibiotic or antibacterial therapy likely to be required within the 72-hour study period?
		4.	Has patient taken any of the following medications during the 12 hours prior to entry into the study:
[redacted]	☐		Topical nasal decongestants
[redacted]	☐		Oral nasal decongestants
[redacted]	☐		Bronchodilators
[redacted]	☐		Antihistamines
[redacted]	☐		ASA, acetaminophen or other analgesics
[redacted]	☐		Anticholinergics
[redacted]	☐		MAO inhibitors
[redacted]	☐		Antibiotics
[redacted]	☐	5.	Evidence of concurrent disease: Diabetes; thyroid, cardiovascular, renal, or hepatic disease; other respiratory diseases, or other systemic disease which may interfere with assessment of study results?
[redacted]	☐	6.	Evidence of anatomical nasal airway obsturction.

Investigator's Signature

AHP1-REG-048-0015181

AHR-4010-3 PROTOCOL 04

ENROLLMENT FORM

Study No.	Patient No.	Patient Initials	Office (Clinic) No.	Enrollment Date Mo. Da. Yr.	Enrollment Time
					☐ A.M. ☐ P.M.

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A. PATIENT CHARACTERISTICS:

Sex	Age	Weight
☐ Female		
☐ Male	_____ Yrs.	_____ Lbs.

B. HISTORY:

1. Specify for the present illness:

   a. _____ hours acute rhinitis has been present (must not exceed 48 hrs).

2. Systemic symptoms with present illness:

Yes	No		
☐	☐	a.	Fever. If *yes* _____ days of duration.
☐	☐	b.	Runny nose. If *yes*, is nasal discharge:
		☐	clear, mucoid
		☐	purulent

3. Rate the following symptoms as 0 = not present, 1 = mild, 2 = moderate, 3 = severe.

   Runny nose or stuffy nose must have at least moderate rating (2) to be eligible for entry into study.

   _____ Runny rose
   _____ Stuffy nose
   _____ Sneezing
   _____ Headache

4. Smoking habits:

   ☐ Non-Smoker
   ☐ Smoker

   If smoker, usual smoking habits over the past three months are:

   _____ Packs Cigarettes/day
   _____ Cigars/day
   _____ Bowls of pipe tobacco/day

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Study No.	Patient No.	Patient Initials	Office (Clinic) No.

PATIENT TAKE-HOME QUESTIONNAIRE

We would appreciate your help in providing the information concerning symptoms indicated below both before and during treatment with the medication assigned by your physician. Please take no other medication unless it is approved by your physician.

PATIENT DOSAGE: Take one teaspoonful at least 4 times per day (before mealtimes and at bedtime) up to as many as 6 times/24 hours.

Go over each item below with your physician and enter into the "beginning of treatment" column the number corresponding to the one most appropriate choice for those items indicated during your initial office visit. Complete the other columns as indicated at the end of 24 and 48 hours of treatment. As on "beginning treatment" complete 72-hour evaluation with your physician at time of final visit.

Item	Responses (select the one best choice)	Beginning of Treatment	End of 24 hours	End of 48 hours	End of 72 hours
1. Runny nose*	0. Not present 1. Mild 2. Moderate 3. Severe				
2. Stuffy nose*	0. Not present 1. Mild 2. Moderate 3. Severe				
3. Sneezing	0. Not present 1. Mild 2. Moderate 3. Severe				
4. Headache	0. Not present 1. Mild 2. Moderate 3. Severe				

TO BE COMPLETED AT 72-HR VISIT ONLY

5. Benefit derived from medication:

☐ Marked ☐ Minimal

☐ Moderate ☐ None

*M.D. NOTE:
Runny nose or stuffy nose must be rated 2 or greater at beginning of treatment to be eligible for enrollment.

AHP1-REG-048-0015183

AHR-4010-3 PROTOCOL 04

(87-001)

FINAL VISIT FORM

Study No.	Patient No.	Patient Initials	Office (Clinic) No.	Date of Visit *Mo. Da. Yr.*

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A. PHYSICAL EXAMINATION

Yes	No		
☐	☐	1.	Evidence of:
☐	☐		a. Paranasal sinus infection?
☐	☐		b. Abnormal nasal mucosa? If yes, *describe* _____. *(unusual pallor, redness, mucoid bridging, turbinate enlargements, polyps, edema)*
☐	☐		c. Abnormal chest signs on ausculation?
☐	☐		d. Other (*specify* _____)

2. Complete the following:

_____ Current Temperature

_____ Blood Pressure

_____ Pulse Rate

B. RATE THE FOLLOWING SYMPTOMS AS 0 = not present, 1 = mild, 2 = moderate, 3 = severe

_____ Runny nose

_____ Stuffy nose

_____ Sneezing

_____ Headache

C. SMOKING HABITS

☐ Non-smoker

☐ Smoker — If smoker, complete the following:

☐ a. I have smoked as much or more than usual.

☐ b. I have smoked noticeably less than usual.

☐ c. I have discontinued smoking.

D. CONCURRENT MEDICATION

Yes	No		
☐	☐	1.	Have excluded drugs been taken. If yes, *explain*: _____
☐	☐	2.	Concurrent therapy taken by patient. If yes, *specify* _____

E. ADVERSE EFFECTS - If Adverse Effects, please complete *"ADVERSE EXPERIENCE REPORT FORM"*.

Yes	No	
☐	☐	_____ Investigator's Signature

AHP1-REG-048-0015184

OVERALL EVALUATION AND DISPOSITION

Study No.	Patient No.	Patient Initials	Office (Clinic) No.	Final Visit Date Mo. Dz. Yr.	Final Visit Time ☐ A.M. ☐ P.M.

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A. PROTOCOL VERIFICATION

Yes	No		
☐	☐	1.	Test medication taken as directed (*i.e., one teaspoonful every 4 hours - 4 to 6 times daily for 72 hours*)?

If "No", indicate the reason below:

☐ a. Intolerable adverse effects. *Complete "ADVERSE EXPERIENCE REPORT FORM".*

☐ b. Occurrence of intercurrent unrelated illness. *Describe* _____

☐ c. Patient refusal of treatment. *Why?* _____

☐ d. Unreliable or uncooperative patient. *Explain:* _____

☐ e. Administrative reasons. *Specify:* _____

☐ f. Other. *Specify:* _____

☐	☐	2.	Medication bottle and Patient Take-Home Questionnaire returned by patient? If no, *explain:* _____

_____ ml. Estimated volume of medication returned.

☐	☐	3.	Did physician review Patient Take-Home Questionnaire for accuracy and completeness? If "no", *explain:* _____

B. OVERALL THERAPEUTIC EFFECT OF STUDY DRUG TREATMENT (Check most appropriately matched box).

☐ 1. Marked - vast improvement. Complete or nearly complete remission of all symptoms.

☐ 2. Moderate - decided improvement. Partial remission of nasal symptoms.

☐ 3. Minimal - slight improvement in nasal symptoms, but not really altering patient status.

☐ 4. Unchanged - no change in nasal symptoms.

☐ 5. Worse - significant nasal symptoms became worse.

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AE

ADVERSE EXPERIENCE REPORT FORM

CRL	PROTOCOL	STUDY	PATIENT NO.	PATIENT INITIALS	CTR	CA	IP
4010-3	04						

INTENSITY RATING SCALE:

1 = MILD — Awareness of sign or symptom but easily tolerated

2 = MODERATE — Discomfort enough to cause interference with usual activity

3 = SEVERE — Incapacitating with inability to work or do usual activity

ADVERSE CLINICAL EXPERIENCE ☐ NONE (or specify)	Date Of Onset (day/mo/yr)	Duration In Days	Maximum Intensity	Action Taken Regarding Test Drug 1=None 2=Discontinued 3=Dosage Reduced 4=Interrupted	Was The Adverse Experience Serious? 1=No 2=Yes* (If YES, complete "Additional Data For Serious Adverse Experiences" section below)	Did The Test Drug Cause The Adverse Experience? 1=Definitely Not 2=Probably Not 3=Possibly 4=Probably 5=Definitely	Patient Outcome To Date 1=Recovered - No Residual Effects 2=Adverse Experience Still Present - No Treatment 3=Adverse Experience Still Present - Being Treated 4=Residual Effects Present - No Treatment 5=Residual Effects Present - Being Treated 6=Died (Give details in comments)
CNS							
Tremors							
Insomnia							
Dizziness							
Hyperexcitability							
Agitation							
Headache							
Lightheadedness							
Jitteriness							
Other:							
C.V.							
Palpitations							
Chest pain							
Other:							
Other:							

IF FEMALE: ☐ Not Pregnant ☐ Pregnant

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Additional Data for Serious Adverse Experiences:

☐ Yes ☐ No *Previous exposure to suspected or related compound:*

☐ Yes ☐ No *Potentially noxious or environmental factors (include household products, industrial and agricultural chemicals):*

☐ Yes ☐ No *Relevant existing or prior disorders and past drug reactions or allergic history:*

If a serious adverse experience is present at the end of the study, reports of the patient's subsequent course must be submitted to the monitor until the adverse experience subsides or until advised otherwise.

Comments:

Signature of Investigator

AE

AHP1-REG-048-0015186

Burton M. Cohen, M.D., F.A.C.P.
230 W. Jersey St., Elizabeth, NJ 07202

AHR -4010-3 Protocol 04
Study 0401

NASAL AIRWAYS FLOW/RESISTANCE DATA

Patient No. _____ Patient Initials _____ Screening Date _____

Time of Nasal flow/resistance studies _____ AM

_____ PM

Timing	Rn (expiration)*	plus	Rn(inspiration)*	=	Rn (total)*
Control					
15'					
30'					
45'					
1 Hour					
2 Hours					
3 Hours					
4 Hours					

* all in cm H20/1/sec, with values measured at standard reference flow/rate of 0.5 1/sec.

Burton M. Cohen, M.D., F.A.C.P.
Clinical Investigator

JUL 26 1978

JUL 26 1978

AHP1-REG-048-0015187

ATTACHMENT E

Patient Accountability Tables

AHP1-REG-048-0015188

Table E.1

Patient Accountability
Study 0401 (Dr. Cohen)

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination	Total
1. Patients:					
Screened	12	12	12	12	48
Screened but not admitted	0	0	0	0	0
2. Patients:					
Enrolled	12	12	12	12	48
Enrolled but excluded from efficacy	0	0	0	0	0
3. Patients Evaluatable					
Baseline	12	12	12	12	48
End of 24 hrs	12	12	12	12	48
End of 48 hrs	12	12	12	12	48
End of 72 hrs	12	12	12	12	48
4. Patients Prematurely Withdrawn					
Baseline	0	0	0	0	0
End of 24 hrs	0	0	0	0	0
End of 48 hrs	0	0	0	0	0
End of 72 hrs	0	0	0	0	0

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Table E.2

Patient Accountability
Study 0402 (Coleman)

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination	Total
1. Patients:					
Screened	6	6	6	5	23
Screened but not admitted	0	0	0	0	0
2. Patients:					
Enrolled	6	6	6	5	23
Enrolled but excluded from efficacy	0	0	0	0	0
3. Patients Evaluatable					
Baseline	6	6	6	5	23
End of 24 hrs	6	6	6	5	23
End of 48 hrs	6	5	5	5	21
End of 72 hrs	6	5	5	5	21
4. Patients Prematurely Withdrawn					
Baseline	0	0	0	0	0
End of 24 hrs	0	0	0	0	0
End of 48 hrs	0	1	1	0	2
End of 72 hrs	0	0	0	0	0

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Table E.3

Patient Accountability
Study 0403 (Esposito)

		Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination	Total
1.	Patients:					
	Screened	12	12	12	12	48
	Screened but not admitted	0	0	0	0	0
2.	Patients:					
	Enrolled	12	12	12	12	48
	Enrolled but excluded from efficacy	0	0	0	0	0
3.	Patients Evaluatable					
	Baseline	12	12	12	12	48
	End of 24 hrs	12	12	12	11	47
	End of 48 hrs	10	12	12	11	45
	End of 72 hrs	10	12	12	11	45
4.	Patients Prematurely Withdrawn					
	Baseline	0	0	0	0	0
	End of 24 hrs	0	0	0	1	1
	End of 48 hrs	2	0	0	0	2
	End of 72 hrs	0	0	0	0	0

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Table E.4

Patient Accountability
Study 0404 (Synder)

		Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination	Total
1.	Patients:					
	Screened	12	12	13	13	50
	Screened but not admitted	0	0	0	0	0
2.	Patients:					
	Enrolled	12	12	13	13	50
	Enrolled but excluded from efficacy	0	0	0	0	0
3.	Patients Evaluatable					
	Baseline	12	12	13	13	50
	End of 24 hrs	12	12	13	13	50
	End of 48 hrs	12	12	13	13	50
	End of 72 hrs	12	12	13	13	50
4.	Patients Prematurely Withdrawn					
	Baseline	0	0	0	0	0
	End of 24 hrs	0	0	0	0	0
	End of 48 hrs	0	0	0	0	0
	End of 72 hrs	0	0	0	0	0

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Table E.5

Patient Accountability
Study 0405 (Miller)

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination	Total	tal
.ients:						
·eened	14	13	14	12	53	
·eened but not admitted	0	0	0	0	0	52
						0
.ients:						
·olled	14	13	14	12	53	
·olled but excluded from efficacy	0	0	0	0	0	52
						0
.ients Evaluatable						
Ba·-eline	14	13	14	12	53	
E. of 24 hrs	13	13	13	10	49	52
End of 48 hrs	13	13	12	10	48	52
End of 72 hrs	12	13	12	10	47	51
						51
:ients Prematurely :hdrawn						
Baseline	0	0	0	0	0	
End of 24 hrs	1	0	1	2	4	0
End of 48 hrs	0	0	1	0	1	0
End of 72 hrs	1	0	0	0	1	1
						0

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Table E.7

Patient Accountability
All Studies Except 0401

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination	Total
1. Patient:					
Screened	57	57	57	55	226
Screened but not admitted	0	0	0	0	0
2. Patients:					
Enrolled	57	57	57	55	226
Enrolled but excluded from efficacy					
3. Patients Evaluatable					
Baseline	57	57	57	55	226
End of 24 hrs	56	57	56	52	221
End of 48 hrs	54	56	54	51	215
End of 72 hrs	53	56	54	51	214
4. Patients Prematurely Withdrawn					
Baseline	0	0	0	0	0
End of 24 hrs	1	0	1	3	5
End of 48 hrs	2	1	2	1	6
End of 72 hrs	1	0	0	0	1

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Table E.8

Patient Accountability
All Studies Combined

		Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination	Total
1.	Patients:					
	Screened	69	69	69	67	274
	Screened but not admitted	0	0	0	0	0
2.	Patients:					
	Enrolled	69	69	69	67	274
	Enrolled but excluded from efficacy	0	0	0	0	0
3.	Patients Evaluatable					
	Baseline	69	69	69	67	274
	End of 24 hrs	68	69	68	64	269
	End of 48 hrs	66	68	66	63	263
	End of 72 hrs	65	68	66	63	262
4.	Patients Prematurely Withdrawn					
	Baseline	0	0	0	0	0
	End of 24 hrs	1	0	1	3	5
	End of 48 hrs	2	1	2	1	6
	End of 72 hrs	1	0	0	0	1

AHP1-REG-048-0015195

ATTACHMENT F

Treatment Group Comparability Tables

AHP1-REG-048-0015196

Table F.1

Comparability of Treatment Groups
Study 0401 (Dr. Cohen)

		Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
1.	Age (years)				
	Mean	41.67	50.00	41.00	58.17
	SD	17.23	17.07	18.30	9.52
	N	12	12	12	12
2.	Weight (lbs)				
	Mean	166.31	162.94	141.79	162.52
	SD	24.71	29.96	20.13	22.38
	N	12	12	12	12
3.	Sex				
	Female	5	7	8	7
	Male	7	5	4	5
4.	Duration (hours) of Rhinitis				
	Mean	34.33	34.33	30.75	33.75
	SD	5.43	6.26	5.74	6.08
	N	12	12	12	12
5.	Smoking Habit				
	Yes	3	4	3	3
	No	9	8	9	9
6.	Fever				
	Yes	2	3	0	2
	No	10	9	12	10
7.	Para-nasal Sinus Infection				
	Yes	0	0	0	0
	No	12	12	12	12
8.	Abnormal Nasal Mucosa				
	Yes	12	12	12	12
	No	0	0	0	0
9.	Abnormal Chest Signs				
	Yes	0	0	0	0
	No	12	12	12	12
10.	Investigator's Rating of Runny Nose				
	None	0	0	0	0
	Mild	0	1	2	2
	Moderate	10	9	8	9
	Severe	2	2	2	1

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Table F.1
Comparability of Treatment Groups
Study 0401 (Dr. Cohen)
Continued

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
11. Investigator's Rating of Stuffy Nose				
None	0	0	0	0
Mild	0	0	0	0
Moderate	5	6	5	5
Severe	7	6	7	7
12. Investigator's Rating of Sneezing				
None	0	0	0	0
Mild	3	5	4	3
Moderate	7	7	8	8
Severe	2	0	0	1
13. Investigator's Rating of Headaches				
None	7	8	11	8
Mild	5	3	1	4
Moderate	0	1	0	0
Severe	0	0	0	0
14. Systolic BP (mmHg)				
Mean	121.25	120.83	120.83	124.58
SD	7.42	5.57	7.93	6.56
N	12	12	12	12
15. Diastolic BP (mmHg)				
Mean	73.75	72.50	71.67	73.83
SD	3.77	5.84	3.26	3.81
N	12	12	12	12
16. Pulse (BPM)				
Mean	77.17	71.33	77.00	71.33
SD	9.20	7.60	8.72	5.87
N	12	12	12	12

AHP1-REG-048-0015198

Table F.2
Comparability of Treatment Groups
Study 0402 (Coleman)

		Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
1.	Age (years)				
	Mean	30.00	38.33	25.67	30.00
	SD	13.58	17.77	4.37	5.70
	N	6	6	6	5
2.	Weight (lbs)				
	Mean	153.67	150.50	143.83	137.00
	SD	24.61	29.98	30.72	27.97
	N	6	6	6	5
3.	Sex				
	Female	3	5	3	4
	Male	3	1	3	1
4.	Duration (hours) of Rhinitis				
	Mean	28.67	29.00	30.00	25.20
	SD	15.06	11.01	10.04	10.73
	N	6	6	6	5
5.	Smoking Habit				
	Yes	2	2	1	0
	No	4	4	5	5
6.	Fever				
	Yes	0	0	0	0
	No	6	6	6	5
7.	Para-nasal Sinus Infection				
	Yes	0	0	0	0
	No	6	6	6	5
8.	Abnormal Nasal Mucosa				
	Yes	6	6	6	5
	No	0	0	0	0
9.	Abnormal Chest Signs				
	Yes	0	0	0	0
	No	6	6	6	5
10.	Investigator's Rating of Runny Nose				
	None	2	0	0	2
	Mild	0	4	1	1
	Moderate	4	1	2	1
	Severe	0	1	3	1

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Table F.2
Comparability of Treatment Groups
Study 0402 (Coleman)
Continued

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
11. Investigator's Rating of Stuffy Nose				
None	0	0	0	0
Mild	0	1	1	1
Moderate	5	3	5	4
Severe	1	2	0	0
12. Investigator's Rating of Sneezing				
None	2	0	2	2
Mild	3	1	0	3
Moderate	1	2	4	0
Severe	0	3	0	0
13. Investigator's Rating of Headaches				
None	2	1	4	5
Mild	2	3	1	0
Moderate	1	2	1	0
Severe	1	0	0	0
14. Systolic BP (mmHg)				
Mean	117.67	119.83	109.67	114.00
SD	6.74	11.50	5.85	5.78
N	6	6	6	5
15. Diastolic BP (mmHg)				
Mean	75.00	75.33	73.67	74.00
SD	5.48	8.64	4.97	5.48
N	6	6	6	5
16. Pulse (BPM)				
Mean	68.67	72.67	69.33	70.80
SD	8.07	4.84	5.47	2.68
N	6	6	6	5

AHP1-REG-048-0015200

Table F.3
Comparability of Treatment Groups
Study 0403 (Esposito)

		Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
1.	Age (years)				
	Mean	35.00	41.00	40.17	43.50
	SD	15.86	14.98	15.72	16.64
	N	12	12	12	12
2.	Weight (lbs)				
	Mean	153.50	154.83	146.00	153.92
	SD	24.15	36.80	32.72	39.40
	N	12	12	12	12
3.	Sex				
	Female	6	8	10	6
	Male	6	4	2	6
4.	Duration (hours) of Rhinitis				
	Mean	37.92	40.00	34.33	37.83
	SD	11.17	10.65	14.42	12.69
	N	12	12	12	12
5.	Smoking Habit				
	Yes	5	6	4	4
	No	7	6	8	8
6.	Fever				
	Yes	0	0	0	0
	No	12	12	12	12
7.	Para-nasal Sinus Infection				
	Yes	0	0	0	0
	No	12	12	12	12
8.	Abnormal Nasal Muscosa				
	Yes	12	12	12	12
	No	0	0	0	0
9.	Abnormal Chest Signs				
	Yes	0	0	0	0
	No	12	12	12	12
10.	Investigator's Rating of Runny Nose				
	None	1	3	0	1
	Mild	4	3	2	3
	Moderate	4	6	7	5
	Severe	3	0	3	3

AHP1-REG-048-0015201

Table F.3
Comparability of Treatment Groups
Study 0403 (Esposito)
Continued

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
11. Investigator's Rating of Stuffy Nose				
None	1	0	0	2
Mild	0	3	2	2
Moderate	7	8	6	7
Severe	4	1	4	1
12. Investigator's Rating of Sneezing				
None	2	7	2	4
Mild	8	4	4	5
Moderate	1	1	4	2
Severe	1	0	2	1
13. Investigator's Rating of Headaches				
None	4	4	8	7
Mild	6	5	3	2
Moderate	2	3	1	2
Severe	0	0	0	1
14. Systolic BP (mmHg)				
Mean	116.08	123.33	117.75	115.50
SD	14.72	13.46	11.74	14.20
N	12	12	12	12
15. Diastolic BP (mmHg)				
Mean	77.75	77.25	72.92	70.00
SD	7.62	8.70	8.70	6.82
N	12	12	12	12
16. Pulse (BPM)				
Mean	77.67	75.83	75.50	75.83
SD	9.87	8.20	8.49	6.79
N	12	12	12	12

AHP1-REG-048-0015202

Table F.4
Comparability of Treatment Groups
Study 0404 (Synder)

		Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
1.	Age (years)				
	Mean	38.90	36.17	35.38	32.08
	SD	17.81	12.98	14.63	11.98
	N	12	12	13	13
2.	Weight (lbs)				
	Mean	135.92	138.25	139.00	139.15
	SD	23.73	23.29	18.78	37.26
	N	12	12	13	13
3.	Sex				
	Female	9	9	10	11
	Male	3	3	3	2
4.	Duration (hours) of Rhinitis				
	Mean	29.00	30.00	26.31	33.23
	SD	8.02	10.85	5.76	9.98
	N	12	12	13	13
5.	Smoking Habit				
	Yes	0	0	0	0
	No	12	12	13	13
6.	Fever				
	Yes	1	3	1	2
	No	11	9	12	11
7.	Para-nasal Sinus Infection				
	Yes	0	2	0	0
	No	12	10	13	13
8.	Abnormal Nasal Muscosa				
	Yes	12	12	13	13
	No	0	0	0	0
9.	Abnormal Chest Signs				
	Yes	0	0	0	0
	No	12	12	13	13
10.	Investigator's Rating of Runny Nose				
	None	0	0	0	0
	Mild	0	0	0	0
	Moderate	1	0	1	0
	Severe	11	12	12	13

AHP1-REG-048-0015203

Table F.4
Comparability of Treatment Groups
Study 0404 (Synder)
Continued

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
11. Investigator's Rating of Stuffy Nose				
None	0	0	0	0
Mild	0	0	0	0
Moderate	0	0	0	0
Severe	12	12	13	13
12. Investigator's Rating of Sneezing				
None	0	0	0	0
Mild	0	0	1	0
Moderate	9	8	7	6
Severe	3	4	5	7
13. Investigator's Rating of Headaches				
None	0	0	1	0
Mild	3	3	5	4
Moderate	6	9	6	8
Severe	3	0	1	1
14. Systolic BP (mmHg)				
Mean	129.58	126.67	128.00	128.77
SD	8.65	6.85	8.58	8.50
N	12	12	13	13
15. Diastolic BP (mmHg)				
Mean	70.42	67.92	71.15	69.23
SD	7.22	6.56	8.93	8.38
N	12	12	13	13
16. Pulse (BPM)				
Mean	73.50	71.25	68.92	72.00
SD	4.60	4.83	7.09	5.31
N	12	12	13	13

AHP1-REG-048-0015204

Table F.5
Comparability of Treatment Groups
Study 0405 (Miller)

		Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
1.	Age (years)				
	Mean	44.93	37.00	42.29	38.33
	SD	12.21	13.08	16.57	9.84
	N	14	13	14	12
2.	Weight (lbs)				
	Mean	168.64	165.54	192.79	177.42
	SD	33.74	40.40	45.11	40.28
	N	14	13	14	12
3.	Sex				
	Female	4	7	4	6
	Male	10	6	10	6
4.	Duration (hours) of Rhinitis				
	Mean	37.86	37.85	39.43	38.00
	SD	13.60	10.78	10.97	10.02
	N	14	13	14	12
5.	Smoking Habit				
	Yes	6	7	6	3
	No	8	6	8	9
6.	Fever				
	Yes	0	0	0	0
	No	14	13	14	12
7.	Para-nasal Sinus Infection				
	Yes	0	0	0	0
	No	14	13	14	12
8.	Abnormal Nasal Mucosa				
	Yes	0	0	0	0
	No	14	13	14	12
9.	Abnormal Chest Signs				
	Yes	0	0	0	0
	No	14	13	14	12
10.	Investigator's Rating of Runny Nose				
	None	0	0	0	0
	Mild	0	3	0	0
	Moderate	13	5	11	11
	Severe	1	5	3	1

AHP1-REG-048-0015205

Table F.5
Comparability of Treatment Groups
Study 0405 (Miller)
Continued

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
11. Investigator's Rating of Stuffy Nose				
None	0	0	0	0
Mild	0	0	0	0
Moderate	9	8	7	9
Severe	5	5	7	3
12. Investigator's Rating of Sneezing				
None	0	1	0	1
Mild	2	3	3	1
Moderate	9	5	10	9
Severe	3	4	1	1
13. Investigator's Rating of Headaches				
None	5	4	6	7
Mild	4	3	2	0
Moderate	4	5	5	3
Severe	1	1	1	2
14. Systolic BP (mmHg)				
Mean	129.00	120.15	122.14	124.00
SD	16.03	14.27	8.54	17.73
N	14	13	14	12
15. Diastolic BP (mmHg)				
Mean	81.86	79.23	84.14	84.83
SD	10.03	14.41	7.86	10.03
N	14	13	14	12
16. Pulse (BPM)				
Mean	79.14	79.08	78.71	81.17
SD	9.27	7.38	8.76	8.24
N	14	13	14	12

AHP1-REG-048-0015206

Table F.6
Comparability of Treatment Groups
Study 0406 (Birkam)

		Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
1.	Age (years)				
	Mean	21.08	21.57	20.92	20.62
	SD	2.18	2.03	1.51	1.56
	N	13	14	12	13
2.	Weight (lbs.)				
	Mean	145.31	165.21	152.25	156.38
	SD	28.33	21.49	30.80	20.10
	N	13	14	12	13
3.	Sex				
	Female	7	4	6	3
	Male	6	10	6	10
4.	Duration (hours) of Rhinitis				
	Mean	35.38	27.50	24.33	35.38
	SD	9.32	10.99	9.18	9.84
	N	13	14	12	13
5.	Smoking Habit				
	Yes	3	2	3	3
	No	10	12	9	10
6.	Fever				
	Yes	0	1	2	1
	No	13	13	10	12
7.	Para-nasal Sinus Infection				
	Yes	3	5	5	4
	No	10	9	7	9
8.	Abnormal Nasal Mucosa				
	Yes	13	14	12	13
	No	0	0	0	0
9.	Abnormal Chest Signs				
	Yes	0	0	1	0
	No	13	14	11	13
10.	Investigator's Rating of Runny Nose				
	None	1	0	0	0
	Mild	2	2	1	3
	Moderate	9	11	10	9
	Severe	1	1	1	1

AHP1-REG-048-0015207

Table F.6
Comparability of Treatment Groups
Study 0406 (Birkam)
Continued

		Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
11.	Investigator's Rating of Stuffy Nose				
	None	0	0	0	1
	Mild	3	1	5	2
	Moderate	9	12	7	9
	Severe	1	1	0	1
12.	Investigator's Rating of Sneezing				
	None	1	2	1	4
	Mild	11	12	7	6
	Moderate	1	0	3	3
	Severe	0	0	1	0
13.	Investigator's Rating of Headaches				
	None	7	6	5	7
	Mild	5	7	5	5
	Moderate	1	1	2	1
	Severe	0	0	0	0
14.	Systolic BP (mmHg)				
	Mean	115.08	117.86	114.33	118.92
	SD	13.41	11.86	10.86	12.53
	N	13	14	12	13
15.	Diastolic BP (mmHg)				
	Mean	74.92	77.00	73.50	74.31
	SD	10.28	7.87	11.06	8.71
	N	13	14	12	13
16.	Pulse (BPM)				
	Mean	78.46	82.43	77.83	79.23
	SD	15.21	10.35	10.63	10.51
	N	13	14	12	13

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Table F.7
Comparability of Treatment Groups
All Studies Except 0401

		Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
1.	Age (years)				
	Mean	34.47	34.02	34.02	33.04
	SD	15.44	14.04	15.17	13.41
	N	57	57	57	55
2.	Weight				
	Mean	151.67	155.88	156.98	154.60
	SD	29.18	31.99	38.39	36.13
	N	57	57	57	55
3.	Sex				
	Female	29	33	33	30
	Male	28	24	24	25
4.	Duration (hours) of Rhinitis				
	Mean	34.47	33.18	31.19	35.05
	SD	11.60	11.68	11.67	10.90
	N	57	57	57	55
5.	Smoking habit				
	Yes	16	17	14	10
	No	41	40	43	45
6.	Fever				
	Yes	1	4	3	3
	No	56	53	54	52
7.	Para-nasal Sinus Infection				
	Yes	3	7	5	4
	No	54	50	52	51
8.	Abnormal Nasal Muscosa				
	Yes	43	44	43	43
	No	14	13	14	12
9.	Abnormal Chest Signs				
	Yes	0	0	1	0
	No	57	57	56	55
10.	Investigator's Rating of Runny Nose				
	None	4	3	0	3
	Mild	6	12	4	7
	Moderate	31	23	31	26
	Severe	16	19	22	19

AHP1-REG-048-0015209

Table F.7
Comparability of Treatment Groups
All Studies Except 0401
Continued

		Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
11.	Investigator's Rating of Stuffy Nose				
	None	1	0	0	3
	Mild	3	5	8	5
	Moderate	30	31	25	29
	Severe	23	21	24	18
12.	Investigator's Rating of Sneezing				
	None	5	10	5	11
	Mild	24	20	15	15
	Moderate	21	16	28	20
	Severe	7	11	9	9
13.	Investigator's Rating of Headaches				
	None	18	15	24	26
	Mild	20	21	16	11
	Moderate	14	20	15	14
	Severe	5	1	2	4
14.	Systolic BP (mmHg)				
	Mean	122.04	121.60	119.60	121.16
	SD	14.31	11.97	11.01	13.68
	N	57	57	57	55
15.	Diastolic BP (mmHg)				
	Mean	76.28	75.47	75.47	74.44
	SD	9.30	10.28	9.91	9.98
	N	57	57	57	55
16.	Pulse (BPM)				
	Mean	76.39	76.89	74.63	76.44
	SD	10.49	8.61	9.20	8.32
	N	57	57	57	55

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Table F.8
Comparability of Treatment Groups
All Studies Combined

		Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
1.	Age (years)				
	Mean	35.72	36.80	35.23	37.54
	SD	15.87	15.71	15.84	16.01
	N	69	69	69	67
2.	Weight (lbs)				
	Mean	154.21	157.11	154.34	156.01
	SD	28.83	31.54	36.23	34.07
	N	69	69	69	67
3.	Sex				
	Female	34	40	41	37
	Male	35	29	28	30
4.	Duration (hours) of Rhinitis				
	Mean	34.45	33.38	31.12	34.82
	SD	10.75	10.90	10.89	10.18
	N	69	69	69	67
5.	Smoking Habit				
	Yes	19	21	17	13
	No	50	48	52	54
6.	Fever				
	Yes	3	7	3	5
	No	66	62	66	62
7.	Para-nasal Sinus Infection				
	Yes	3	7	5	4
	No	66	62	64	63
8.	Abnormal Nasal Mucosa				
	Yes	55	56	55	55
	No	14	13	14	12
9.	Abnormal Chest Signs				
	Yes	0	0	1	0
	No	69	69	68	67
10.	Investigator's Rating of Runny Nose				
	None	4	3	0	3
	Mild	6	13	6	9
	Moderate	41	32	39	35
	Severe	18	21	24	20

AHP1-REG-048-0015211

Table F.8
Comparability of Treatment Groups
All Studies Combined
Continued

	Placebo	Phenyl-propanolamine	Phenyl-ephrine	Combination
11. Investigator's Rating of Stuffy Nose				
None	1	0	0	3
Mild	3	5	8	5
Moderate	35	37	30	34
Severe	30	27	31	25
12. Investigator's Rating of Sneezing				
None	5	10	5	11
Mild	27	25	19	18
Moderate	28	23	36	28
Severe	9	11	9	10
13. Investigator's Rating of Headaches				
None	25	23	35	34
Mild	25	24	17	15
Moderate	14	21	15	14
Severe	5	1	2	4
14. Systolic BP (mmHg)				
Mean	121.90	121.46	119.81	121.78
SD	13.33	11.10	10.50	12.73
N	69	69	69	67
15. Diastolic BP (mmHg)				
Mean	75.84	74.96	74.81	74.33
SD	8.63	9.69	9.21	9.16
N	69	69	69	67
16. Pulse (BPM)				
Mean	76.52	75.93	75.04	75.52
SD	10.22	8.66	9.10	8.14
N	69	69	69	67

AHP1-REG-048-0015212

ATTACHMENT G

ANOVA Tables for All Efficacy Parameters

AHP1-REG-048-0015213

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF RATINGS OF OVERALL THERAPEUTIC EFFECT

STUDY=401

ANOVA TABLE FOR INVESTIGATOR'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
TRTMENT	3	21.500	38.61	0.0001
ERROR	44	8.167		

STUDY=402

ANOVA TABLE FOR INVESTIGATOR'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
TRTMENT	3	4.367	0.87	0.4737
ERROR	17	28.300		

STUDY=403

ANOVA TABLE FOR INVESTIGATOR'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
TRTMENT	3	1.533	0.30	0.8246
ERROR	41	69.667		

AHP1-REG-048-0015214

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF RATINGS OF OVERALL THERAPEUTIC EFFECT

STUDY=404

ANOVA TABLE FOR INVESTIGATOR'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
TRTMENT	3	2.880	0.60	0.6195
ERROR	46	73.840		

STUDY=405

ANOVA TABLE FOR INVESTIGATOR'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
TRTMENT	3	0.795	0.26	0.8551
ERROR	43	44.141		

STUDY=406

ANOVA TABLE FOR INVESTIGATOR'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
TRTMENT	3	2.991	1.19	0.3236
ERROR	47	39.362		

AHP1-REG-048-0015215

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF RATINGS OF OVERALL THERAPEUTIC EFFECT

STUDY=401

ANOVA TABLE FOR PATIENT'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
TRTMENT	3	23.457	32.02	0.0001
ERROR	43	10.500		

STUDY=402

ANOVA TABLE FOR PATIENT'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
TRTMENT	3	4.367	1.11	0.3726
ERROR	17	22.300		

STUDY=403

ANOVA TABLE FOR PATIENT'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
TRTMENT	3	4.191	1.59	0.2074
ERROR	41	36.120		

AHP1-REG-048-0015216

AHR 4010 O I M E T A P P PROTOCOL 04
ANALYSIS OF RATINGS OF OVERALL THERAPEUTIC EFFECT

STUDY=404

ANOVA TABLE FOR PATIENT'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
TRTMENT	3	2.271	0.66	0.5797
ERROR	46	52.609		

STUDY=405

ANOVA TABLE FOR PATIENT'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
TRTMENT	3	0.142	0.05	0.9855
ERROR	42	40.814		

STUDY=406

ANOVA TABLE FOR PATIENT'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
TRTMENT	3	3.394	1.94	0.1353
ERROR	47	27.351		

AHP1-REG-048-0015217

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF RATINGS OF OVERALL THERAPEUTIC EFFECT
ANALYSIS FOR DATA FROM STUDIES 0402,0403,0404,0405 & 0406.

ANOVA TABLE FOR INVESTIGATOR'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
STUDY	4	12.951	2.46	0.0468
TRTMENT	3	6.256	1.58	0.1928
STUDY*TRTMENT	12	7.633	0.48	0.9229
ERROR	194	255.309		

ANOVA TABLE FOR PATIENT'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
STUDY	4	3.309	0.89	0.4704
TRTMENT	3	5.891	2.12	0.0981
STUDY*TRTMENT	12	10.006	0.90	0.5499
ERROR	193	179.194		

AHP1-REG-048-0015218

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF RATINGS OF OVERALL THERAPEUTIC EFFECT
ANALYSIS FOR DATA FROM STUDIES 0401,0402,0403,0404,0405 & 0406.

ANOVA TABLE FOR INVESTIGATOR'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
STUDY	5	18.895	3.41	0.0055
TRTMENT	3	4.056	1.22	0.3023
STUDY*TRTMENT	15	30.294	1.82	0.0321
ERROR	238	263.476		

ANOVA TABLE FOR PATIENT'S RATING AT 72 HRS

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
STUDY	5	7.989	1.99	0.0803
TRTMENT	3	5.673	2.35	0.0716
STUDY*TRTMENT	15	32.662	2.71	0.0008
ERROR	236	189.694		

AHP1-REG-048-0015219

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=401

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	1.122	2.90	0.0661
TRTMENT	3	1.589	2.74	0.0553
ERROR	42	8.128		

STUDY=401

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	0.137	0.30	0.7430
TRTMENT	3	3.075	4.48	0.0081
ERROR	42	9.613		

STUDY=401

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	0.363	0.61	0.5473
TRTMENT	3	5.947	6.68	0.0009
ERROR	42	12.470		

AHP1-REG-048-0015220

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=402

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	9.241	13.72	0.0001
TRTMENT	3	1.208	1.79	0.1890
ERROR	16	3.592		

STUDY=402

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	6.742	3.89	0.0326
TRTMENT	3	3.534	2.04	0.1548
ERROR	14	8.091		

STUDY=402

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	3.168	2.25	0.1273
TRTMENT	3	2.859	2.03	0.1556
ERROR	14	6.566		

AHP1-REG-048-0015221

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=403

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	16.382	13.93	0.0001
TRTMENT	3	1.937	1.65	0.1937
ERROR	40	15.679		

STUDY=403

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	4.018	2.16	0.1091
TRTMENT	3	0.823	0.44	0.7245
ERROR	38	23.597		

STUDY=403

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	2.827	1.30	0.2891
TRTMENT	3	2.485	1.14	0.3449
ERROR	38	27.583		

AHP1-REG-048-0015222

AHR 4010 O T M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=404

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	1	0.087	0.24	0.6241
TRTMENT	3	2.010	1.97	0.1488
ERROR	45	16.156		

STUDY=404

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	1	0.126	0.14	0.7089
TRTMENT	3	2.361	0.88	0.4571
ERROR	45	40.118		

STUDY=404

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	1	0.423	0.38	0.5406
TRTMENT	3	4.396	1.32	0.2807
ERROR	45	50.083		

AHP1-REG-048-0015223

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=405

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	2.366	1.78	0.1804
TRTMENT	3	4.834	2.43	0.0783
ERROR	43	28.534		

STUDY=405

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	2.014	1.18	0.3176
TRTMENT	3	1.400	0.55	0.6535
ERROR	42	35.886		

STUDY=405

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	3.915	2.68	0.0803
TRTMENT	3	2.313	1.06	0.3780
ERROR	41	29.910		

AHP1-REG-048-0015224

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=406

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	1.314	0.73	0.5402
TRTMENT	3	0.586	0.33	0.8071
ERROR	45	27.033		

STUDY=406

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	1.247	0.69	0.5647
TRTMENT	3	0.686	0.38	0.7692
ERROR	44	26.616		

STUDY=406

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	0.456	0.30	0.8284
TRTMENT	3	0.065	0.04	0.9883
ERROR	44	22.626		

AHP1-REG-048-0015225

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS FOR DATA POOLED ACROSS STUDIES 0402,0403,0404,0405,AND 0406.

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	22.447	15.13	0.0001
STUDY	4	19.121	9.66	0.0001
TRTMENT	3	2.878	1.94	0.1228
TRTMENT*STUDY	12	6.481	1.09	0.3687
ERROR	198	97.937		

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	7.482	3.40	0.0188
STUDY	4	11.887	4.05	0.0036
TRTMENT	3	1.521	0.69	0.5624
TRTMENT*STUDY	12	6.359	0.72	0.7292
ERROR	192	140.974		

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	1.260	0.55	0.6539
STUDY	4	14.090	4.60	0.0014
TRTMENT	3	1.492	0.65	0.5883
TRTMENT*STUDY	12	6.834	0.74	0.7075
ERROR	191	146.296		

AHP1-REG-048-0015226

ANALYSIS FOR DATA POOLED ACROSS STUDIES 0401,0402,0403,0404,0405,AND 0406.

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	23.559	17.92	0.0001
STUDY	5	23.645	10.79	0.0001
TRTMENT	3	2.855	2.17	0.0905
TRTMENT*STUDY	15	8.402	1.28	0.2161
ERROR	242	106.074		

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	6.569	3.41	0.0182
STUDY	5	18.856	5.87	0.0001
TRTMENT	3	0.564	0.29	0.8322
TRTMENT*STUDY	15	10.373	1.08	0.3797
ERROR	236	151.636		

ANOVA TABLE FOR RUNNY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	1.549	0.76	0.5184
STUDY	5	17.875	5.29	0.0002
TRTMENT	3	1.482	0.73	0.5379
TRTMENT*STUDY	15	12.223	1.21	0.2677
ERROR	235	158.841		

AHP1-REG-048-0015227

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF INVESTIGATOR'S RATING OF SYMPTOMS

STUDY=401

ANOVA TABLE FOR RUNNY NOSE(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	0.712	1.39	0.2612
TRTMENT	3	3.615	4.69	0.0065
ERROR	42	10.788		

STUDY=402

ANOVA TABLE FOR RUNNY NOSE(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	3.168	2.25	0.1273
TRTMENT	3	2.859	2.03	0.1556
ERROR	14	6.566		

STUDY=403

ANOVA TABLE FOR RUNNY NOSE(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	2.537	1.34	0.2750
TRTMENT	3	3.865	2.05	0.1239
ERROR	38	23.941		

AHP1-REG-048-0015228

AHR 4010 D I M E T A P P PROTOCOL 04

ANALYSIS FOR DATA FROM STUDIES 0402,0403,0404,0405 & 0406.

ANOVA TABLE FOR RUNNY NOSE(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	1.398	0.67	0.5736
STUDY	4	19.346	6.98	0.0001
TRTMENT	3	3.345	1.61	0.1871
STUDY*TRTMENT	12	6.955	0.84	0.6129
ERROR	191	132.359		

AHP1-REG-048-0015229

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF RATINGS OF OVERALL THERAPEUTIC EFFECT
ANALYSIS FOR DATA FROM STUDIES 0401,0402,0403,0404,0405 & 0406.

ANOVA TABLE FOR RUNNY NOSE(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	1.846	1.01	0.3908
STUDY	5	24.615	8.07	0.0001
TRTMENT	3	3.202	1.75	0.1559
STUDY*TRTMENT	15	10.697	1.17	0.2970
ERROR	235	143.411		

AHP1-REG-048-0015230

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=401

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	1	0.387	2.19	0.1465
TRTMENT	3	0.793	1.49	0.2298
ERROR	43	7.413		

STUDY=401

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	1	1.301	4.85	0.0330
TRTMENT	3	5.718	7.11	0.0006
ERROR	43	11.532		

STUDY=401

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	1	0.646	2.62	0.1129
TRTMENT	3	6.365	8.60	0.0001
ERROR	43	10.604		

AHP1-REG-048-0015231

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=402

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	4.531	5.63	0.0133
TRTMENT	3	0.615	0.51	0.6808
ERROR	17	6.836		

STUDY=402

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	1.672	1.57	0.2394
TRTMENT	3	1.105	0.69	0.5699
ERROR	15	7.962		

STUDY=402

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	2.616	2.28	0.1369
TRTMENT	3	0.983	0.57	0.6431
ERROR	15	8.617		

AHP1-REG-048-0015232

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=403

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	7.974	5.11	0.0043
TRTMENT	3	4.150	2.66	0.0610
ERROR	40	20.791		

STUDY=403

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	6.521	5.11	0.0045
TRTMENT	3	2.015	1.58	0.2101
ERROR	38	16.155		

STUDY=403

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	5.889	3.59	0.0222
TRTMENT	3	1.642	1.00	0.4026
ERROR	38	20.764		

AHP1-REG-048-0015233

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=404

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	0	0.000		
TRTMENT	3	1.856	2.33	0.0869
ERROR	46	12.224		

STUDY=404

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	0	0.000		
TRTMENT	3	2.341	1.15	0.3387
ERROR	46	31.179		

STUDY=404

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	0	0.000		
TRTMENT	3	1.455	0.54	0.6549
ERROR	46	41.045		

AHP1-REG-048-0015234

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=405

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	1	0.297	0.53	0.4690
TRTMENT	3	4.629	2.77	0.0525
ERROR	44	24.472		

STUDY=405

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	1	1.738	2.32	0.1350
TRTMENT	3	3.427	1.53	0.2215
ERROR	43	32.202		

STUDY=405

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	1	0.009	0.01	0.9221
TRTMENT	3	1.294	0.46	0.7148
ERROR	42	39.766		

AHP1-REG-048-0015235

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=406

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	5.974	6.41	0.0010
TRTMENT	3	1.118	1.20	0.3210
ERROR	45	13.982		

STUDY=406

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	4.202	3.85	0.0156
TRTMENT	3	0.863	0.79	0.5051
ERROR	44	15.995		

STUDY=406

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	6.109	5.28	0.0034
TRTMENT	3	2.557	2.21	0.1001
ERROR	44	16.960		

AHP1-REG-048-0015236

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS FOR DATA POOLED ACROSS STUDIES 0402,0403,0404,0405,AND 0406.

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	16.731	13.74	0.0001
STUDY	4	9.219	5.68	0.0002
TRTMENT	3	2.924	2.40	0.0677
TRTMENT*STUDY	12	8.370	1.72	0.0650
ERROR	198	80.350		

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	12.857	7.85	0.0001
STUDY	4	8.928	4.09	0.0033
TRTMENT	3	2.402	1.47	0.2234
TRTMENT*STUDY	12	6.320	0.97	0.4836
ERROR	192	104.769		

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	9.354	4.50	0.0047
STUDY	4	20.217	7.29	0.0001
TRTMENT	3	4.666	2.24	0.0832
TRTMENT*STUDY	12	2.598	0.31	0.9867
ERROR	191	132.422		

AHP1-REG-048-0015237

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS FOR DATA POOLED ACROSS STUDIES 0401,0402,0403,0404,0405,AND 0406.

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	16.694	15.24	0.0001
STUDY	5	11.841	6.48	0.0001
TRTMENT	3	2.597	2.37	0.0699
TRTMENT*STUDY	15	10.079	1.84	0.0302
ERROR	242	88.386		

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	14.103	9.53	0.0001
STUDY	5	10.722	4.35	0.0009
TRTMENT	3	0.877	0.59	0.6243
TRTMENT*STUDY	15	14.308	1.93	0.0209
ERROR	236	116.356		

ANOVA TABLE FOR STUFFY NOSE(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	9.631	5.26	0.0017
STUDY	5	21.724	7.12	0.0001
TRTMENT	3	2.652	1.45	0.2280
TRTMENT*STUDY	15	11.905	1.30	0.2020
ERROR	235	143.395		

AHP1-REG-048-0015238

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF INVESTIGATOR'S RATING OF SYMPTOMS

STUDY=401

ANOVA TABLE FOR STUFFY NOSE(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	1	0.191	0.92	0.3435
TRTMENT	3	6.781	10.83	0.0001
ERROR	43	8.975		

STUDY=402

ANOVA TABLE FOR STUFFY NOSE(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	2.254	1.73	0.2111
TRTMENT	3	0.621	0.32	0.8127
ERROR	15	9.779		

STUDY=403

ANOVA TABLE FOR STUFFY NOSE(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	4.823	2.67	0.0612
TRTMENT	3	1.843	1.02	0.3943
ERROR	38	22.876		

AHP1-REG-048-0015239

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF INVESTIGATOR'S RATING OF SYMPTOMS

STUDY=404

ANOVA TABLE FOR STUFFY NOSE(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	0	0.000		
TRTMENT	3	0.985	0.39	0.7576
ERROR	46	38.295		

STUDY=405

ANOVA TABLE FOR STUFFY NOSE(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	1	0.199	0.21	0.6518
TRTMENT	3	1.116	0.39	0.7638
ERROR	42	40.510		

STUDY=406

ANOVA TABLE FOR STUFFY NOSE(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	7.439	5.11	0.0040
TRTMENT	3	1.923	1.32	0.2798
ERROR	44	21.360		

AHP1-REG-048-0015240

AHR 4010 D I M E T A P P PROTOCOL 04

ANALYSIS FOR DATA FROM STUDIES 0402,0403,0404,0405 & 0406.

ANOVA TABLE FOR STUFFY NOSE(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	7.019	3.18	0.0249
STUDY	4	29.941	10.17	0.0001
TRTMENT	3	3.156	1.43	0.2341
STUDY*TRTMENT	12	2.921	0.33	0.9829
ERROR	191	140.516		

AHP1-REG-048-0015241

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF RATINGS OF OVERALL THERAPEUTIC EFFECT
ANALYSIS FOR DATA FROM STUDIES 0401,0402,0403,0404,0405 & 0406.

ANOVA TABLE FOR STUFFY NOSE(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	6.799	3.55	0.0151
STUDY	5	33.170	10.40	0.0001
TRTMENT	3	2.110	1.10	0.3492
STUDY*TRTMENT	15	11.278	1.18	0.2888
ERROR	235	149.903		

AHP1-REG-048-0015242

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=401

ANOVA TABLE FOR SNEEZING(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	4.410	10.89	0.0002
TRTMENT	3	0.852	1.40	0.2554
ERROR	42	8.507		

STUDY=401

ANOVA TABLE FOR SNEEZING(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	0.789	1.13	0.3338
TRTMENT	3	5.629	5.36	0.0032
ERROR	42	14.711		

STUDY=401

ANOVA TABLE FOR SNEEZING(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	1.935	2.86	0.0688
TRTMENT	3	8.077	7.95	0.0003
ERROR	42	14.232		

AHP1-REG-048-0015243

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=402

ANOVA TABLE FOR SNEEZING(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	0.723	0.31	0.8185
TRTMENT	3	2.523	1.08	0.3862
ERROR	16	12.477		

STUDY=402

ANOVA TABLE FOR SNEEZING(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	3.098	2.52	0.1001
TRTMENT	3	1.465	1.19	0.3485
ERROR	14	5.735		

STUDY=402

ANOVA TABLE FOR SNEEZING(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	0.779	0.69	0.5721
TRTMENT	3	0.760	0.67	0.5816
ERROR	14	5.254		

AHP1-REG-048-0015244

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=403

ANOVA TABLE FOR SNEEZING(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	10.351	10.87	0.0001
TRTMENT	3	1.336	1.40	0.2560
ERROR	40	12.702		

STUDY=403

ANOVA TABLE FOR SNEEZING(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	0.773	0.51	0.6760
TRTMENT	3	0.546	0.36	0.7807
ERROR	38	19.090		

STUDY=403

ANOVA TABLE FOR SNEEZING(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	1.005	0.73	0.5412
TRTMENT	3	2.698	1.96	0.1370
ERROR	38	17.471		

AHP1-REG-048-0015245

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=404

ANOVA TABLE FOR SNEEZING(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	1	3.227	6.24	0.0162
TRTMENT	3	0.628	0.40	0.7506
ERROR	45	23.285		

STUDY=404

ANOVA TABLE FOR SNEEZING(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	1	0.326	0.33	0.5702
TRTMENT	3	1.461	0.49	0.6914
ERROR	45	44.796		

STUDY=404

ANOVA TABLE FOR SNEEZING(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	1	2.267	1.71	0.1973
TRTMENT	3	2.926	0.74	0.5355
ERROR	45	59.566		

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AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=405

ANOVA TABLE FOR SNEEZING(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	4.989	2.13	0.1106
TRTMENT	3	1.594	0.68	0.5687
ERROR	42	32.765		

STUDY=405

ANOVA TABLE FOR SNEEZING(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	3.230	1.12	0.3533
TRTMENT	3	0.206	0.07	0.9750
ERROR	41	39.516		

STUDY=405

ANOVA TABLE FOR SNEEZING(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	2.122	1.11	0.3566
TRTMENT	3	1.790	0.94	0.4324
ERROR	40	25.503		

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AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF PATIENT'S RATING OF SYMPTOMS

STUDY=406

ANOVA TABLE FOR SNEEZING(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	10.238	10.11	0.0001
TRTMENT	3	3.478	3.44	0.0246
ERROR	45	15.184		

STUDY=406

ANOVA TABLE FOR SNEEZING(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	6.233	6.85	0.0007
TRTMENT	3	0.531	0.58	0.6291
ERROR	44	13.355		

STUDY=406

ANOVA TABLE FOR SNEEZING(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	2.704	3.75	0.0175
TRTMENT	3	0.571	0.79	0.5048
ERROR	44	10.572		

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AHR 4010 O I M E T A P P PROTOCOL 04
ANALYSIS FOR DATA POOLED ACROSS STUDIES 0402,0403,0404,0405,AND 0406.

ANOVA TABLE FOR SNEEZING(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	21.766	13.79	0.0001
STUDY	4	10.873	5.17	0.0006
TRTMENT	3	2.125	1.35	0.2596
TRTMENT*STUDY	12	5.577	0.88	0.5649
ERROR	198	104.175		

ANOVA TABLE FOR SNEEZING(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	9.385	4.74	0.0034
STUDY	4	9.327	3.53	0.0083
TRTMENT	3	0.680	0.34	0.7964
TRTMENT*STUDY	12	2.948	0.37	0.9719
ERROR	192	126.766		

ANOVA TABLE FOR SNEEZING(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	5.084	2.65	0.0493
STUDY	4	15.261	5.97	0.0002
TRTMENT	3	0.396	0.21	0.8905
TRTMENT*STUDY	12	7.630	0.99	0.4560
ERROR	191	122.160		

AHP1-REG-048-0015249

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS FOR DATA POOLED ACROSS STUDIES 0401,0402,0403,0404,0405,AND 0406.

ANOVA TABLE FOR SNEEZING(PAT RATING,24 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	25.853	18.45	0.0001
STUDY	5	18.767	8.04	0.0001
TRTMENT	3	1.323	0.94	0.4215
TRTMENT*STUDY	15	7.464	1.07	0.3893
ERROR	242	113.005		

ANOVA TABLE FOR SNEEZING(PAT RATING,48 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	10.148	5.64	0.0011
STUDY	5	12.580	4.20	0.0012
TRTMENT	3	0.074	0.04	0.9835
TRTMENT*STUDY	15	8.943	0.99	0.4620
ERROR	236	141.503		

ANOVA TABLE FOR SNEEZING(PAT RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	5.195	2.94	0.0332
STUDY	5	16.121	5.48	0.0001
TRTMENT	3	0.331	0.19	0.9028
TRTMENT*STUDY	15	14.588	1.65	0.0612
ERROR	235	138.216		

AHP1-REG-048-0015250

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF INVESTIGATOR'S RATING OF SYMPTOMS

STUDY=401

ANOVA TABLE FOR SNEEZING(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	0.563	0.87	0.4265
TRTMENT	3	2.797	2.88	0.0472
ERROR	42	13.603		

STUDY=402

ANOVA TABLE FOR SNEEZING(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	0.610	0.52	0.6725
TRTMENT	3	0.910	0.78	0.5231
ERROR	14	5.424		

STUDY=403

ANOVA TABLE FOR SNEEZING(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	0.921	0.66	0.5790
TRTMENT	3	2.754	1.99	0.1323
ERROR	38	17.555		

AHP1-REG-048-0015251

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF INVESTIGATOR'S RATING OF SYMPTOMS

STUDY=404

ANOVA TABLE FOR SNEEZING(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	2	1.725	0.63	0.5383
TRTMENT	3	2.574	0.62	0.6028
ERROR	44	60.416		

STUDY=405

ANOVA TABLE FOR SNEEZING(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	1.693	1.04	0.3868
TRTMENT	3	0.487	0.30	0.8266
ERROR	40	21.771		

STUDY=406

ANOVA TABLE FOR SNEEZING(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	0.296	0.73	0.5380
TRTMENT	3	0.472	1.17	0.3329
ERROR	44	5.928		

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AHR 4010 D I M E T A P P PROTOCOL 04

ANALYSIS FOR DATA FROM STUDIES 0402,0403,0404,0405 & 0406.

ANOVA TABLE FOR SNEEZING(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	2.988	1.68	0.1714
STUDY	4	23.616	9.95	0.0001
TRTMENT	3	0.456	0.26	0.8571
STUDY*TRTMENT	12	5.621	0.79	0.6612
ERROR	191	113.351		

AHP1-REG-048-0015253

AHR 4010 D I M E T A P P PROTOCOL 04
ANALYSIS OF RATINGS OF OVERALL THERAPEUTIC EFFECT
ANALYSIS FOR DATA FROM STUDIES 0401,0402,0403,0404,0405 & 0406.

ANOVA TABLE FOR SNEEZING(INV RATING,72 HRS)

SOURCE OF VARIATION	DEGREES OF FREEDOM	SUMS OF SQUARES	F VALUE	P VALUE
BASELINE	3	3.008	1.85	0.1374
STUDY	5	24.292	8.95	0.0001
TRTMENT	3	0.388	0.24	0.8693
STUDY*TRTMENT	15	8.558	1.05	0.4033
ERROR	235	127.497		

AHP1-REG-048-0015254

Summary of Analysis of Covariance of Change from Baseline of NAR for Study 0401

Time of Evaluation	Source of Variation	Degrees of Freedom	Sums of Squares	F-value	P-value
15 minutes	Baseline NAR	1	1.956	7.10	0.011
	Treatment	3	0.875	1.06	0.377
	Error	43	11.851		
30 minutes	Baseline NAR	1	8.575	43.18	<0.001
	Treatment	3	3.709	6.23	0.001
	Error	43	8.539		
45 minutes	Baseline NAR	1	8.915	78.83	<0.001
	Treatment	3	12.320	36.31	<0.001
	Error	43	4.863		
60 minutes	Baseline NAR	1	11.347	62.04	<0.001
	Treatment	3	8.693	15.84	<0.001
	Error	43	7.864		
120 minutes	Baseline NAR	1	10.561	35.36	<0.001
	Treatment	3	10.122	11.30	<0.001
	Error	43	12.843		
180 minutes	Baseline NAR	1	9.709	22.72	<0.001
	Treatment	3	4.939	3.85	0.016
	Error	43	18.378		
240 minutes	Baseline NAR	1	10.225	45.03	<0.001
	Treatment	3	3.444	5.06	0.004
	Error	43	9.764		

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Summary of Analysis of Covariance for Area Between Total
Nasal Airway Resistance Curve and Baseline (NARAREA) for Study 0401

Source of Variation	Degrees of Freedom	Sums of Squares	F-value	P-value
Baseline NAR	1	509622.157	83.01	<0.001
Treatment	3	312664.831	16.98	<0.001
Error	43	263992.108		

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Summary of Analysis of Covariance for Change (Decrease) From Baseline of NAR in Study 0401 with the Additional Covariables Age, Weight, and Duration (hr) of Allergic Rhinitis

Time of Evaluation	Source of Variation	Degrees of Freedom	Sums of Squares	F-value	P-value
15 minutes	Age	1	0.248	0.86	0.360
	Duration of Rhinitis	1	0.007	0.02	0.880
	Weight	1	0.006	0.02	0.882
	Baseline NAR	1	1.849	6.41	0.015
	Treatment	3	0.596	0.69	0.564
	Error	40	11.543		
30 minutes	Age	1	<0.001	0.00	0.995
	Duration of Rhinitis	1	0.005	0.03	0.875
	Weight	1	0.032	0.15	0.700
	Baseline NAR	1	8.306	39.07	<0.001
	Treatment	3	3.327	5.22	0.004
	Error	40	8.504		
45 minutes	Age	1	<0.001	0.00	0.987
	Duration of Rhinitis	1	0.005	0.04	0.838
	Weight	1	0.410	3.69	0.062
	Baseline NAR	1	8.317	74.83	<0.001
	Treatment	3	11.940	35.81	<0.001
	Error	40	4.446		
60 minutes	Age	1	0.592	3.53	0.068
	Duration of Rhinitis	1	0.631	3.76	0.060
	Weight	1	0.315	1.88	0.178
	Baseline NAR	1	11.498	68.55	<0.001
	Treatment	3	8.833	17.55	<0.001
	Error	40	6.709		
120 minutes	Age	1	0.797	2.71	0.105
	Duration of Rhinitis	1	0.013	0.05	0.832
	Weight	1	0.459	1.59	0.215
	Baseline NAR	1	9.468	32.78	<0.001
	Treatment	3	7.867	9.08	<0.001
	Error	40	11.554		
180 minutes	Age	1	0.288	0.67	0.419
	Duration of Rhinitis	1	0.021	0.05	0.828
	Weight	1	0.636	1.97	0.233
	Baseline NAR	1	9.176	21.22	<0.001
	Treatment	3	5.787	4.46	0.009
	Error	40	17.294		
240 minutes	Age	1	0.008	0.03	0.860
	Duration of Rhinits	1	0.012	0.05	0.822
	Weight	1	F0.001	0.00	0.974
	Baseline NAR	1	10.024	41.14	F0.001
	Treatment	3	2.743	3.76	0.018
	Error	40	9.747		

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Summary of Analysis of Covariance of NARAREA for Study 0401
with the Additional Covariables Age, Weight, and Duration (hr)
of Allergic Rhinitis

Source of Variation	Degrees of Freedom	Sums of Squares	F-value	P-value
Age	1	6.622	0.00	0.975
Duration of Rhinitis	1	565.999	0.09	0.768
Weight	1	6242.358	0.97	0.330
Baseline NAR	1	483580.256	75.37	F0.001
Treatment	3	283913.588	14.75	F0.001
Error	40	256643.569		

AHP1-REG-048-0015258

ATTACHMENT H

Comparison of Results from Analysis of Variance and Generalized Cochran-Mantel-Haenszel Strategy for Runny Nose, Stuffy Nose, and Sneezing Data.

AHP1-REG-048-0015259

Comparison of P-Values[a] from Analysis of Variance (ANOVA) and Generalized Cochran-Mantel-Haenszel Strategy (GCMH) for Data from Patient's and Investigator's Ratings of Runny Nose, Stuffy Nose, and Sneezing

Studies Analyzed	Response Variable	Patient's Rating 24 hours ANOVA	24 hours GCMH	48 hours ANOVA	48 hours GCMH	72 hours ANOVA	72 hours GCMH	Investigator's Rating 72 hours ANOVA	72 hours GCMH
0401[b]	Runny Nose	.0553	.0566	.0081	.0118	.009	.0026	.0065	.0097
	Stuffy Nose	.2298	.2253	.0006	.0018	.0001	.0006	.0001	.0002
	Sneezing	.2559	.2406	.0032	.0095	.0003	.0012	.0472	.0448
	(Total Sample Size)	(48)	(48)	(48)	(48)	(48)	(48)	(48)	(48)
0402-0406[c]	Runny Nose	.1228	.1178	.5624	.6195	.5883	.5248	.1871	.1062
	Stuffy Nose	.0677	.0318	.2234	.1317	.0832	.0433	.2341	.1212
	Sneezing	.2596	.2448	.7964	.6875	.8905	.6907	.8571	.6015
	(Total Sample Size)	(221)	(221)	(215)	(215)	(214)	(214)	(214)	(214)

[a]For both procedures, P-values are the results of tests of a global hypothesis:
H_0: No difference among treatment groups with respect to mean scores.
H_a: not H_0.

[b]Terms included in ANOVA were baseline severity (used as a block effect) and treatment group. GCMH strategy, the mean score test for ordinal data [Case II of Landis, et al. (1978)], utilized baseline severity as a covariable.

[c]Terms included in ANOVA were baseline severity (used as a block effect), investigator, treatment, and investigator treatment interaction. GCMH strategy [Case II of Landis, et al. (1978)] utilized baseline severity and investigator as covariables.

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ATTACHMENT I

Enrollment Raw Data Listings

AHP1-REG-048-0015261

AHR-4011-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=401 GROUP=PLACEBO

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
1	M	57	166	99	125/ 75	68	38	NO	CLEAR	MOD	MOD	MILD	MILD	NO	NO	NO	RED SWOLLEN MUCOID
3	M	20	174	99	115/ 75	76	40	NO	CLEAR	MOD	MOD	SEV	NONE	NO	NO	NO	RED SWOLLEN MOIST
4	F	29	119	99	120/ 70	76	36	NO	CLEAR	MOD	SEV	MILD	NONE	NO	NO	NO	RED SWOLLEN MOIST
9	F	61	149	99	130/ 75	76	30	NO	CLEAR	MOD	MOD	MILD	NONE	YES	NO	NO	RED SWOLLEN MOIST
13	M	62	192	99	125/ 80	64	27	NO	CLEAR	MOD	SEV	SEV	MILD	NO	NO	NO	RED MOIST SWOLLEN
17	F	50	139	99	115/ 70	88	27	NO	CLEAR	MOD	MOD	MOD	MILD	NO	NO	NO	RED SWOLLEN MOIST
22	F	38	151	99	115/ 75	92	38	YES	CLEAR	MOD	SEV	MOD	NONE	YES	NO	NO	RED SWOLLEN MOIST
27	M	33	146	99	125/ 80	78	30	NO	CLEAR	MOD	SEV	MOD	NONE	NO	NO	NO	RED SWOLLEN DISCHARG
36	M	49	187	99	125/ 70	84	36	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	RED SWOLLEN MOIST
43	F	62	169	99	135/ 70	68	36	YES	CLEAR	SEV	SEV	MOD	MILD	YES	NO	NO	R SIDE SWOLLEN MOIST
45	M	21	196	99	115/ 70	68	44	NO	CLEAR	MOD	SEV	MOD	MILD	NO	NO	NO	RED SWOLLEN MOIST
46	M	18	198	99	110/ 75	88	30	NO	CLEAR	SEV	SEV	MOD	NONE	NO	NO	NO	RED SWOLLEN DISCHARG

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AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=401 GROUP=PHENYLPROPANOLAMINE

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
2	M	50	184	99	120/ 70	60	26	NO	CLEAR	MOD	SEV	MOD	MILD	NO	NO	NO	RED SWOLLEN MOIST
20	M	46	163	99	125/ 85	72	36	NO	CLEAR	MOD	SEV	MILD	MILD	NO	NO	NO	RED SWOLLEN MOIST
26	F	67	136	99	120/ 65	72	38	YES	CLEAR	MOD	MOD	MILD	NONE	YES	NO	NO	RED SWOLLEN MOIST
28	F	53	145	99	120/ 70	76	36	NO	CLEAR	SEV	SEV	MOD	MILD	YES	NO	NO	RED SWOLLEN MOIST
32	M	18	164	99	115/ 70	64	36	NO	CLEAR	MILD	MOD	MOD	NONE	NO	NO	NO	RED SWOLLEN DISCHARG
33	F	76	112	99	130/ 75	80	36	NO	PRID.NT	MOD	SEV	MOD	MOD	NO	NO	NO	RED MOIST NASAL DRIP
35	M	31	210	99	125/ 75	80	24	NO	CLEAR	MOD	MOD	MILD	NONE	NO	NO	NO	INJECTED EDEMA PND
37	M	43	210	99	125/ 75	80	36	YES	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	RED SWOLLEN EDEMA
39	F	49	171	100	120/ 70	76	48	NO	CLEAR	MOD	SEV	MOD	NONE	NO	NO	NO	EDEMA RED MOIST
41	F	77	171	99	125/ 80	64	30	NO	CLEAR	SEV	MOD	MILD	NONE	NO	NO	NO	RED SWOLLEN MOIST
42	F	45	128	99	110/ 65	72	36	NO	CLEAR	MOD	MOD	MILD	NONE	YES	NO	NO	RED SWOLLEN EXUDATE
48	F	45	142	99	115/ 70	60	30	YES	CLR+PR	MOD	SEV	MOD	NONE	YES	NO	NO	RED SWOLLEN MOIST

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AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=401 GROUP=PHENYLEPHRINE

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RHNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
5	F	50	136	99	120/ 70	76	27	NO	CLEAR	MOD	MOD	MILD	NONE	NO	NO	NO	RED SWOLLEN MOIST
6	F	62	163	99	130/ 75	84	24	NO	CLEAR	MOD	SEV	MOD	NONE	YES	NO	NO	RED SWOLLEN MOIST
8	M	77	179	99	130/ 75	68	24	NO	CLEAR	MILD	SEV	MOD	NONE	NO	NO	NO	RED SWOLLEN MOIST
12	M	38	140	99	120/ 75	68	36	NO	CLEAR	MOD	MOD	MILD	NONE	YES	NO	NO	RED SWOLLEN MOIST
16	F	20	110	99	110/ 70	88	36	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	RED HYPEREMIC MOIST
19	M	23	146	99	120/ 70	64	24	NO	CLEAR	MILD	SEV	MOD	MILD	NO	NO	NO	RED SWOLLEN MOIST
21	F	44	122	96	120/ 70	80	36	NO	CLEAR	SEV	SEV	MOD	NONE	NO	NO	NO	RED SWOLLEN MOIST
24	F	37	121	99	105/ 65	80	36	NO	CLEAR	MOD	SEV	MILD	NONE	YES	NO	NO	TURB SWOLLEN MOIST
31	F	45	128	99	125/ 75	76	36	NO	CLEAR	MOD	SEV	MILD	NONE	NO	NO	NO	RED SWOLLEN MOIST
38	F	47	158	99	125/ 70	68	30	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	RED SWOLLEN MOIST
44	M	20	159	99	115/ 70	80	36	NO	CLEAR	SEV	MOD	MOD	NONE	NO	NO	NO	RED MOIST SWOLLEN
47	F	24	141	99	130/ 75	92	24	NO	CLEAR	MOD	SEV	MOD	NONE	NO	NO	NO	RED SWOLLEN MOIST

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AHR-4010-3 NIMETAPP PROTOCOL 04
ENRICHMENT RAW DATA LISTING

STUDY=401 GROUP=COMBINATION

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
7	F	64	160	99	130/ 75	76	24	NO	CLEAR	MOD	SEV	MOD	MILD	YES	NO	NO	RED SWOLLEN MOIST
10	F	52	121	99	115/ 70	76	27	NO	CLEAR	SEV	SEV	MOD	NONE	NO	NO	NO	RED SWOLLEN MOIST
11	F	70	170	99	120/ 80	68	24	NO	CLEAR	MOD	SEV	SEV	MILD	NO	NO	NO	RED SWOLLEN MOIST
14	M	53	158	99	125/ 70	76	33	NO	CLEAR	MILD	SEV	MOD	NONE	YES	NO	NO	RED FORMATION MOIST
15	F	63	138	99	120/ 75	80	36	NO	CLEAR	MILD	SEV	MOD	NONE	NO	NO	NO	RED SWOLLEN MOIST
18	F	49	142	99	120/ 70	64	33	NO	CLEAR	MOD	MOD	MILD	MILD	NO	NO	NO	RED SWOLLEN MOIST
23	M	43	211	99	125/ 75	76	44	NO	CLEAR	MOD	SEV	MOD	NONE	NO	NO	NO	RED SWOLLEN MOIST
25	M	62	176	100	130/ 76	68	36	YES	CLEAR	MOD	MOD	MILD	MILD	NO	NO	NO	RED SWOLLEN DISCHARG
29	M	74	146	99	135/ 70	68	36	NO	CLEAR	MOD	MOD	MOD	NONE	YES	NO	NO	RED SWOLLEN TENDER
30	M	61	176	100	120/ 75	72	36	NO	CLEAR	MOD	SEV	MOD	NONE	NO	NO	NO	RED SWOLLEN MOIST
34	F	52	160	99	120/ 70	60	40	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	RED SWOLLEN DRIP
40	F	64	173	99	135/ 80	72	36	YES	CLEAR	MOD	MOD	MILD	NONE	NO	NO	NO	FORMA INJECTED MOIST

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AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=402 GROUP=PLACEBO

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ADNOR CHEST SIGNS	NASAL MUCOSA
4	M	18	170	99	120/ 80	70	24	NO	NONE	NONE	MOD	MILD	MILD	NO	NO	NO	EDEMA
5	M	23	150	99	120/ 80	54	4	NO	CLEAR	MOD	MOD	NONE	NONE	YES	NO	NO	EDEMA REDNESS
6	F	28	124	98	104/ 70	68	36	NO	CLEAR	MOD	MOD	MILD	NONE	YES	NO	NO	RED EDEMA
9	M	20	175	98	122/ 70	76	48	NO	NONE	NONE	MOD	MOD	MILD	NO	NO	NO	RED EDEMA WET
10	F	54	125	98	120/ 70	68	36	NO	CLEAR	MOD	MOD	NONE	MOD	NO	NO	NO	PALE WET
14	F	37	178	98	120/ 80	76	24	NO	PRULNT	MOD	SEV	MILD	SEV	NO	NO	NO	REDNESS EDEMA

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AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=402 GROUP=PHENYLPROPANOLAMINE

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (RPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
3	F	27	146	98	110/ 70	76	48	NO	CLEAR	SEV	SEV	MOD	MILD	YES	NO	NO	PALE MUCOID BRTHGING
12	F	67	195	98	140/ 88	72	24	NO	CLEAR	MOD	MILD	SEV	NONE	YES	NO	NO	PALE EDEMA
13	F	34	130	99	125/ 80	74	24	NO	CLEAR	MILD	MOD	MILD	MOD	NO	NO	NO	REDNESS EDEMA
17	F	22	140	98	110/ 66	64	18	NO	NONE	MILD	SEV	SEV	MOD	NO	NO	NO	TURB SWOLLEN RED
20	M	53	177	98	120/ 80	72	24	NO	CLEAR	MILD	MOD	MOD	MILD	NO	NO	NO	RED EDEMA
23	F	27	115	99	114/ 68	78	36	NO	CLEAR	MILD	MOD	SEV	MILD	NO	NO	NO	RED EDEMA MUCOID DR

AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=402 GROUP=PHENYLEPHRINE

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
1	M	27	194	98	110/ 80	68	48	NO	CLEAR	SEV	MOD	NONE	NONE	NO	NO	NO	RED MUCOID BRIDGING
7	M	31	125	98	110/ 70	68	24	NO	CLEAR	MILD	MOD	NONE	MILD	NO	NO	NO	RED EDEMA
8	F	21	144	99	110/ 70	72	24	NO	CLEAR	SEV	MILD	MOD	NONE	NO	NO	NO	RED EDEMA BRIDGING
11	M	29	165	99	120/ 80	60	36	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	EDEMA MUCOID
21	F	26	115	98	104/ 70	76	24	NO	CLEAR	SEV	MOD	MOD	MOD	YES	NO	NO	RED MUCOUS SWOLLEN
22	F	20	120	98	104/ 72	72	24	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	RED ENLARGED TURB

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AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=402 GROUP=COMBINATION

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RUNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
2	F	29	115	98	110/ 80	72	36	NO	CLEAR	SEV	MOD	MILD	NONE	NO	NO	NO	BRIDGIN EREMA MUCOID
15	F	30	130	98	120/ 80	68	12	NO	NONE	NONE	MOD	NONE	NONE	NO	NO	NO	REDNESS CONGESTION
16	F	38	120	97	110/ 70	74	36	NO	CLEAR	MOD	MILD	NONE	NONE	NO	NO	NO	RED MUCOID BRIDGING
18	M	31	185	98	120/ 70	68	18	NO	CLEAR	MILD	MOD	MILD	NONE	NO	NO	NO	RED WET EDEMA
19	F	22	135	98	110/ 70	72	24	NO	CLEAR	NONE	MOD	MILD	NONE	NO	NO	NO	RED EDEMA

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AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=403 GROUP=PLACEBO

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
2	M	57	159	98	122/ 88	74	48	NO	NONE	NONE	MOD	MILD	MILD	NO	NO	NO	REDDENED
4	F	18	113	98	95/ 78	74	48	NO	CLEAR	MOD	MOD	SEV	MOD	YES	NO	NO	MOD EDEMA HYPEREMIA
7	F	71	135	98	115/ 74	84	24	NO	CLEAR	MOD	SEV	MILD	MILD	NO	NO	NO	MOD HYPEREMIA CONG
9	M	24	174	99	104/ 84	80	48	NO	CLEAR	MILD	SEV	MILD	NONE	NO	NO	NO	HYPEREMIC BOGGY
16	F	50	163	99	120/ 78	84	48	NO	CLEAR	MILD	MOD	NONE	MOD	YES	NO	NO	HYPEREMIA BOGGY TURB
27	M	19	175	98	110/ 60	66	24	NO	CLEAR	MILD	MOD	NONE	NONE	NO	NO	NO	BOGGY HYPEREMIA TURB
29	F	20	120	99	115/ 75	80	47	NO	CLEAR	MILD	MOD	MILD	MILD	YES	NO	NO	BOGGY HYPEREMIA TURB
31	F	55	170	96	117/ 74	96	24	NO	CLEAR	SEV	NONE	MILD	MILD	NO	NO	NO	SL HYPEREMIA TURB
33	M	23	144	99	110/ 72	76	36	NO	PRINT	SEV	MOD	MOD	NONE	NO	NO	NO	BOGGY HYPEREMIA TURB
36	M	54	184	99	145/ 85	60	36	NO	CLEAR	MOD	MOD	MILD	MILD	NO	NO	NO	HYPEREMIA TURBINATE
39	M	36	175	99	100/ 80	88	24	NO	PRINT	SEV	SEV	MILD	NONE	YES	NO	NO	HYPEREMIA TURBINATES
47	F	43	130	98	140/ 85	70	48	NO	CLEAR	MOD	SEV	MILD	MILD	YES	NO	NO	BULGING TURB

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AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=403 — GROUP=PHENYLPROPANOLAMINE

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
8	F	21	133	98	112/ 84	72	48	NO	NONE	NONE	MOD	MILD	MILD	NO	NO	NO	BOGGY HYPEREMIC
11	F	22	123	98	115/ 70	68	36	NO	CLEAR	MILD	MOD	MILD	MOD	NO	NO	NO	HYPEREMIA BOGGY
12	M	37	215	98	120/ 72	94	48	NO	CLEAR	MOD	MOD	NONE	MOD	YES	NO	NO	HYPEREMIA BOGGY
13	M	54	189	99	130/ 77	80	24	NO	CLEAR	MOD	MILD	NONE	MILD	NO	NO	NO	SLIGHT HYPEREMIA
19	F	61	138	98	120/ 80	74	36	NO	CLEAR	MILD	MOD	MOD	NONE	NO	NO	NO	BOGGY TURBINATES
23	F	51	133	98	142/ 90	86	48	NO	PRULNT	MOD	MILD	MILD	MILD	YES	NO	NO	HYPEREMIA BOGGY MUCO
24	F	54	120	98	132/ 75	78	48	NO	CLEAR	MOD	MILD	NONE	NONE	YES	NO	NO	HYPEREMIA/TURBINATES
25	M	26	152	98	104/ 68	68	48	NO	NONE	NONE	MOD	NONE	MILD	NO	NO	NO	BOGGY HYPEREMIA TURB
28	F	50	135	99	115/ 75	76	48	NO	CLEAR	MILD	MOD	NONE	MOD	NO	NO	NO	HYPEREMIA BOGGY TURB
32	F	50	210	98	150/ 90	74	48	NO	NONE	NONE	SEV	NONE	NONE	YES	NO	NO	BOGGY HYPEREMIA TURB
47	M	46	195	98	128/ 84	64	24	NO	CLEAR	MOD	MOD	NONE	MILD	YES	NO	NO	HYPEREMIA ENL TURB
48	F	20	115	99	112/ 62	76	24	NO	CLEAR	MOD	MOD	MILD	NONE	YES	NO	NO	HYPEREMIA SWOLLEN TU

AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=403 GROUP=PHENYLEPHRINE

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	AUNIR CHEST SIGNS	NASAL MUCOSA
5	M	23	225	98	120/ 80	80	48	NO	CLR+PR	SEV	MILD	SEV	MILD	YES	NO	NO	MOD EDEMA HYPERFMIA
6	F	47	116	98	112/ 70	64	48	NO	CLEAR	MOD	SEV	MILD	MILD	YES	NO	NO	MOD CONGESTION
10	F	27	129	98	100/ 60	68	24	NO	CLEAR	MILD	MOD	MILD	NONE	NO	NO	NO	BOGGY NASAL MUCOSA
14	M	29	173	99	120/ 78	74	36	NO	CLEAR	MOD	SEV	MOD	NONE	YES	NO	NO	BOGGY TURBINATES
20	F	50	137	97	120/ 78	80	24	NO	CLEAR	MOD	MOD	NONE	NONE	NO	NO	NO	BOGGY TURBINATES
21	F	57	130	98	145/ 85	92	48	NO	CLEAR	MOD	SEV	NONE	NONE	NO	NO	NO	BOGGY HYPER NASAL MU
22	F	18	145	99	104/ 78	76	24	NO	PRUNT	SEV	SEV	MOD	NONE	NO	NO	NO	BOGGY HYPERFMIA
35	F	48	185	98	122/ 76	64	4	NO	CLEAR	MILD	MOD	MILD	MOD	NO	NO	NO	HYPERFMIA BOGGY TURB
38	F	59	118	98	128/ 74	84	48	NO	CLEAR	MOD	MOD	MOD	NONE	YES	NO	NO	BOGGY HYPERFMIC TURB
40	F	19	117	99	110/ 55	82	24	NO	CLEAR	MOD	MOD	SEV	NONE	NO	NO	NO	HYPERFMIA CONG TURB
45	F	48	142	98	112/ 66	72	48	NO	PRULNT	MOD	MOD	MOD	MILD	NO	NO	NO	HYPERFMIA ENL TURB
46	F	57	135	98	120/ 75	70	36	NO	CLEAR	SEV	MILD	MILD	NONE	NO	NO	NO	HYPERFMIA ENL TURB

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AHR-4010-3 NIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=403 GROUP=COMBINATION

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	MINRS RHNITS	FEVER	NASAL DISCHG	RHNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
1	F	59	125	98	122/ 72	76	48	NO	CLEAR	MILD	MOD	MILD	NONE	YES	NO	NO	SLIGHTLY ENLARGED
3	F	50	125	98	120/ 65	76	48	NO	CLEAR	MOD	NONE	NONE	NONE	NO	NO	NO	ABNORMAL HYPEREMIA
15	M	66	165	98	125/ 78	74	40	NO	CLEAR	MILD	MOD	MILD	MILD	NO	NO	NO	BOGGY TURBINATES
17	F	31	121	99	102/ 64	80	48	NO	NONE	NONE	MOD	NONE	NONE	YES	NO	NO	BOGGY TURBINATES
18	M	18	132	98	108/ 60	68	40	NO	PRUNT	SEV	MOD	MILD	NONE	YES	NO	NO	BOGGY TURBINATES
26	F	48	118	98	90/ 75	84	14	NO	CLEAR	MOD	NONE	MOD	NONE	NO	NO	NO	HYPEREMIA BOGGY TURB
30	M	29	187	97	100/ 70	74	24	NO	CLEAR	MOD	MILD	MOD	MOD	NO	NO	NO	HYPEREMIA BOGGY TURB
34	M	65	187	98	138/ 70	72	48	NO	CLEAR	SEV	MILD	NONE	NONE	NO	NO	NO	HYPEREMIA BOGGY TURB
37	M	52	166	98	120/ 68	74	48	NO	PRUNT	MILD	MOD	MILD	MOD	NO	NO	NO	HYPEREMIA ENL TURB
41	F	27	126	99	110/ 65	92	24	NO	CLEAR	MOD	MOD	MILD	NONE	YES	NO	NO	HYPEREMIC ENGURGED
43	M	25	250	98	135/ 85	72	48	NO	CLEAR	MOD	SEV	NONE	MILD	NO	NO	NO	BOGGY TURB HYPEREMIA
44	F	52	145	98	116/ 68	68	24	NO	CLEAR	SEV	MOD	SEV	SEV	NO	NO	NO	HYPEREMIA ENL TURB

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AHR-4011B-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=404 GROUP=PLACEBO

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	AHNOR CHEST SIGNS	NASAL MUCOSA
4	F	30	90	99	115/ 60	70	24	NO	PRULNT	MOD	SEV	MOD	MOD	NO	NO	NO	PURULENT DISCHARGE
6	F	55	140	99	135/ 75	80	24	NO	CLEAR	SEV	SEV	MOD	MOD	NO	NO	NO	PINK MEMBRANES
7	F	18	118	99	115/ 60	75	24	NO	PRULNT	SEV	SEV	MOD	SEV	NO	NO	NO	SWOLLEN TURBINATE
9	F	52	140	100	140/ 80	80	24	YES	PRULNT	SEV	SEV	MOD	MOD	NO	NO	NO	SWOLLEN TURBINATES
13	F	68	120	99	140/ 80	78	24	NO	CLEAR	SEV	SEV	MOD	MILD	NO	NO	NO	RED TURBINATES
18	F	19	135	99	130/ 70	74	24	NO	PRULNT	SEV	SEV	MOD	MILD	NO	NO	NO	NASAL SWOLLEN
26	F	25	118	99	120/ 60	70	36	NO	CLEAR	SEV	SEV	SEV	MILD	NO	NO	NO	SWOLLEN
28	M	20	160	99	130/ 70	75	48	NO	CLEAR	SEV	SEV	MOD	MOD	NO	NO	NO	EDEMA OF MEMBRANES
33	F	53	130	99	130/ 70	75	36	NO	PRULNT	SEV	SEV	MOD	SEV	NO	NO	NO	HEAVY DISCHARGE
37	F	57	140	99	135/ 75	70	24	NO	CLEAR	SEV	SEV	SEV	MOD	NO	NO	NO	RED SWOLLEN
38	M	24	160	99	130/ 70	65	36	NO	CLEAR	SEV	SEV	SEV	SEV	NO	NO	NO	SWOLLEN MEMBRANES
46	M	41	180	99	135/ 75	70	24	NO	CLEAR	SEV	SEV	MOD	MOD	NO	NO	NO	RED SWOLLEN

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AHR-4010-3 DIMETAPP PROTOCOL 04
ENRICHMENT RAW DATA LISTING

STUDY=404 — GROUP=PHENYLPROPANOLAMINE

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
5	F	35	175	101	130/ 75	80	36	YES	PRULNT	SEV	SEV	MOD	MOD	NO	YES	NO	TENDERNESS REG
11	M	45	170	99	135/ 75	75	24	YES	PRULNT	SEV	SEV	MOD	MOD	NO	NO	NO	NASAL MUCUS MEMBRANE
12	F	30	120	99	120/ 60	70	24	NO	PRULNT	SEV	SEV	MOD	MILD	NO	NO	NO	RED AND EDEMATOUS
15	F	51	152	101	125/ 75	70	12	YES	PRULNT	SEV	SEV	MOD	MOD	NO	YES	NO	RED MEMBRANES
16	M	18	145	99	120/ 60	70	24	NO	CLEAR	SEV	SEV	SEV	MILD	NO	NO	NO	SWOLLEN TURBINATE
17	F	22	130	99	120/ 60	70	36	NO	PRULNT	SEV	SEV	MOD	MOD	NO	NO	NO	SWOLLEN TURBINATE
19	F	19	115	99	120/ 65	70	24	NO	CLEAR	SEV	SEV	SEV	MOD	NO	NO	NO	RED MEMBRANES
32	F	50	112	99	130/ 70	75	24	NO	CLEAR	SEV	SEV	SEV	MOD	NO	NO	NO	SWOLLEN MEMBRANES
39	M	51	170	99	140/ 70	70	48	NO	CLEAR	SEV	SEV	MOD	MILD	NO	NO	NO	PALLOR OF MEMBRANES
40	F	48	120	99	130/ 75	75	24	NO	CLEAR	SEV	SEV	MOD	MOD	NO	NO	NO	RED SWOLLEN
41	F	25	120	99	120/ 60	70	36	NO	CLEAR	SEV	SEV	MOD	MOD	NO	NO	NO	RED SWOLLEN
43	F	40	130	99	130/ 70	60	48	NO	CLEAR	SEV	SEV	SEV	MOD	NO	NO	NO	EDEMATOUS TURBINATES

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AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=404 GROUP=PHENYLEPHRINE

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RHNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
1	F	36	140	99	125/ 70	78	24	NO	PRUENT	MOD	SEV	MOD	NONE	NO	NO	NO	REDNESS
2	F	23	120	100	120/ 65	68	18	YES	CLEAR	SEV	SEV	MILD	MOD	NO	NO	NO	RED MEMBRANES
8	F	68	135	99	145/ 90	85	24	NO	CLEAR	SEV	SEV	MOD	MILD	NO	NO	NO	EDEMA ERYTHEMATOUS
10	F	30	140	99	125/ 70	70	36	NO	CLEAR	SEV	SEV	SEV	MILD	NO	NO	NO	ERYTHEMA MEMBRANES
20	F	23	120	99	124/ 75	70	24	NO	CLEAR	SEV	SEV	MOD	MOD	NO	NO	NO	RED SWOLLEN
25	F	35	120	99	125/ 70	70	24	NO	CLEAR	SEV	SEV	SEV	MOD	NO	NO	NO	RED SWOLLEN MEMBRANE
31	F	41	135	99	130/ 70	70	24	NO	CLEAR	SEV	SEV	MOD	MOD	NO	NO	NO	SWOLLEN MEMBRANES
34	F	33	116	99	120/ 60	65	24	NO	CLEAR	SEV	SEV	MOD	MILD	NO	NO	NO	RED SWOLLEN MEMBRANE
36	M	29	155	99	130/ 75	70	24	NO	CLEAR	SEV	SEV	MOD	MOD	NO	NO	NO	EDEMA OF TURBINATES
42	F	53	126	99	140/ 80	60	36	NO	CLEAR	SEV	SEV	SEV	SEV	NO	NO	NO	RED SWOLLEN MEMBRANE
45	M	19	170	99	120/ 60	60	24	NO	CLEAR	SEV	SEV	SEV	MILD	NO	NO	NO	BOGGY MEMBRANES
48	F	51	150	99	140/ 80	70	36	NO	CLEAR	SEV	SEV	MOD	MILD	NO	NO	NO	INFLAMED MEMBRANES
49	M	19	170	99	120/ 60	60	24	NO	CLEAR	SEV	SEV	SEV	MOD	NO	NO	NO	PALE SWOLLEN

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AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=404 GROUP=COMBINATION

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
3	F	18	98	99	120/ 60	70	24	NO	PRULNT	SEV	SEV	MOD	MILD	NO	NO	NO	RED MEMBRANES
14	F	32	116	101	140/ 60	65	36	YES	PRULNT	SEV	SEV	SEV	SEV	NO	NO	NO	PURULENT DISCHARGE
21	F	19	100	100	115/ 60	70	24	YES	PRULNT	SEV	SEV	SEV	MOD	NO	NO	NO	RED SWOLLEN
22	F	30	140	99	130/ 75	64	24	NO	CLEAR	SEV	SEV	SEV	MOD	NO	NO	NO	SWOLLEN TURBINATE
23	F	38	125	99	130/ 75	80	36	NO	CLEAR	SEV	SEV	MOD	MOD	NO	NO	NO	RED SWOLLEN
24	M	29	170	99	130/ 75	80	24	NO	CLEAR	SEV	SEV	SEV	MOD	NO	NO	NO	RED SWOLLEN MEMBRANE
27	F	20	115	99	120/ 60	70	36	NO	CLEAR	SEV	SEV	SEV	MOD	NO	NO	NO	EDEMA OF TURBINATES
29	F	28	125	99	124/ 65	80	36	NO	CLEAR	SEV	SEV	SEV	MILD	NO	NO	NO	RED SWOLLEN MEMBRANE
30	F	49	135	99	130/ 75	75	48	NO	CLEAR	SEV	SEV	MOD	MOD	NO	NO	NO	ERYTHEMATOUS
35	F	23	130	99	120/ 60	70	24	NO	CLEAR	SEV	SEV	SEV	MOD	NO	NO	NO	SWOLLEN TURBINATES
44	M	39	235	99	140/ 80	70	24	NO	CLEAR	SEV	SEV	MOD	MILD	NO	NO	NO	SWOLLEN MEMBRANES
47	F	33	180	99	135/ 75	70	48	NO	CLEAR	SEV	SEV	MOD	MILD	NO	NO	NO	RED SWOLLEN
50	F	59	140	99	140/ 80	72	48	NO	CLEAR	SEV	SEV	MOD	MOD	NO	NO	NO	SWOLLEN TURBINATES

AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=405 GROUP=PLACEBO

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RHINY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
2	F	30	136	98	140/ 80	76	48	NO	CLEAR	MOD	MOD	MOD	MOD	NO	NO	NO	NORMAL
3	M	58	151	98	130/ 76	90	36	NO	CLEAR	MOD	MOD	MILD	MILD	NO	NO	NO	NORMAL
4	M	43	160	97	116/ 64	72	48	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	NORMAL
12	M	64	156	98	130/ 96	74	24	NO	CLEAR	MOD	MOD	MOD	MOD	NO	NO	NO	NORMAL
13	M	20	159	98	98/ 66	76	2	NO	CLEAR	SEV	SEV	SEV	SEV	NO	NO	NO	NORMAL
16	F	56	140	98	136/ 84	72	24	NO	CLEAR	MOD	MOD	SEV	MILD	NO	NO	NO	NORMAL
21	F	56	200	98	140/ 84	84	36	NO	CLEAR	MOD	MOD	MOD	MILD	NO	NO	NO	NORMAL
30	M	46	258	98	130/100	62	36	NO	CLEAR	MOD	MOD	MOD	MILD	YES	NO	NO	NORMAL
31	M	47	192	98	126/ 88	68	48	NO	CLEAR	MOD	MOD	MOD	NONE	YES	NO	NO	NORMAL
36	M	30	135	98	110/ 86	90	36	NO	CLEAR	MOD	SEV	MOD	NONE	YES	NO	NO	NORMAL
41	M	41	167	98	136/ 80	86	48	NO	CLEAR	MOD	MOD	MILD	MOD	NO	NO	NO	NORMAL
46	M	40	170	98	162/ 74	78	48	NO	CLEAR	MOD	SEV	SEV	NONE	YES	NO	NO	NORMAL
50	F	51	197	99	140/ 80	92	48	NO	CLEAR	MOD	SEV	MOD	NONE	YES	NO	NO	NORMAL
52	M	47	160	98	112/ 88	88	48	NO	CLEAR	MOD	SEV	MOD	MOD	YES	NO	NO	NORMAL

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AHR-4010-3 DEMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=405 GROUP=PHENYLPROPANOLAMINE

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RUNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SNORE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
5	F	33	165	98	110/ 58	90	24	NO	CLEAR	SEV	SEV	SEV	NONE	YES	NO	NO	NORMAL
8	F	30	127	98	108/ 66	80	36	NO	CLEAR	SEV	SEV	MILD	MOD	YES	NO	NO	NORMAL
10	F	36	136	98	118/ 84	74	24	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	NORMAL
15	M	43	230	98	140/ 96	80	48	NO	CLEAR	SEV	SEV	SEV	MILD	YES	NO	NO	NORMAL
17	M	34	156	98	108/ 80	72	48	NO	CLEAR	MILD	MOD	MOD	MOD	NO	NO	NO	NORMAL
23	F	41	150	98	110/ 80	64	48	NO	CLEAR	MOD	MOD	MOD	MOD	YES	NO	NO	NORMAL
24	M	37	147	98	122/ 70	74	36	NO	CLEAR	SEV	SEV	SEV	MILD	NO	NO	NO	NORMAL
27	F	19	118	98	98/ 68	78	36	NO	CLEAR	MOD	MOD	MILD	NONE	YES	NO	NO	NORMAL
37	M	36	205	99	150/110	84	48	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	NORMAL
40	M	25	143	99	120/ 82	86	48	NO	CLEAR	MILD	MOD	MOD	MOD	YES	NO	NO	NORMAL
43	M	25	179	98	128/ 80	80	24	NO	CLEAR	SEV	SEV	SEV	SEV	YES	NO	NO	NORMAL
47	F	70	135	99	130/ 64	90	48	NO	CLEAR	MOD	MOD	MILD	MILD	NO	NO	NO	NORMAL
53	F	52	251	98	120/ 92	76	24	NO	CLEAR	MILD	MOD	NONE	MOD	NO	NO	NO	NORMAL

AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=405 GROUP=PHENYLEPHRINE

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RHINY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
7	F	37	200	98	120/ 76	88	24	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	NORMAL
14	F	63	145	98	140/ 68	86	24	NO	CLEAR	MOD	SEV	SEV	MOD	NO	NO	NO	NORMAL
18	M	19	240	98	122/ 80	74	48	NO	CLEAR	MOD	MOD	MOD	MOD	NO	NO	NO	NORMAL
19	M	53	165	98	126/ 92	88	48	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	NORMAL
20	F	26	135	98	112/ 84	72	48	NO	CLEAR	MOD	MOD	MOD	NONE	YES	NO	NO	NORMAL
22	F	64	140	98	110/ 80	76	36	NO	CLEAR	SEV	SEV	MOD	MOD	NO	NO	NO	NORMAL
25	M	21	220	98	120/ 98	68	24	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	NORMAL
28	M	58	220	98	118/ 94	68	24	NO	CLEAR	MOD	MOD	MILD	MILD	NO	NO	NO	NORMAL
34	M	35	184	99	130/ 82	88	48	NO	CLEAR	MOD	MOD	MILD	MOD	YES	NO	NO	NORMAL
35	M	48	190	99	130/ 88	68	48	NO	CLEAR	MOD	SEV	MOD	NONE	YES	NO	NO	NORMAL
45	M	46	230	98	130/ 86	72	48	NO	CLEAR	SEV	SEV	MILD	NONE	YES	NO	NO	NORMAL
48	M	65	180	98	122/ 90	88	36	NO	CLEAR	SEV	SEV	MOD	MOD	NO	NO	NO	NORMAL
49	M	32	295	98	110/ 80	90	48	NO	CLEAR	MOD	SEV	MOD	MILD	YES	NO	NO	NORMAL
51	M	25	155	99	120/ 80	76	48	NO	CLEAR	MOD	SEV	MOD	SEV	YES	NO	NO	NORMAL

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AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=405 GROUP=COMBINATION

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HRS RHNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
1	M	45	205	98	132/ 82	74	48	NO	CLEAR	MOD	MOD	NONE	NONE	NO	NO	NO	NORMAL
6	F	30	130	98	90/ 60	88	36	NO	CLEAR	MOD	MOD	MOD	MOD	NO	NO	NO	NORMAL
9	M	35	165	98	110/ 80	76	24	NO	CLEAR	MOD	MOD	MILD	SEV	NO	NO	NO	NORMAL
11	F	17	150	98	102/ 78	64	36	NO	CLEAR	MOD	SEV	SEV	NONE	NO	NO	NO	NORMAL
26	F	47	158	98	134/ 94	86	24	NO	CLEAR	MOD	MOD	MOD	NONE	YES	NO	NO	NORMAL
29	F	29	120	98	114/ 90	76	36	NO	CLEAR	MOD	SEV	MOD	NONE	NO	NO	NO	NORMAL
32	F	54	169	98	120/ 80	76	48	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	NORMAL
33	M	42	181	98	120/ 90	80	48	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	NORMAL
38	M	36	245	97	150/ 98	92	24	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	NORMAL
39	F	45	250	98	138/ 92	90	36	NO	CLEAR	MOD	MOD	MOD	MOD	NO	NO	NO	NORMAL
42	M	42	191	98	140/ 90	88	48	NO	CLEAR	MOD	MOD	MOD	MOD	YES	NO	NO	NORMAL
44	M	38	169	98	138/ 84	84	48	NO		SEV	SEV	MOD	SEV	YES	NO	NO	NORMAL

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AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=406 GROUP=PLACEBO

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RUNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
5	M	22	140	99	110/ 78	58	40	NO	CLEAR	MOD	MOD	MILD	NONE	NO	NO	NO	REDNESS
6	F	19	115	98	126/ 76	120	44	NO	PRULNT	MOD	MOD	MILD	MOD	YES	YES	NO	REDNESS TURB ENLARGE
8	M	23	185	98	120/ 80	60	46	NO	NONE	NONE	MOD	MILD	MILD	NO	NO	NO	REDNESS TURB ENLARGE
9	F	18	103	99	100/ 60	80	44	NO	CLEAR	MOD	MOD	MILD	NONE	NO	NO	NO	PALLOR TURB ENLARGE
15	F	20	116	98	140/ 92	72	44	NO	CLEAR	MOD	MILD	MILD	NONE	NO	NO	NO	REDNESS EDEMA
20	M	24	150	99	130/ 92	80	40	NO	CLEAR	MOD	MILD	MILD	NONE	NO	NO	NO	RED M-BRIDG EDEMA
25	M	24	170	98	108/ 80	84	36	NO	PRULNT	MOD	MOD	MILD	MILD	YES	NO	NO	RED M-BR TURB EDEMA
29	F	20	130	99	100/ 60	68	30	NO	CLEAR	MILD	SEV	MILD	NONE	NO	NO	NO	REDNESS M-BRIDG TURB
38	F	22	145	98	128/ 78	84	24	NO	CLEAR	MOD	MOD	MILD	NONE	NO	NO	NO	RED M-BR TURB EDEMA
39	M	24	185	99	122/ 74	80	16	NO	PRULNT	SEV	MOD	NONE	MILD	NO	NO	NO	RED MUCOID-BR EDEMA
40	M	19	185	99	110/ 70	78	36	NO	CLEAR	MILD	MOD	MOD	MILD	YES	YES	NO	REDNESS
45	F	19	125	98	102/ 64	84	24	NO	CLEAR	MOD	MILD	MILD	MILD	NO	YES	NO	RED M-BRIDG TURB END
51	F	20	140	98	100/ 70	72	36	NO	CLEAR	MOD	MOD	MILD	NONE	NO	NO	NO	RED MUCOID-BRID TURB

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AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=406 GROUP=PHENYLPROPANOLAMINE

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RHNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SWOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
1	M	25	190	97	134/ 80	88	31	NO	PRUNT	MOD	MOD	MILD	NONE	NO	NO	NO	REDNESS
4	M	21	160	97	100/ 70	80	30	NO	CLEAR	MOD	MOD	MILD	MILD	NO	YES	NO	REDNESS TURB ENLARGE
13	F	21	148	99	120/ 90	72	12	NO	CLEAR	MOD	MOD	MILD	MOD	NO	YES	NO	REDNESS EDEMA
14	F	20	128	98	120/ 80	88	24	NO	CLEAR	MOD	MOD	MILD	MILD	NO	YES	NO	RED MUC BRIDG EDEMA
16	M	24	180	98	110/ 70	72	24	NO	CLEAR	MOD	MOD	MILD	NONE	NO	NO	NO	RED M-BRIDG TURB ENL
22	F	25	180	98	108/ 74	72	48	YES	CLEAR	MOD	MOD	MILD	NONE	YES	NO	NO	RED TURB ENLAR EDEMA
26	M	22	155	98	114/ 70	100	12	NO	CLEAR	MOD	MOD	MILD	MILD	NO	NO	NO	RED M-BRIDGING TURB
35	M	21	155	99	112/ 68	82	24	NO	CLEAR	MOD	MOD	MILD	MILD	NO	NO	NO	RED TURB ENL EDEMA
36	F	21	122	99	108/ 74	80	48	NO	CLEAR	SEV	SEV	MILD	MILD	NO	NO	NO	RED M-BR TURB EDEMA
43	M	21	180	99	136/ 86	84	36	NO	CLEAR	MOD	MOD	MILD	MILD	NO	NO	NO	RED MUCOID-BR EDEMA
46	M	18	170	98	134/ 84	84	24	NO	CLEAR	MOD	MOD	MILD	MILD	NO	YES	NO	REDNESS EDEMA
47	M	19	175	98	120/ 72	88	18	NO	CLEAR	MOD	MILD	NONE	NONE	NO	NO	NO	REDNESS EDEMA
49	M	22	180	98	104/ 70	64	24	NO	CLEAR	MILD	MOD	MILD	NONE	NO	NO	NO	REDNESS TURBINATE EN
50	M	22	190	98	130/ 90	100	30	NO	CLEAR	MILD	MOD	NONE	NONE	YES	YES	NO	REDNESS TURBINATE EN

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AHR-4010-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=406 GROUP=PHENYLEPHRINE

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RHNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
3	F	22	135	98	108/ 60	76	30	NO	CLEAR	MOD	MILD	MILD	NONE	NO	NO	NO	RED MUC BRIDG POLYPS
12	M	21	165	99	128/ 70	64	24	NO	CLEAR	MOD	MOD	MILD	NONE	NO	NO	NO	PALLOR TURB ENLARGE
18	M	24	180	97	110/ 80	72	12	NO	PRULNT	MOD	MOD	MILD	MOD	NO	NO	NO	RED M-BRIDG TURB ENL
19	F	20	125	98	110/ 90	88	30	NO	CLEAR	MOD	MOD	MOD	NONE	NO	NO	NO	RED M-BR TURB EDEMA
21	F	19	150	97	128/ 88	88	12	NO	CLEAR	MOD	MOD	MILD	MILD	NO	NO	NO	RED M-BR TURB EDEMA
24	M	21	215	100	130/ 82	100	16	YES	PRULNT	MOD	MOD	MILD	MILD	NO	YES	NO	RED M-BR TURB EDEMA
30	F	21	104	99	100/ 58	80	42	NO	CLEAR	MOD	MOD	MOD	MILD	YES	YES	YES	RED M-BR TURB EDEMA
31	M	21	185	98	115/ 78	84	36	NO	CLEAR	MILD	MOD	MILD	NONE	YES	NO	NO	RED M-BRIDGING EDEMA
32	F	22	123	100	102/ 60	66	24	YES	CLEAR	MOD	MILD	SEV	MILD	NO	YES	NO	RED TURB ENL EDEMA
33	F	19	145	99	105/ 66	68	24	NO	CLEAR	MOD	MILD	MOD	MILD	NO	YES	NO	RED M-BR TURB EDEMA
42	M	22	140	98	110/ 70	76	18	NO	CLEAR	SEV	MILD	NONE	MOD	YES	YES	NO	PALLOR TURB EN EDEMA
44	M	19	160	98	126/ 80	72	24	NO	CLEAR	MOD	MILD	MILD	NONE	NO	NO	NO	REDNESS TURBINATE EN

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AHR-4810-3 DIMETAPP PROTOCOL 04
ENROLLMENT RAW DATA LISTING

STUDY=406 GROUP=COMBINATION

PAT	SEX	AGE (YRS)	WEIGHT (LBS)	TEMP (F)	BP (MM HG)	PULSE (BPM)	HOURS RHNITS	FEVER	NASAL DISCHG	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	SMOKE	P-NASAL SINUS INFECT	ABNOR CHEST SIGNS	NASAL MUCOSA
2	F	21	140	99	110/ 80	90	45	NO	CLEAR	MOD	MOD	NONE	NONE	NO	NO	NO	TURB ENLARGE PALLOR
7	M	19	170	99	126/ 82	76	48	NO	CLEAR	MOD	MILD	NONE	NONE	NO	NO	NO	REDNESS TURB ENLARGE
10	M	20	170	99	110/ 80	80	36	NO	PRNT	SEV	MOD	MILD	MILD	YES	YES	NO	REDNESS TURB ENLARGE
11	M	20	148	98	122/ 66	80	36	NO	CLEAR	MILD	MOD	MILD	MOD	NO	YES	NO	REDNESS TURB ENLARGE
17	M	21	190	97	100/ 70	68	44	NO	CLEAR	MOD	MOD	NONE	NONE	YES	NO	NO	RED M-BRNG TURB ENL
23	F	20	115	99	110/ 60	80	40	NO	CLEAR	MOD	MOD	MILD	MILD	NO	YES	NO	PALLOR RED M-BR TURB
27	F	23	140	98	100/ 60	68	17	NO	CLEAR	MILD	MOD	MILD	NONE	NO	YES	NO	RED TURB ENL EDEMA
28	M	21	180	99	130/ 80	108	24	NO	CLEAR	MOD	SEV	MILD	NONE	NO	NO	NO	RED M-BRNG TURB ENL
34	M	23	165	99	128/ 80	80	24	NO	PRNT	MILD	MOD	MOD	MILD	NO	NO	NO	RED TURB ENL EDEMA
37	M	19	150	98	124/ 72	72	42	NO	PRNT	MOD	MOD	MILD	MILD	NO	NO	NO	RED M-BR TURB EDEMA
41	M	19	140	99	120/ 70	72	24	NO	CLEAR	MOD	NONE	MOD	NONE	YES	NO	NO	PALLOR EDEMA
48	M	23	160	100	144/ 88	80	40	YES	CLEAR	MOD	MILD	MOD	NONE	NO	NO	NO	REDNESS EDEMA
52	M	19	165	99	122/ 78	76	40	NO	CLEAR	MOD	MOD	NONE	MILD	NO	NO	NO	RED M-BRIDGING EDEMA

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ATTACHMENT J

Raw Data Listing For All Subjective Efficacy Parameters

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The code for patient's and investigators' ratings of severity of runny nose, stuffy nose, sneezing, and headache is: 0=none, 1=mild, 2=moderate, 3=severe.

The code for patients' global evaluation of overall therapeutic effect is: 1=marked benefit. 2=moderate benefit, 3=minimal benefit, 4=no benefit.

The code for investigators' global evaluation of overall therapeutic effect is: 1=marked effect, 2=moderate effect, 3=minimal effect, 4=no effect, 5=worse.

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=401 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
1	0	2	2	2	1		2	2	1	1	
	24	2	2	1	0						
	48	2	1	1	0						
	72	1	1	1	0	4	1	1	1	0	3
3	0	2	3	2	0		2	2	3	0	
	24	2	2	2	0						
	48	2	3	2	0						
	72	1	2	2	0	3	1	2	1	0	3
4	0	3	2	3	0		2	3	1	0	
	24	3	2	3	0						
	48	2	2	2	0						
	72	2	2	2	0	3	2	2	1	0	3
9	0	3	2	3	0		2	2	1	0	
	24	2	2	3	0						
	48	2	2	2	0						
	72	1	2	2	0	3	2	2	1	0	3
13	0	3	3	2	0		2	3	3	1	
	24	2	2	3	0						
	48	2	2	2	0						
	72	1	2	2	0	3	1	2	1	0	3
17	0	2	3	1	1		2	2	2	1	
	24	2	2	1	0						

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=401 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	48	?	3	?	0						
	72	2	2	0	0	4	1	2	0	0	3
22	0	2	3	2	0		2	3	2	0	
	24	2	3	2	1						
	48	2	2	2	0						
	72	2	2	2	0	3	1	2	2	0	3
27	0	2	3	2	0		2	3	2	0	
	24	2	2	2	1						
	48	1	2	1	0						
	72	2	2	0	0	3	1	2	2	0	3
36	0	3	3	2	0		2	2	2	0	
	24	3	3	2	0						
	48	2	3	2	0						
	72	2	2	1	0	3	2	2	1	0	3
43	0	2	2	2	1		3	3	2	1	
	24	2	3	2	0						
	48	2	1	2	0						
	72	2	1	2	0	3	1	2	2	0	3
45	0	2	?	2	0		?	3	2	1	
	24	2	2	1	0						
	48	?	?	1	0						

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=401 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	1	2	1	0	2	1	2	0	0	2
46	0	2	3	2	1		3	3	2	0	
	24	2	3	2	1						
	48	1	2	2	0						
	72	1	2	1	0	2	2	2	1	0	

STUDY=401 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
2	0	3	3	2	1		2	3	2	1	
	24	2	2	2	1						
	48	2	2	3	0						
	72	1	1	2	0	3	1	1	1	0	3
20	0	2	3	2	1		2	3	1	1	
	24	2	2	2	1						
	48	2	2	2	0						
	72	1	2	1	0	2	2	2	1	0	2
26	0	3	3	2	0		2	2	1	0	
	24	2	2	2	0						
	48	2	1	1	0						
	72	2	1	2	0	2	1	2	0	0	2
28	0	3	3	2	1		3	3	2	1	

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=401 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	2	2	2	0						
	48	2	2	1	0						
	72	1	2	1	0	2	2	1	1	0	2
32	0	2	2	1	0		1	2	2	0	
	24	2	2	1	0						
	48	2	2	1	0						
	72	1	2	1	0	2	1	2	0	0	2
33	0	2	3	2	1		2	3	2	2	
	24	2	2	2	0						
	48	1	2	2	0						
	72	1	2	2	0	2	1	2	1	0	2
35	0	3	3	2	0		2	2	1	0	
	24	3	3	2	0						
	48	2	3	2	0						
	72	2	2	2	0	3	2	2	1	0	3
37	0	2	2	2	0		2	2	2	0	
	24	2	2	2	0						
	48	2	1	2	0						
	72	2	1	1	0	2	1	2	2	0	2
39	0	3	3	2	0		2	3	2	0	
	24	2	2	2	0						
	48	2	2	1	0						

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=401 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	2	2	1	0	2	0	2	1	0	2
41	0	2	3	2	0		3	2	1	0	
	24	2	3	2	0						
	48	2	2	2	0						
	72	2	2	1	0	3	1	1	1	0	3
42	0	1	3	2	0		2	2	1	0	
	24	1	2	2	0						
	48	2	2	1	0						
	72	1	2	1	0	2	1	2	1	0	2
48	0	2	2	2	0		2	3	2	0	
	24	2	2	1	0						
	48	2	1	1	0						
	72	0	1	2	0	2	1	1	0	0	2

STUDY=401 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
5	0	2	2	2	1		2	2	1	0	
	24	1	2	2	0						
	48	1	2	2	0						
	72	1	0	1	0	2	1	1	0	0	2
6	0	3	3	2	0		2	3	2	0	

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=401 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	2	3	2	0						
	48	2	2	2	2						
	72	1	1	1	0	2	1	2	0	0	2
8	0	2	3	2	1		1	3	2	0	
	24	1	2	2	1						
	48	2	2	1	0						
	72	1	1	1	0	2	1	1	0	0	2
12	0	2	3	1	0		2	2	1	0	
	24	2	2	1	0						
	48	2	1	0	0						
	72	1	1	1	0	2	1	1	1	0	2
16	0	2	2	2	0		2	2	2	0	
	24	2	2	1	0						
	48	1	2	0	1						
	72	1	1	0	0	2	1	2	1	0	2
19	0	1	2	1	0		1	3	2	1	
	24	2	2	1	1						
	48	2	2	1	0						
	72	1	1	1	0	3	1	2	1	0	3
21	0	3	3	2	0		3	3	2	0	
	24	2	2	2	0						

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=401 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	48	1	2	2	0						
	72	1	2	2	0	2	2	2	1	0	2
24	0	2	3	2	0		2	3	1	0	
	24	3	3	1	0						
	48	2	3	2	0						
	72	2	2	2	0	4	1	3	1	0	4
31	0	2	2	2	0		2	3	1	0	
	24	2	2	1	0						
	48	1	2	1	0						
	72	1	2	1	0	2	1	1	0	0	2
38	0	2	3	2	0		2	2	2	0	
	24	2	2	2	0						
	48	2	2	2	0						
	72	2	1	1	0	2	2	1	1	0	2
44	0	2	2	2	0		3	2	2	0	
	24	2	2	1	0						
	48	1	2	1	0						
	72	1	1	2	0	2	1	2	1	0	2
47	0	2	3	2	0		2	3	2	0	
	24	2	2	2	0						
	48	2	2	2	0						
	72	2	0	1	0	2	2	2	1	0	2

AHR-4010-3 DINETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=401 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
7	0	3	2	2	1		2	3	2	1	
	24	2	2	2	0						
	48	1	1	1	0						
	72	1	1	0	0	1	0	1	0	0	1
10	0	3	3	2	0		3	3	2	0	
	24	2	2	2	0						
	48	1	1	1	0						
	72	0	1	1	0	1	1	1	0	0	
11	0	2	3	3	1		2	3	3	1	
	24	2	1	2	1						
	48	0	1	1	0						
	72	0	1	1	0		1	1	1	0	1
14	0	3	3	2	0		1	3	2	0	
	24	1	2	2	0						
	48	1	2	1	0						
	72	1	2	1	0	1	1	1	0	0	1
15	0	2	3	2	0		1	3	2	0	
	24	1	2	2	0						

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=401 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	48	1	2	1	1						
	72	0	1	1	0	1	0	1	1	0	1
18	0	2	3	2	1		2	2	1	1	
	24	1	3	2	0						
	48	1	1	0	0						
	72	0	1	0	0	1	0	1	0	0	1
23	0	2	3	3	0		2	3	2	0	
	24	1	2	2	0						
	48	2	1	0	0						
	72	1	1	0	1	1	1	1	1	0	1
25	0	2	3	1	1		2	2	1	1	
	24	2	2	1	0						
	48	1	1	1	0						
	72	1	1	0	0	1	1	1	0	0	1
29	0	2	3	2	0		2	2	2	0	
	24	2	2	1	0						
	48	2	1	1	0						
	72	1	1	0	0	1	0	1	1	0	1
30	0	3	3	2	0		2	3	2	0	
	24	2	2	2	1						
	48	1	1	1	0						

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=401 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	1	0	0	0	1	1	1	0	0	1
34	0	2	2	2	0		2	2	2	0	
	24	2	2	1	0						
	48	2	1	1	0						
	72	0	1	1	0	1	0	0	1	0	1
40	0	2	2	2	1		2	2	1	0	
	24	2	2	2	1						
	48	2	2	1	0						
	72	1	1	0	0	1	1	1	0	0	1

STUDY=402 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
4	0	0	2	1	1		0	2	1	1	
	24	0	1	1	0						
	48	0	0	0	0						
	72	0	0	0	0	2	0	0	0	0	2
5	0	2	2	0	0		2	2	0	0	
	24	2	1	0	0						
	48	1	1	0	0						
	72	1	1	0	0	3	1	1	0	0	3
6	0	2	2	1	0		2	2	1	0	

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=402 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	2	2	0	2						
	48	2	1	0	0						
	72	1	0	0	0	2	1	0	0	0	2
9	0	0	2	2	1		0	2	2	1	
	24	0	1	0	0						
	48	0	1	1	0						
	72	0	1	0	0	3	0	1	0	0	3
10	0	2	2	0	2		2	2	0	2	
	24	2	2	1	2						
	48	1	2	0	0						
	72	1	2	1	0	3	1	2	1	0	3
14	0	2	3	1	3		2	3	1	3	
	24	2	3	0	2						
	48	1	2	0	1						
	72	1	1	0	1	2	1	1	0	1	2

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=402 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
3	0	3	3	2	1		3	3	2	1	
	24	2	2	0	0						
	48	1	1	0	0						
	72	1	0	0	0	1	1	0	0	0	1
12	0	2	1	3	0		2	1	3	0	
	24	1	1	1	0						
	48	0	1	1	0						
	72	0	0	0	0	1	0	0	0	0	1
13	0	2	2	1	2		1	2	1	2	
	24	2	1	1	1						
17	0	1	3	3	2		1	3	3	2	
	24	1	2	2	1						
	48	1	1	1	0						
	72	0	0	0	0	1	0	0	0	0	1
20	0	1	2	2	1		1	2	2	1	
	24	2	2	2	2						
	48	1	2	2	1						
	72	2	2	2	1	4	2	2	2	1	5
23	0	1	2	3	1		1	2	3	1	
	24	1	1	2	0						
	48	0	1	1	0						

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=402 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	0	1	1	0	?	0	1	1	0	2

STUDY=402 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
1	0	3	2	0	0		3	2	0	0	
	24	2	1	0	0						
	48	0	0	0	0						
	72	0	0	0	0	2	0	0	0	0	1
7	0	1	2	0	1		1	2	0	1	
	24	3	3	3	2						
	48	1	2	0	1						
	72	0	1	0	0	4	0	1	0	0	4
8	0	3	1	2	0		3	1	2	0	
	24	2	1	0	0						
	48	1	0	0	0						
	72	1	0	0	0	1	1	0	0	0	1
11	0	2	2	2	0		2	2	2	0	
	24	1	2	1	0						
	48	0	1	1	1						
	72	0	1	0	0	?	0	1	0	0	?
21	0	3	?	?	?		3	?	?	2	

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AHP1-REG-048-0015301

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=402 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	2	2	2	1						
22	0	2	2	2	0		2	2	2	0	
	24	2	1	2	0						
	48	2	0	1	0						
	72	1	0	1	0	1	1	0	1	0	1

STUDY=402 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
2	0	3	2	1	0		3	2	1	0	
	24	2	2	1	0						
	48	3	2	2	0						
	72	2	2	1	0	4	2	2	1	0	4
15	0	0	2	0	0		0	2	0	0	
	24	0	1	0	0						
	48	0	1	0	0						
	72	1	0	0	1	4	1	0	0	1	4
16	0	2	1	0	0		2	1	0	0	
	24	1	0	1	0						
	48	0	0	0	0						
	72	0	0	0	0	1	0	0	0	0	1
18	0	1	2	2	0		1	2	1	0	

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=402 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	2	2	1	0						
	48	2	2	2	0						
	72	2	2	1	0	4	2	2	1	0	4
19	0	0	2	1	0		0	2	1	0	
	24	0	2	0	0						
	48	0	1	0	0						
	72	0	1	0	0	2	0	0	0	0	2

STUDY=403 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
2	0	0	2	1	1		0	2	1	1	
	24	0	3	0	1						
4	0	2	2	3	2		2	2	3	2	
	24	2	2	2	1						
	48	1	2	1	1						
	72	2	2	1	1	3	2	2	1	1	4
7	0	2	3	1	1		2	3	1	1	
	24	3	1	2	1						
	48	1	1	0	0						
	72	1	0	0	0	2	1	0	0	0	3
9	0	1	3	1	0		1	3	1	0	

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=403 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	1	3	1	0						
	48	0	2	1	0						
	72	0	1	0	0	4	0	0	0	0	4
16	0	1	2	0	2		1	2	0	2	
	24	0	3	0	1						
	48	0	3	0	1						
	72	0	2	0	1	4	0	2	0	1	4
27	0	1	2	0	0		1	2	0	0	
	24	0	1	0	0						
	48	0	1	0	0						
	72	0	1	0	0	2	0	1	0	0	1
29	0	1	2	1	1		1	2	1	1	
	24	2	2	1	1						
	48	1	1	0	0						
	72	0	1	0	0	3	0	1	0	0	1
31	0	3	0	1	1		3	0	1	1	
	24	2	3	1	3						
33	0	3	2	2	0		3	2	2	0	
	24	3	2	1	0						
	48	1	1	0	0						
	72	1	1	0	0	2	1	1	0	0	1

AHR-4010-3 DIHETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=403 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
36	0	2	2	1	1		2	2	1	1	
	24	2	2	1	1						
	48	0	1	0	0						
	72	0	1	0	0	2	0	1	0	0	1
39	0	3	3	1	0		3	3	1	0	
	24	3	3	1	0						
	48	2	3	1	1						
	72	2	2	1	0	4	2	2	1	0	3
42	0	2	3	1	1		2	3	1	1	
	24	2	3	1	2						
	48	2	2	1	1						
	72	1	2	2	1	3	1	2	2	1	3

STUDY=403 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
8	0	0	2	1	1		0	2	1	1	
	24	0	2	1	1						
	48	0	1	0	1						
	72	1	0	0	1	4	1	0	0	0	4
11	0	1	2	1	2		1	2	1	2	
	24	1	1	0	2						
	48	2	1	0	2						

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=403 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	2	0	0	2	3	1	0	0	2	3
12	0	2	2	0	2		2	2	0	2	
	24	2	2	0	1						
	48	1	2	0	0						
	72	1	1	0	0	3	0	0	0	0	4
13	0	2	1	0	1		2	1	0	1	
	24	1	0	0	0						
	48	2	1	2	0						
	72	1	0	0	0	2	1	0	0	0	2
19	0	1	2	2	0		1	2	2	0	
	24	1	1	1	0						
	48	1	1	0	0						
	72	0	1	0	0	1	0	1	0	0	1
23	0	2	1	1	1		2	1	1	1	
	24	1	1	0	1						
	48	1	1	0	0						
	72	0	0	0	0	1	0	0	0	0	1
24	0	2	1	0	0		2	1	0	0	
	24	1	1	0	0						
	48	1	1	0	0						
	72	1	0	0	0	2	0	0	0	0	1

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=403 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
25	0	0	2	0	1		0	2	0	1	
	24	0	2	0	1						
	48	0	2	0	1						
	72	0	2	0	1	4	0	2	0	1	4
28	0	1	2	0	2		1	2	0	2	
	24	0	2	0	0						
	48	0	1	0	0						
	72	0	1	0	0	2	0	1	0	0	1
32	0	0	3	0	0		0	3	0	0	
	24	0	2	0	0						
	48	2	1	1	1						
	72	2	0	1	1	2	2	0	1	1	2
47	0	2	2	0	1		2	2	0	1	
	24	2	2	1	2						
	48	1	1	0	1						
	72	0	1	0	0	2	0	1	0	0	1
48	0	2	2	1	0		2	2	1	0	
	24	1	2	0	0						
	48	0	1	0	0						
	72	0	1	0	0	2	0	1	0	0	1

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=403 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
5	0	3	1	3	1		3	1	3	1	
	24	2	1	2	0						
	48	2	1	1	0						
	72	2	1	1	0	3	2	1	1	0	3
6	0	2	3	1	1		2	3	1	1	
	24	1	3	0	2						
	48	1	2	0	0						
	72	0	1	0	0	2	0	1	0	0	2
10	0	1	2	1	0		1	2	1	0	
	24	1	2	1	0						
	48	1	2	1	0						
	72	3	3	3	0	3	3	3	3	0	5
14	0	2	3	2	0		2	3	2	0	
	24	2	2	2	0						
	48	2	2	2	0						
	72	1	1	1	0	2	1	1	1	0	2
20	0	2	2	0	0		2	2	0	0	
	24	0	1	0	0						
	48	0	0	0	0						
	72	0	0	0	0	2	0	0	0	0	1
21	0	2	3	0	0		2	3	0	0	

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=403 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	2	2	0	0						
	48	1	1	0	0						
	72	0	1	0	0	1	0	0	0	0	1
22	0	3	3	2	0		3	3	2	0	
	24	1	2	0	0						
	48	0	1	0	0						
	72	1	1	0	0	2	1	1	0	0	1
35	0	1	2	1	2		1	2	1	2	
	24	1	2	1	2						
	48	0	1	2	1						
	72	1	1	2	1	3	1	1	2	1	4
38	0	2	2	2	0		2	2	2	0	
	24	2	2	2	0						
	48	2	2	2	0						
	72	3	3	2	0	4	3	3	2	0	5
40	0	2	2	3	0		2	2	3	0	
	24	2	0	0	0						
	48	2	0	0	0						
	72	1	0	0	0	1	1	0	0	0	1
45	0	2	2	2	1		2	2	2	1	
	24	2	1	1	0						
	48	1	0	0	0						

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=403 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	0	0	0	0	1	0	0	0	0	1
46	0	3	1	1	0		3	1	1	0	
	24	2	1	0	0						
	48	1	0	0	0						
	72	1	0	0	0	1	1	0	0	0	1

STUDY=403 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
1	0	1	3	2	0		1	2	1	0	
	24	1	3	1	1						
	48	0	2	0	1						
	72	0	1	0	0	2	0	1	0	0	3
3	0	2	0	0	0		2	0	0	0	
	24	2	0	0	0						
	48	1	0	0	0						
	72	1	0	0	0	2	1	0	0	0	2
15	0	1	2	1	1		1	2	1	1	
17	0	0	2	0	0		0	2	0	0	
	24	0	1	0	0						
	48	0	1	0	1						
	72	0	1	0	1	2	0	1	0	1	2

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AHP1-REG-048-0015310

AHR-4010-3 DINETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=403 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
18	0	3	2	1	0		3	2	1	0	
	24	3	1	1	0						
	48	2	1	1	0						
	72	2	2	0	0	3	1	1	0	0	3
26	0	2	0	2	0		2	0	2	0	
	24	2	0	2	0						
	48	2	0	2	0						
	72	0	0	0	0	4	0	0	0	0	1
30	0	2	1	2	2		2	1	2	2	
	24	1	2	2	1						
	48	0	1	0	0						
	72	0	0	0	0	1	0	0	0	0	1
34	0	3	1	0	0		3	1	0	0	
	24	1	0	0	0						
	48	0	0	0	0						
	72	0	0	0	0	1	0	0	0	0	1
37	0	1	2	1	2		1	2	1	2	
	24	1	1	0	1						
	48	0	1	0	1						
	72	0	1	0	1	2	0	1	0	1	2
41	0	2	2	1	0		2	2	1	0	

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=403 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	2	2	1	0						
	48	2	2	1	0						
	72	1	1	1	0	3	1	1	1	0	3
43	0	2	3	0	1		2	3	0	1	
	24	1	2	0	1						
	48	0	2	0	2						
	72	0	2	0	1	2	0	2	0	1	2
44	0	3	2	3	3		3	2	3	3	
	24	2	2	2	1						
	48	1	2	0	1						
	72	1	1	0	0	2	1	1	0	0	2

STUDY=404 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
4	0	3	3	2	2		2	3	2	2	
	24	2	2	2	1						
	48	2	2	2	1						
	72	2	2	1	1	3	2	2	1	1	3
6	0	3	3	3	3		3	3	2	2	
	24	2	2	1	1						
	48	1	1	0	0						

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=404 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	1	1	0	0	1	1	1	0	0	1
7	0	3	3	3	3		3	3	2	3	
	24	3	3	3	3						
	48	3	3	2	3						
	72	3	3	2	1	4	3	3	2	3	5
9	0	3	3	3	1		3	3	2	2	
	24	1	1	1	1						
	48	0	0	0	0						
	72	0	0	0	0	1	0	0	0	0	1
13	0	3	3	2	1		3	3	2	1	
	24	2	2	1	1						
	48	1	1	0	0						
	72	1	1	0	0	1	1	1	0	0	1
18	0	3	3	2	1		3	3	2	1	
	24	3	3	2	1						
	48	2	2	2	1						
	72	2	2	2	1	3	2	2	2	1	3
24	0	3	3	3	1		3	3	3	1	
	24	3	3	2	0						
	48	2	3	1	0						
	72	2	2	0	0	2	2	2	0	0	2

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=404 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
28	0	3	3	2	2		3	3	2	2	
	24	3	3	2	2						
	48	3	3	2	2						
	72	3	3	2	2	4	3	3	2	2	4
33	0	3	3	2	3		3	3	2	3	
	24	3	3	3	3						
	48	3	3	3	2						
	72	3	3	3	2	4	3	3	3	2	5
37	0	3	3	3	2		3	3	3	2	
	24	3	3	2	1						
	48	2	2	1	0						
	72	2	2	1	0	2	2	2	1	0	2
38	0	3	3	3	3		3	3	3	3	
	24	3	3	3	3						
	48	3	3	3	3						
	72	3	3	3	3	4	3	3	3	3	4
46	0	3	3	2	2		3	3	2	2	
	24	3	3	2	2						
	48	3	3	3	2						
	72	3	3	3	3	4	3	3	3	3	5

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AHP1-REG-048-0015314

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=404 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
5	0	3	3	2	2		3	3	2	2	
	24	1	1	0	0						
	48	0	0	0	0						
	72	0	0	0	0	1	0	1	0	0	1
11	0	3	3	2	2		3	3	2	2	
	24	2	2	1	1						
	48	1	1	0	0						
	72	0	0	0	0	1	0	0	0	0	1
12	0	3	3	2	1		3	3	2	1	
	24	2	2	1	0						
	48	2	2	1	0						
	72	1	2	0	0	2	1	2	0	0	2
15	0	3	3	2	3		3	3	2	2	
	24	3	3	2	3						
	48	3	3	2	1						
	72	3	3	2	1	4	3	3	2	3	4
16	0	3	3	3	1		3	3	3	1	
	24	2	3	2	1						
	48	1	2	1	0						
	72	1	2	1	0	2	1	2	1	0	2
17	0	3	3	2	1		3	3	2	2	

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AHR-4010-3 DINETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=404 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	3	3	2	2						
	48	2	3	2	1						
	72	2	2	2	1	3	2	2	2	1	4
19	0	3	3	3	2		3	3	3	2	
	24	2	2	2	1						
	48	1	2	1	0						
	72	1	2	0	0	2	1	2	0	0	2
32	0	3	3	3	2		3	3	3	2	
	24	1	2	2	0						
	48	1	2	1	0						
	72	0	1	0	0	1	0	1	0	0	1
39	0	3	3	2	1		3	3	2	1	
	24	3	3	2	1						
	48	2	3	2	0						
	72	1	2	1	0	2	1	2	1	0	2
40	0	3	3	2	2		3	3	2	2	
	24	3	3	2	2						
	48	3	3	3	2						
	72	3	3	3	2	4	3	3	3	2	4
41	0	3	3	2	2		3	3	2	2	
	24	3	3	2	2						
	48	3	3	2	2						

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STUDY=404 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	3	3	2	2	4	3	3	2	2	4
43	0	3	3	3	2		3	3	3	2	
	24	2	3	2	1						
	48	2	2	1	0						
	72	1	2	0	0	2	1	2	0	0	2

STUDY=404 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
1	0	2	3	2	1		2	3	2	0	
	24	2	3	1	0						
	48	2	2	0	0						
	72	1	1	0	0	2	1	1	0	0	2
2	0	2	3	2	1		3	3	1	2	
	24	3	3	2	1						
	48	2	3	1	0						
	72	2	2	1	0	3	2	2	2	1	3
8	0	3	3	3	2		3	3	2	1	
	24	3	3	2	2						
	48	2	2	2	2						
	72	2	2	2	1	3	2	2	2	1	3
10	0	3	3	3	2		3	3	3	1	

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=404 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	2	2	1	1						
	48	1	1	0	0						
	72	0	0	0	0	1	0	0	0	0	1
20	0	3	3	2	2		3	3	2	2	
	24	3	3	2	1						
	48	3	3	2	1						
	72	3	3	2	1	3	3	3	2	2	4
25	0	3	3	3	2		3	3	3	2	
	24	3	3	3	2						
	48	3	3	2	2						
	72	3	3	2	2	4	3	3	2	2	4
31	0	3	3	2	2		3	3	2	2	
	24	2	2	0	0						
	48	0	1	0	0						
	72	0	1	0	0	1	0	1	0	0	1
34	0	3	3	2	1		3	3	2	1	
	24	3	3	2	1						
	48	3	3	3	2						
	72	3	3	3	2	4	3	3	3	2	5
36	0	3	3	2	2		3	3	2	2	
	24	3	3	3	2						

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=404 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	48	3	3	2	2						
	72	3	3	3	2	4	3	3	3	2	4
42	0	3	3	3	3		3	3	3	3	
	24	3	3	2	3						
	48	3	3	2	3						
	72	2	3	1	2	3	2	3	1	2	3
45	0	3	3	3	1		3	3	3	1	
	24	2	2	3	0						
	48	2	2	2	0						
	72	1	2	1	0	2	1	2	1	0	2
48	0	3	3	2	1		3	3	2	1	
	24	3	3	1	0						
	48	2	2	1	0						
	72	2	2	0	0	2	2	2	0	0	2
49	0	3	3	3	2		3	3	3	2	
	24	3	3	3	2						
	48	3	3	2	2						
	72	3	3	2	2	3	3	3	2	2	4

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=404 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
3	0	3	3	2	2		3	3	2	1	
	24	3	3	2	2						
	48	2	2	1	1						
	72	1	1	0	0	2	1	1	0	0	2
14	0	3	3	3	3		3	3	3	3	
	24	3	3	3	3						
	48	3	3	3	3						
	72	3	3	3	3	4	3	3	3	3	4
21	0	3	3	3	2		3	3	3	2	
	24	2	3	2	2						
	48	1	2	1	0						
	72	1	2	0	0	2	1	2	0	0	2
22	0	3	3	3	2		3	3	3	2	
	24	3	3	2	1						
	48	2	2	1	0						
	72	1	2	0	0	2	1	2	0	0	2
23	0	3	3	2	2		3	3	2	2	
	24	3	3	2	2						
	48	3	3	3	2						
	72	3	3	3	2	4	3	3	3	2	5
24	0	3	3	3	2		3	3	3	2	

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=404 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	3	3	3	2						
	48	3	3	2	2						
	72	2	3	2	2	3	2	3	2	2	3
27	0	3	3	3	2		3	3	3	2	
	24	3	3	2	1						
	48	3	3	2	0						
	72	2	2	1	0	3	2	2	1	0	3
29	0	3	3	3	1		3	3	3	1	
	24	2	3	3	0						
	48	1	3	2	0						
	72	1	2	2	0	3	1	2	2	0	3
30	0	3	3	2	2		3	3	2	2	
	24	3	3	2	2						
	48	3	3	3	2						
	72	3	3	3	2	4	3	3	3	2	4
35	0	3	3	3	2		3	3	3	2	
	24	3	3	2	1						
	48	2	3	2	1						
	72	2	2	2	1	3	2	2	2	1	3
44	0	3	3	2	1		3	3	2	1	
	24	3	3	2	1						
	48	3	3	2	0						

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=404 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	3	3	1	0	3	3	3	1	0	3
47	0	3	3	2	1		3	3	2	1	
	24	2	3	1	1						
	48	1	2	0	0						
	72	1	1	0	0	2	1	1	0	0	2
50	0	3	3	2	2		3	3	2	2	
	24	3	3	1	2						
	48	3	3	1	1						
	72	3	3	2	2	3	3	3	2	2	3

STUDY=405 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
2	0	2	2	2	2		2	2	2	2	
3	0	2	2	1	1		2	2	1	1	
	24	2	1	0	0						
	48	2	0	0	0						
	72	2	1	0	0	2	2	0	0	0	2
4	0	2	2	2	0		2	2	2	0	
	24	2	2	2	0						
	48	2	2	2	0						
	72	2	2	2	0	4	2	2	2	0	4

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=405 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
12	0	2	2	2	2		2	2	2	2	
	24	0	2	0	3						
	48	2	2	0	3						
	72	0	2	0	1	2	0	2	0	1	2
13	0	2	3	2	3		3	3	3	3	
	24	2	3	2	3						
	48	3	3	3	3						
16	0	2	2	3	1		2	2	3	1	
	24	0	2	2	1						
	48	0	0	1	1						
	72	0	0	1	1	2	0	0	1	1	2
21	0	2	2	2	1		2	2	2	1	
	24	1	2	1	2						
	48	2	2	2	1						
	72	0	2	0	2	4	0	2	0	2	3
30	0	2	2	2	1		2	2	2	1	
	24	1	1	1	1						
	48	1	1	1	0						
	72	0	1	0	0	2	0	1	0	0	1
31	0	2	2	2	0		2	2	2	0	
	24	0	0	0	0						

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=405 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	48	2	1	0	0						
	72	2	1	1	0	3	1	1	1	0	3
36	0	2	3	2	0		2	3	2	0	
	24	2	2	1	0						
	48	2	2	0	0						
	72	1	2	0	0	2	1	2	0	0	3
41	0	2	2	1	2		2	2	1	2	
	24	2	2	0	3						
	48	0	2	2	3						
	72	0	2	0	1	2	0	1	0	1	2
46	0	2	3	3	0		2	3	3	0	
	24	0	0	0	0						
	48	0	0	0	0						
	72	0	0	0	0	1	0	0	0	0	1
50	0	2	3	2	0		2	3	2	0	
	24	1	2	1	0						
	48	0	1	0	0						
	72	0	0	0	0	1	0	0	0	0	1
52	0	2	3	2	2		2	3	2	2	
	24	2	2	1	0						
	48	2	3	1	0						

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=405 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	2	3	1	0	3	1	2	1	0	2

STUDY=405 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
5	0	3	3	3	0		3	3	3	0	
	24	1	1	0	0						
	48	0	0	0	0						
	72	0	1	0	0	2	0	1	0	0	1
8	0	3	3	1	3		3	3	1	2	
	24	2	3	0	3						
	48	1	3	0	3						
	72	0	3	0	3	3	0	3	0	3	3
10	0	2	2	2	0		2	2	2	0	
	24	0	1	0	0						
	48	1	1	1	1						
	72	2	3	2	0	2	0	0	0	0	2
15	0	3	3	3	1		3	3	3	1	
	24	1	1	1	1						
17	0	1	2	2	2		1	2	2	2	
	24	0	1	0	1						
	48	0	1	0	0						

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=405 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	0	1	0	0	2	0	1	0	0	2
23	0	2	2	2	2		2	2	2	2	
	24	2	2	2	2						
	48	1	2	3	2						
	72	1	2	3	2	4	1	2	3	2	5
24	0	3	3	3	1		3	3	3	1	
	24	1	1	1	1						
	48	3	1	3	0						
	72	1	0	1	0	2	0	0	0	0	3
27	0	2	2	1	0		2	2	1	0	
	24	1	1	1	0						
	48	1	1	1	0						
	72	2	1	1	0	3	0	1	1	0	3
37	0	2	2	2	0		2	2	2	0	
	24	2	2	2	0						
	48	1	1	1	0						
	72	1	1	1	0	3	0	1	1	1	2
40	0	2	2	2	2		1	2	2	2	
	24	2	2	2	2						
	48	2	2	2	2						
	72	2	2	2	2	4	2	2	2	2	3

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AHR-4010-3 DIHETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=405 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
43	0	3	3	3	3		3	3	3	3	
	24	0	0	0	0						
	48	0	0	0	0						
	72	0	0	0	0	1	0	0	0	0	1
47	0	2	2	1	1		2	2	1	1	
	24	1	1	0	0						
	48	1	1	0	0						
	72	1	1	1	0	2	0	0	0	0	2
53	0	1	2	0	2		1	2	0	2	
	24	0	1	0	0						
	48	0	1	0	0						
	72	0	0	0	0	2	0	0	0	0	1

STUDY=405 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
7	0	2	2	2	0		2	2	2	0	
	24	3	1	2	1						
	48	3	2	2	1						
	72	1	1	1	3	3	1	1	1	3	2
14	0	3	3	3	2		2	3	3	2	
	24	2	2	2	1						
	48	2	2	2	1						

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=405 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	2	2	2	1	3	1	2	1	1	2
18	0	2	2	2	2		2	2	2	2	
	24	3	3	3	3						
	48										
	72					4	3	3	3	3	5
19	0	2	2	2	0		2	2	2	0	
	24	1	2	0	0						
	48	0	1	0	0						
	72	0	1	0	0	1	0	0	0	0	1
20	0	2	2	2	0		2	2	2	0	
22	0	3	3	2	2		3	3	2	2	
	24	2	2	1	1						
	48	1	2	1	0						
	72	1	1	1	0	2	1	1	1	0	2
25	0	2	2	2	0		2	2	2	0	
	24	1	2	1	1						
	48	1	2	1	0						
	72	2	2	1	0	3	2	3	1	0	3
28	0	2	2	1	1		2	2	1	1	
	24	2	2	1	0						
	48	2	2	1	0						

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=405 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATOR				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	2	2	1	1	4	1	2	1	0	3
34	0	2	3	1	2		2	2	1	2	
	24	2	3	1	2						
	48	2	3	1	2						
	72	2	3	0	2	3	0	1	0	0	3
35	0	2	3	2	0		2	3	2	0	
	24	2	2	2	0						
	48	2	2	2	0						
	72	2	2	1	0	3	1	0	0	0	3
45	0	2	2	1	0		3	3	1	0	
	24	1	2	0	0						
	48	1	1	0	0						
	72	0	1	0	0	1	0	0	0	0	1
48	0	3	3	2	2		3	3	2	2	
	24	1	2	1	1						
	48	1	2	1	1						
	72	0	1	0	0	2	0	0	0	0	2
49	0	2	3	2	1		2	3	2	1	
	24	1	1	0	0						
	48	1	1	1	0						
	72	0	0	0	0	1	0	0	0	0	1

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=405 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
51	0	2	3	2	3		2	3	2	3	
	24	2	3	1	2						
	48	2	3	0	3						
	72	2	3	0	0	3	2	2	0	0	3

STUDY=405 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
1	0	2	2	0	1		2	2	0	0	
6	0	2	2	2	2		2	2	2	2	
	24	1	3	1	3						
	48	1	3	1	3						
	72	1	2	1	2	4	1	2	1	2	4
9	0	2	2	1	3		2	2	1	3	
	24	0	2	0	1						
	48	0	1	0	0						
	72	0	1	0	0	1	0	1	0	0	1
11	0	2	3	3	0		2	3	3	0	
	24	2	2	3	0						
	48	3	2	3	0						
	72	2	2	2	0	2	1	2	1	0	3
26	0	2	2	2	0		2	2	2	0	

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=405 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	1	1	2	0						
	48	1	1	1	0						
	72	0	0	1	0	2	0	0	1	0	2
29	0	2	3	2	0		2	3	2	0	
	24	1	2	0	0						
	48	1	2	0	0						
	72	1	1	0	0	2	0	1	0	0	2
32	0	2	2	2	0		2	2	2	0	
	24	0	2	0	1						
	48	2	0	2	0						
	72	2	2	2	1	4	2	3	2	1	4
33	0	2	2	2	0		2	2	2	0	
	24	0	2	2	0						
	48	0	2	0	0						
	72	0	1	0	0	2	0	0	0	0	2
38	0	2	2	2	0		2	2	2	0	
	24	2	2	2	0						
	48	1	2	1	0						
	72	1	2	0	0	3	1	1	0	0	3
39	0	2	2	2	2		2	2	2	2	
	24	0	1	0	1						

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=405 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	48	0	1	0	0						
	72	0	1	0	0	1	0	1	0	0	1
42	0						2	2	2	2	
44	0	3	3	2	3		3	3	2	3	
	24	2	3	2	3						
	48	2	3	1	1						
	72	1	3	1	2		1	2	1	0	3

STUDY=406 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
5	0	2	2	1	0		2	2	1	0	
	24	2	2	0	0						
	48	2	1	0	0						
	72	2	1	0	0	3	2	1	0	0	3
6	0	2	2	1	2		2	2	1	2	
	24	1	0	1	1						
	48	1	0	1	0						
	72	1	0	1	0	2	1	0	1	0	2
8	0	0	2	1	1		0	2	1	1	
	24	1	2	0	1						
	48	1	1	0	0						

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=406 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	1	0	0	0	2	1	0	0	0	2
9	0	2	2	1	0		2	2	1	0	
	24	2	1	1	0						
	48	1	1	0	0						
	72	1	1	0	0	3	1	1	0	0	3
15	0	2	1	1	0		2	1	1	0	
	24	1	1	0	0						
	48	1	2	0	0						
	72	1	1	0	0	3	1	1	0	0	3
20	0	2	1	1	0		2	1	1	0	
	24	1	1	1	0						
	48	0	0	0	0						
	72	0	0	0	0	2	0	0	0	0	2
25	0	2	2	1	1		2	2	1	1	
	24	1	1	1	0						
	48	1	1	1	0						
	72	1	1	0	0	3	0	1	0	0	3
29	0	1	3	1	0		1	3	1	0	
	24	0	2	1	0						
	48	0	2	0	0						
	72	0	1	0	1	2	0	1	0	1	2

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=406 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
38	0	2	2	1	0		2	2	1	0	
	24	2	2	0	1						
	48	2	2	0	1						
	72	1	1	0	1	2	2	2	1	0	3
39	0	3	2	0	1		3	2	0	1	
	24	3	2	0	1						
	48	2	1	0	0						
	72	1	1	0	0	2	1	1	0	0	2
40	0	1	2	2	2		1	2	2	1	
	24	1	2	1	2						
	48	2	1	2	1						
	72	1	2	0	0	3	1	2	0	0	3
45	0	2	1	1	1		2	1	1	1	
	24	2	1	1	0						
	48	1	0	1	0						
	72	0	0	1	0	2	0	0	1	0	?
51	0	2	2	1	0		2	2	1	0	
	24	1	?	1	0						
	48	0	?	1	0						
	72	0	1	0	0	?	0	1	0	0	?

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=406 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
1	0	2	2	1	0		2	2	1	0	
	24	2	2	0	0						
	48	1	1	0	0						
	72	1	1	0	0	2	1	1	0	0	2
4	0	2	2	1	1		2	2	1	1	
	24	2	1	1	0						
	48	2	1	1	0						
	72	0	0	0	0	1	0	0	0	0	1
13	0	2	2	1	2		2	2	1	2	
	24	3	2	2	2						
	48	1	1	0	0						
	72	0	1	0	0	2	0	1	0	0	2
14	0	2	2	1	1		2	2	1	1	
	24	1	2	0	1						
	48	1	2	0	1						
	72	1	1	0	1	3	1	1	0	1	3
16	0	2	2	1	0		2	2	1	0	
	24	2	2	1	0						
	48	1	2	1	0						
	72	1	1	0	0	3	1	1	0	0	3
22	0	2	2	1	0		2	2	1	0	

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=406 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	1	1	1	0						
	48	1	1	1	0						
	72	1	0	0	0	1	0	0	0	0	1
26	0	2	2	1	1		2	2	1	1	
	24	1	1	1	1						
	48	1	1	0	1						
	72	0	0	0	0	1	0	0	0	0	1
35	0	2	2	1	1		2	2	1	1	
	24	0	1	0	0						
	48	0	1	0	0						
	72	0	0	0	0	1	0	0	0	0	1
36	0	3	3	1	1		3	3	1	1	
	24	2	3	0	1						
	48	3	2	0	0						
	72	1	2	0	0	2	1	2	0	0	2
43	0	2	2	1	1		2	2	1	1	
	24	1	1	0	0						
	48	1	1	0	0						
	72	1	0	0	0	3	1	0	0	0	3
46	0	2	2	1	1		2	2	1	1	
	24	2	2	1	2						
	48	2	2	0	0						

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=406 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	72	1	1	0	1	3	2	1	0	0	3
47	0	2	1	0	0		2	1	0	0	
	24	2	1	0	0						
	48	1	1	0	0						
	72	1	0	0	0	3	1	0	0	0	3
49	0	1	2	1	0		1	2	1	0	
	24	1	1	1	0						
	48	1	1	0	0						
	72	1	1	0	0	3	1	1	0	0	3
50	0	1	2	0	0		1	2	0	0	
	24	1	1	0	0						
	48	1	0	0	0						
	72	1	0	0	0	3	2	2	0	0	5

STUDY=406 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
3	0	2	1	1	0		2	1	1	0	
	24	1	1	1	0						
	48	1	1	0	0						
	72	1	0	0	0	2	1	0	0	0	2
12	0	2	2	1	0		2	2	1	0	

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=406 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	2	2	1	0						
	48	1	1	0	0						
	72	0	1	1	0	2	0	1	1	0	2
18	0	2	2	1	2		2	2	1	2	
	24	2	2	0	2						
	48	2	2	0	2						
	72	1	1	0	1	3	1	1	0	1	3
19	0	2	2	2	0		2	2	2	0	
	24	1	1	0	0						
	48	1	1	0	0						
	72	0	1	0	0	2	0	1	0	0	2
21	0	2	2	1	1		2	2	1	1	
	24	2	2	0	0						
	48	1	1	1	0						
	72	1	0	1	0	2	0	0	1	0	2
24	0	2	2	1	1		2	2	1	1	
	24	1	1	0	1						
	48	2	2	0	1						
	72	2	1	0	1	3	2	2	0	1	3
30	0	2	2	2	1		2	2	2	1	
	24	1	2	1	1						

AHR-4010-3 DIHETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=406 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	48	1	2	1	1						
	72	1	2	1	1	4	1	2	1	1	4
31	0	1	2	1	0		1	2	1	0	
	24	1	2	0	0						
	48	1	1	1	1						
	72	1	1	0	0	3	1	1	0	0	3
32	0	2	1	3	1		2	1	3	1	
	24	3	1	3	2						
	48	2	1	2	1						
	72	0	0	0	0	1	0	0	0	0	1
33	0	2	1	2	1		2	1	2	1	
	24	2	1	1	1						
	48	2	1	1	1						
	72	2	1	1	0	2	2	0	0	0	2
42	0	3	1	0	2		3	1	0	2	
	24	1	1	0	1						
	48	0	1	0	0						
	72	0	1	0	0	3	0	2	0	0	3
44	0	2	1	1	0		2	1	1	0	
	24	1	1	0	0						
	48	0	1	0	0						
	72	0	1	0	0	3	1	2	0	0	4

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=406 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
2	0	2	2	0	0		2	2	0	0	
	24	2	2	1	0						
	48	2	1	0	0						
	72	1	1	0	0	3	1	1	0	0	3
7	0	2	1	0	0		2	1	0	0	
	24	1	1	0	0						
	48	1	0	0	0						
	72	1	0	0	0	3	1	0	0	0	3
10	0	3	2	1	1		3	2	1	1	
	24	2	2	1	1						
	48	2	2	1	0						
	72	2	1	0	0	2	2	1	0	0	2
11	0	1	2	1	2		1	2	1	2	
	24	1	1	0	1						
	48	0	1	0	1						
	72	0	1	0	0	3	0	1	0	0	3
17	0	2	2	0	0		2	2	0	0	
	24	1	2	0	0						

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AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=406 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	48	1	2	0	0						
	72	1	2	0	0	4	1	2	0	0	4
23	0	2	2	1	1		2	2	1	1	
	24	3	3	2	3						
27	0	1	2	1	0		1	2	1	0	
	24	3	2	2	2						
	48	2	1	2	1						
	72	0	0	1	0	3	0	0	1	0	3
28	0	2	3	1	0		2	3	1	0	
	24	1	2	0	0						
	48	1	2	0	0						
	72	0	2	0	0	2	0	2	0	0	2
34	0	1	2	2	1		1	2	2	1	
	24	3	3	2	1						
	48	3	3	2	2						
	72	3	3	3	1	4	2	2	1	1	5
37	0	2	2	1	1		2	2	1	1	
	24	1	2	1	0						
	48	0	1	0	0						
	72	0	1	0	0	2	0	1	0	0	2
41	0	2	0	2	0		2	0	2	0	

AHR-4010-3 DIMETAPP PROTOCOL 04
RAW DATA LISTING OF EFFICACY PARAMETERS

STUDY=406 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
	24	1	1	1	0						
	48	2	1	0	0						
	72	1	2	0	0	4	1	3	0	0	4
48	0	2	1	2	0		2	1	2	0	
	24	2	1	2	0						
	48	2	1	1	0						
	72	1	0	1	0	3	1	1	0	0	3
52	0	2	2	0	1		2	2	0	1	
	24	1	1	1	0						
	48	1	1	0	0						
	72	0	1	0	0	2	0	1	0	0	2

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AHR-4010-3 DIMETAPP PROTOCOL 04
EFFICACY PARAMETERS FOR PATIENTS THAT BECAME INELIGIBLE FOR ANALYSES

STUDY=402 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
13	48										
	72										

STUDY=402 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
21	48										
	72										

STUDY=403 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
2	48	0	3	0	2						
	72	0	1	0	0	3	0	1	0	0	4
31	48	2	3	1	0						
	72	2	3	0	0	3	2	3	0	0	4

STUDY=403 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION

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AHR-4010-3 DIMETAPP PROTOCOL 04
EFFICACY PARAMETERS FOR PATIENTS THAT BECAME INELIGIBLE FOR ANALYSES

STUDY=403 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
15	24	1	1	1	1						
	48	1	1	1	1						
	72	2	2	1	1	4	2	2	1	1	4

STUDY=405 GROUP=PLACEBO

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
7	24	1	1	0	1						
	48	1	1	1	1						
	72	1	1	1	1	3	1	1	1	1	3
13	72					4	3	3	3	3	5

STUDY=405 GROUP=PHENYLPROPANOLAMINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
15	48	1	1	1	1						
	72	0	0	0	0	2	0	0	0	0	1

STUDY=405 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION

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AHR-4010-3 DIMETAPP PROTOCOL 04
EFFICACY PARAMETERS FOR PATIENTS THAT BECAME INELIGIBLE FOR ANALYSES

STUDY=405 GROUP=PHENYLEPHRINE

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
20	24	3	3	1	0						
	48	2	2	1	1						
	72	0	1	0	0	2	0	1	0	0	2

STUDY=405 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
1	24	1	1	0	2						
	48	0	1	0	1						
	72	0	0	0	0	1	0	0	0	0	1
47	24										
	48										
	72										

STUDY=406 GROUP=COMBINATION

		RATING BY PATIENTS					RATING BY INVESTIGATORS				
PATIENT	HOUR	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION	RUNNY NOSE	STUFFY NOSE	SNEEZE	HEAD ACHE	GLOBAL EVALUATION
23	48										
	72										

AHP1-REG-048-0015344

ATTACHMENT K

Nasal Airway Resistance Raw Data Listings

AHP1-REG-048-0015345

AHR-4010 - - DIMETAPP - - PROTOCOL 04

STUDY 401 TOTAL AIRWAY RESISTANCE RAW DATA

AIRWAY RESISTANCE IS IN CM H20/L/SEC WITH A STANDARD REFERENCE FLOW/RATE OF 0.5 liters/second

MIN REPRESENTS THE NUMBER OF MINUTES AFTER THE INITIAL DOSE

MAX DEC REPRESENTS THE MAXIMUM DECREASE IN AIRWAY RESISTANCE

MAX TIME REPRESENTS THE NUMBER OF MINUTES AT WHICH THE MAXIMUM DECREASE OCCURRED

---------- DR=PLACEBO ----------

	PATIENT	MIN 0	MIN 15	MIN 30	MIN 45	MIN 60	MIN 120	MIN 180	MIN 240	MAX DEC	MAX TIME
	1	4.10	3.45	3.45	4.00	4.25	4.40	3.65	4.30	0.70	120.00
	3	4.25	4.05	4.20	4.30	4.35	4.40	4.05	4.10	0.00	60.00
	4	4.00	4.30	3.60	4.20	4.00	5.05	5.30	5.25	0.40	30.00
	9	5.25	4.80	4.65	5.35	4.95	4.05	4.60	5.00	1.20	120.00
	13	5.10	4.85	3.75	4.80	4.25	4.80	5.55	5.25	1.45	30.00
	17	4.55	4.45	4.00	4.40	4.90	4.40	4.00	4.15	0.65	60.00
	22	4.55	4.80	3.50	4.80	4.40	4.60	5.10	4.10	1.05	30.00
	27	4.90	4.00	3.95	4.35	3.35	4.80	4.95	4.85	1.55	60.00
	36	4.45	4.55	5.25	3.40	4.75	4.80	4.90	5.35	1.85	45.00
	43	3.15	4.65	4.50	3.95	4.60	4.05	4.70	4.00	0.00	0.00
	45	5.35	4.95	4.10	4.05	4.45	4.20	4.45	4.70	1.30	45.00
	46	5.70	4.90	4.70	4.80	4.45	4.95	4.60	5.05	1.25	60.00
MEAN		4.61	4.40	4.14	4.37	4.22	4.46	4.65	4.67	0.95	53.00
STD ERR		0.20	0.15	0.16	0.15	0.14	0.14	0.16	0.15	0.13	10.17

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AIR-4010 - - DIFFAPP - - PROTOCOL 04
STUDY 401 TOTAL AIRWAY RESISTANCE RAW DATA
AIRWAY RESISTANCE IS IN CM H20/L/SEC WITH A STANDARD REFERENCE FLOW/RATE OF 0.5 liters/second
MIN REPRESENTS THE NUMBER OF MINUTES AFTER THE INITIAL DOSE
MAX DEC REPRESENTS THE MAXIMUM DECREASE IN AIRWAY RESISTANCE
MAX TIME REPRESENTS THE NUMBER OF MINUTES AT WHICH THE MAXIMUM DECREASE OCCURRED

---------- DRUG=EPHRINE ----------

PATIENT	MIN 0	MIN 15	MIN 30	MIN 45	MIN 60	MIN 120	MIN 180	MIN 240	MAX DEC	MAX TIME
5	4.45	4.25	3.75	3.25	2.40	3.25	4.40	4.45	1.65	60.00
6	4.75	3.80	3.40	3.40	4.45	3.55	4.80	4.00	1.35	45.00
8	5.50	5.05	4.25	3.40	3.85	3.45	4.85	5.70	2.10	45.00
12	4.40	3.40	4.45	3.25	4.60	3.05	3.95	4.45	1.35	120.00
16	4.55	3.75	3.15	3.10	3.10	3.00	4.00	4.10	1.55	180.00
19	5.50	5.10	4.85	2.95	4.40	5.40	4.95	5.55	2.55	45.00
21	5.15	4.90	3.80	3.85	4.25	4.30	4.90	4.85	1.35	30.00
24	3.20	2.80	3.05	2.95	3.10	3.35	4.35	4.70	0.40	15.00
31	5.30	4.95	3.50	4.20	3.10	4.20	4.80	5.05	2.20	60.00
38	4.45	4.10	3.40	3.25	3.50	4.05	5.10	5.65	1.20	45.00
44	3.55	3.40	2.40	3.10	3.40	3.40	3.35	4.50	0.65	30.00
47	3.90	2.60	3.35	3.10	3.50	2.95	4.30	4.30	1.30	15.00
MEAN	4.56	4.01	3.69	3.32	3.50	4.66	4.01	4.77	1.47	57.50
STD ERR	0.21	0.25	0.17	0.11	0.14	0.21	0.20	0.17	0.18	14.67

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AHR-4010 - - DIMETAPP - - PROTOCOL 04
STUDY 401 TOTAL AIRWAY RESISTANCE RAW DATA
AIRWAY RESISTANCE IS IN CM H20/L/SEC WITH A STANDARD REFERENCE FLOW/RATE OF 0.5 liters/second
MIN REPRESENTS THE NUMBER OF MINUTES AFTER THE INITIAL DOSE
MAX DEL REPRESENTS THE MAXIMUM DECREASE IN AIRWAY RESISTANCE
MAX TIME REPRESENTS THE NUMBER OF MINUTES AT WHICH THE MAXIMUM DECREASE OCCURRED

---------- DR=P-PROPANOLAMINE ----------

PATIENT	MIN 0	MIN 15	MIN 30	MIN 45	MIN 60	MIN 120	MIN 180	MIN 240	MAX DEL	MAX TIME
2	3.75	4.10	3.00	2.70	2.80	3.25	3.20	3.00	1.05	45.00
20	4.30	4.25	3.50	3.45	3.45	3.20	3.40	4.25	1.10	120.00
26	4.50	3.60	3.75	3.20	3.00	4.40	4.00	4.25	1.50	60.00
28	3.80	4.10	3.30	2.55	3.90	3.25	4.45	4.00	1.25	45.00
32	3.65	4.45	3.30	2.55	2.80	4.15	3.30	4.00	1.10	45.00
33	4.10	3.80	3.30	2.75	3.20	3.15	4.85	4.00	1.35	45.00
35	3.50	4.35	3.45	2.90	2.85	3.00	3.95	4.00	0.65	60.00
37	5.50	4.15	3.10	3.25	4.00	3.60	3.75	4.25	2.40	30.00
39	5.50	4.65	4.30	3.60	4.40	4.80	4.60	5.60	1.90	45.00
41	4.25	3.15	3.20	2.95	4.05	3.10	4.50	4.50	1.30	45.00
42	5.10	5.30	4.45	4.00	3.40	4.00	3.35	4.80	1.75	180.00
48	4.50	3.20	3.55	3.30	3.25	4.20	4.95	4.45	1.30	120.00
MEAN	4.37	4.01	3.52	3.10	3.46	3.67	4.11	4.09	1.37	70.83
STD ERR	0.20	0.14	0.13	0.13	0.16	0.21	0.19	0.16	0.11	14.10

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AIR-4010 - - DIAGRAPP - - PROTOCOL 04

STUDY 401 TOTAL AIRWAY RESISTANCE RAW DATA

AIRWAY RESISTANCE IS IN CM H20/L/SEC WITH A STANDARD REFERENCE FLOW/RATE OF 0.5 liters/second

MIN REPRESENTS THE NUMBER OF MINUTES AFTER THE INITIAL DOSE

MAX DEC REPRESENTS THE MAXIMUM DECREASE IN AIRWAY RESISTANCE

MAX TIME REPRESENTS THE NUMBER OF MINUTES AT WHICH THE MAXIMUM DECREASE OCCURRED

DR=COORDINATION

	PATIENT	MIN 0	MIN 15	MIN 30	MIN 45	MIN 60	MIN 120	MIN 180	MIN 240	MAX DEC	MAX TIME
	7	5.25	4.60	4.45	3.25	2.95	4.35	4.80	4.15	2.30	60.00
	10	5.05	5.05	3.90	3.80	3.20	4.05	4.80	4.60	1.85	60.00
	11	4.00	2.80	2.65	2.85	2.45	2.60	3.50	4.35	1.55	60.00
	14	5.50	4.00	4.60	4.40	3.20	3.20	4.75	4.80	2.30	60.00
	15	4.55	4.50	3.75	3.25	2.60	4.05	4.60	4.05	1.95	60.00
	18	4.05	3.25	3.55	3.10	2.95	3.25	4.35	3.80	1.10	60.00
	23	4.35	4.25	3.05	3.15	2.90	4.10	3.25	3.85	1.45	60.00
	25	3.60	3.10	2.40	2.60	2.80	3.10	2.60	3.10	1.20	30.00
	29	3.65	3.40	2.95	2.50	2.80	2.60	4.00	4.00	1.15	45.00
	30	4.95	4.90	3.95	2.95	3.10	3.00	3.60	4.05	2.00	45.00
	34	3.50	3.40	3.10	2.75	3.15	4.10	3.50	4.00	0.75	45.00
	40	5.50	5.20	3.50	3.05	3.70	3.35	5.30	4.60	2.45	45.00
MEAN		4.50	4.00	3.42	3.05	2.98	3.63	4.22	4.08	1.67	52.50
STD ERR		0.21	0.23	0.14	0.10	0.09	0.10	0.24	0.14	0.16	2.42

AHP1-REG-048-0015349

ATTACHMENT L

Raw Data Listing for Blood Pressure and Pulse Rate

AHP1-REG-048-0015350

This attachment contains raw data listings for blood pressure and pulse rate measured in mmHg and beats/minute, respectively.

AHP1-REG-048-0015351

AHP1-REG-048-0015352

STUDY = 401 TREATMENT = PLACEBO

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
1	125/ 75	120/ 70	68	64
3	115/ 75	105/ 70	76	64
4	120/ 70	125/ 70	76	60
9	140/ 75	130/ 70	76	76
13	125/ 80	120/ 75	64	68
17	115/ 70	120/ 80	88	84
22	115/ 75	115/ 70	92	84
27	125/ 80	130/ 70	78	64
36	125/ 70	130/ 75	84	80
43	135/ 70	135/ 70	68	64
45	115/ 70	105/ 70	68	76
46	110/ 75	105/ 60	88	84
MEAN	121.3/ 73.8	120.0/ 70.8	77.2	72.4
STD ERR	2.1/ 1.1	3.1/ 1.4	2.7	2.1

STUDY = 401 TREATMENT = P-PROPANOLAMINE

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
2	120/ 70	120/ 70	60	68
20	125/ 85	125/ 70	72	84
26	120/ 65	115/ 70	72	72
28	120/ 70	125/ 80	76	76
32	115/ 70	110/ 70	64	80
33	130/ 75	135/ 80	80	84
35	125/ 75	115/ 80	80	76
37	125/ 75	135/ 75	80	56
39	120/ 70	130/ 80	76	72
41	125/ 80	120/ 85	64	80
42	110/ 65	125/ 70	72	88
48	115/ 70	120/ 60	60	72
MEAN	120.8/ 72.5	122.9/ 74.2	71.1	75.1
STD ERR	1.6/ 1.7	2.4/ 2.0	2.2	2.5

STUDY = 401 TREATMENT = P-EPHRINE

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
5	120/ 70	115/ 66	76	72
6	140/ 75	130/ 70	84	88
8	130/ 75	145/ 70	68	84
12	120/ 75	110/ 70	78	84
16	110/ 70	110/ 70	78	76
19	120/ 70	115/ 70	66	68

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STATISTICAL ANALYSIS SYSTEM

STUDY 401 TREATMENT = D-PROPINE

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
21	120/ 70	120/ 75	80	84
24	105/ 65	110/ 60	80	84
31	125/ 75	115/ 80	76	72
38	125/ 70	115/ 60	68	84
44	115/ 70	120/ 60	80	60
47	130/ 75	130/ 80	92	80
MEAN	120.8/ 71.7	118.8/ 70.8	77.0	78.0
STD ERR	2.3/ 0.9	2.5/ 2.3	2.5	2.4

STUDY = 401 TREATMENT = COMBINATION

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
7	130/ 75	125/ 80	76	80
10	115/ 70	120/ 70	76	72
11	120/ 80	125/ 75	68	64
14	125/ 70	120/ 70	76	80
15	120/ 75	120/ 70	80	76
18	120/ 70	115/ 75	64	68
23	125/ 75	130/ 70	76	68
25	130/ 76	120/ 70	68	68
29	135/ 70	125/ 85	68	68
30	120/ 75	120/ 70	72	60
34	120/ 70	125/ 70	60	60
40	135/ 80	120/ 65	72	84
MEAN	124.6/ 73.8	122.1/ 72.5	71.3	70.7
STD ERR	1.9/ 1.1	1.1/ 1.6	1.7	2.1

STUDY = 402 TREATMENT = PLACEBO

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
4	120/ 80	120/ 75	70	66
5	120/ 80	120/ 80	56	56
6	104/ 70	104/ 65	68	64
9	122/ 70	120/ 70	76	60
10	120/ 70	140/ 70	68	64
14	120/ 80	122/ 76	76	68
MEAN	117.7/ 75.0	121.0/ 72.1	68.1	64.2
STD ERR	2.8/ 2.2	4.7/ 2.1	4.1	1.8

STUDY = 402 TREATMENT = COMBINATION

S T A T I S T I C A L A N A L Y S E S S Y S T E M

PATIENT		BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
4		110/ 70	104/ 70	76	72
12		140/ 88	140/ 86	72	68
13		125/ 80	./ .	74	.
17		110/ 66	100/ 60	66	68
20		120/ 80	122/ 74	72	68
24		114/ 68	108/ 68	78	72
	MEAN	119.8/ 75.3	114.8/ 71.6	72.7	69.6
	STD ERR	4.7/ 3.5	7.3/ 4.3	2.0	1.0

STUDY = 402 TREATMENT = P-EPIRINE

PATIENT		BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
1		110/ 80	108/ 78	68	72
7		110/ 70	110/ 72	68	76
8		110/ 70	110/ 70	72	72
11		120/ 80	120/ 78	60	72
21		104/ 70	./ .	76	.
22		104/ 72	140/ 70	72	68
	MEAN	109.7/ 73.7	121.6/ 73.6	69.3	72.0
	STD ERR	2.4/ 2.0	9.8/ 1.8	2.2	1.3

STUDY = 402 TREATMENT = COMBINATION

PATIENT		BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
2		110/ 80	110/ 80	72	76
15		120/ 80	120/ 80	68	72
14		110/ 70	115/ 72	74	72
18		120/ 70	122/ 80	68	72
19		110/ 70	104/ 68	72	64
	MEAN	114.0/ 74.0	114.2/ 76.0	70.8	71.2
	STD ERR	2.4/ 2.4	3.3/ 2.5	1.2	2.0

STUDY = 403 TREATMENT = PLACEBO

PATIENT		BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
2		122/ 80	134/ 80	76	80
4		96/ 70	96/ 70	76	76
7		114/ 74	114/ 74	84	84
9		104/ 84	104/ 84	80	80
10		120/ 70	120/ 80	76	84
21		110/ 70	120/ 70	64	72

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STUDY = 403 TREATMENT = PLACEBO

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
29	116/ 76	110/ 62	80	76
31	117/ 74	140/ 85	96	76
33	110/ 72	105/ 70	76	72
36	145/ 85	145/ 88	60	74
39	100/ 80	110/ 65	88	82
43	140/ 85	142/100	70	72
MEAN	116.1/ 77.8	120.1/ 78.1	77.1	77.2
STD ERR	4.3/ 2.2	4.8/ 3.0	2.8	1.4

STUDY = 403 TREATMENT = P-PROPANOLAMINE

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
8	112/ 84	112/ 84	72	72
11	115/ 70	124/ 80	68	80
12	120/ 72	125/ 80	94	80
13	130/ 77	130/ 80	80	76
19	120/ 80	120/ 80	74	72
23	142/ 90	128/ 76	86	78
24	132/ 76	128/ 82	78	80
25	104/ 68	104/ 68	68	68
28	115/ 75	112/ 72	76	76
32	150/ 90	130/ 86	74	72
41	128/ 84	122/ 82	64	68
48	112/ 62	114/ 64	76	72
MEAN	123.3/ 77.3	120.8/ 77.8	76.8	74.5
STD ERR	3.9/ 2.5	2.4/ 1.9	2.4	1.4

STUDY = 403 TREATMENT = P-EPHRINE

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
5	120/ 80	112/ 70	80	64
6	112/ 70	112/ 70	64	64
10	100/ 60	100/ 70	68	66
14	120/ 78	112/ 72	74	84
20	120/ 78	120/ 78	98	76
21	144/ 85	136/ 90	92	86
22	104/ 70	104/ 74	76	76
35	122/ 76	124/ 85	64	72
38	124/ 74	126/ 78	84	88
40	110/ 66	106/ 66	84	72
45	112/ 64	100/ 60	72	68
46	140/ 76	116/ 62	70	68

STUDY = 403 TREATMENT = P-I PIPELINE

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
MEAN	117.8/ 72.9	114.8/ 72.0	75.5	72.0
STD ERR	3.4/ 2.5	3.0/ 2.1	2.5	3.2

STUDY = 403 TREATMENT = COMBINATION

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
1	122/ 72	110/ 70	76	64
3	120/ 65	120/ 65	76	76
15	125/ 70	140/ 82	74	76
17	102/ 64	105/ 75	80	80
18	108/ 60	108/ 70	68	72
26	90/ 75	118/ 62	84	72
30	100/ 74	112/ 62	74	70
34	138/ 70	132/ 68	72	68
37	120/ 68	130/ 78	74	72
41	110/ 69	114/ 80	92	68
43	135/ 85	135/ 90	72	80
44	116/ 68	112/ 68	68	70
MEAN	115.5/ 70.0	119.7/ 72.5	75.8	72.3
STD ERR	4.1/ 2.0	3.4/ 2.5	2.0	1.4

STUDY = 404 TREATMENT = PLACEBO

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
4	115/ 60	115/ 60	70	76
6	145/ 75	130/ 70	80	80
7	115/ 60	115/ 60	75	80
9	140/ 80	140/ 80	80	80
13	140/ 80	135/ 75	70	80
18	130/ 70	130/ 70	74	70
26	120/ 60	125/ 65	70	76
28	130/ 70	130/ 70	75	75
33	140/ 70	140/ 70	75	75
37	135/ 75	135/ 75	70	70
38	140/ 70	140/ 70	60	60
46	135/ 75	135/ 75	70	70
MEAN	129.4/ 70.4	128.2/ 70.0	73.5	74.1
STD ERR	3.0/ 2.1	3.2/ 1.7	1.3	1.7

STUDY = 405 TREATMENT = P-I COMBINATION

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S T A T I S T I C A L A N A L Y S I S S Y S T E M

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
6	130/ 75	140/ 70	80	75
11	135/ 75	130/ 75	75	75
12	120/ 60	120/ 60	70	70
15	125/ 75	140/ 75	70	70
16	120/ 60	120/ 60	70	70
17	120/ 60	125/ 70	70	70
19	120/ 65	120/ 60	70	70
32	130/ 70	135/ 75	75	75
39	160/ 70	140/ 70	70	70
40	140/ 75	130/ 75	75	70
41	120/ 60	120/ 60	70	70
43	130/ 70	130/ 70	60	60
MEAN	126.7/ 67.9	127.5/ 68.3	71.3	70.8
STD ERR	2.0/ 1.9	1.9/ 1.9	1.4	1.2

STUDY = 404 TREATMENT = P-EPHRINE

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
1	125/ 70	125/ 70	78	80
2	120/ 65	120/ 65	68	70
8	145/ 90	150/ 90	85	85
10	125/ 70	125/ 65	70	70
20	124/ 75	130/ 70	70	70
25	125/ 70	130/ 70	70	70
31	130/ 70	125/ 70	70	70
34	120/ 60	120/ 60	65	65
36	130/ 75	130/ 75	70	70
42	140/ 80	140/ 80	60	60
45	120/ 60	120/ 60	60	60
48	140/ 80	140/ 80	70	70
49	120/ 60	120/ 60	60	60
MEAN	128.0/ 71.2	128.8/ 70.4	68.9	69.2
STD ERR	2.4/ 2.5	2.6/ 2.5	2.0	2.0

STUDY = 404 TREATMENT = CIMETIDINE

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
3	120/ 60	120/ 60	70	70
14	140/ 80	145/ 85	85	85
21	115/ 60	115/ 70	70	70
22	140/ 75	140/ 75	66	70
24	140/ 75	140/ 75	80	80
26	140/ 75	140/ 75	80	75
27	120/ 60	120/ 70	70	70
29	125/ 65	130/ 70	90	90

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STATISTICAL ANALYSIS SYSTEM

STUDY = 404 TREATMENT = COMBINATION

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
30	130/ 75	130/ 75	75	75
35	120/ 60	120/ 60	70	70
44	140/ 80	140/ 80	70	70
47	135/ 75	135/ 75	70	70
50	140/ 80	140/ 80	72	70
MEAN	128.8/ 69.2	128.1/ 70.0	72.0	71.4
STD ERR	2.4/ 2.3	2.3/ 2.2	1.5	1.2

STUDY = 405 TREATMENT = PLACEBO

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
2	140/ 80	138/ 80	76	74
3	130/ 76	128/ 74	90	86
4	116/ 64	100/ 70	72	72
12	130/ 96	142/ 86	74	80
13	98/ 66	100/ 70	76	78
16	136/ 84	134/ 82	72	74
21	140/ 84	138/ 84	84	80
30	130/100	120/ 88	62	82
31	126/ 88	134/ 86	68	80
36	110/ 86	122/ 84	98	82
41	136/ 80	138/ 90	86	94
46	162/ 74	110/ 70	78	84
50	140/ 80	120/ 86	92	88
52	112/ 88	108/ 74	88	96
MEAN	129.0/ 81.9	124.7/ 80.1	79.1	82.1
STD ERR	4.4/ 2.1	3.9/ 1.9	2.5	1.9

STUDY = 406 TREATMENT = P-PROPANOLAMINE

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
5	110/ 58	116/ 62	90	78
8	100/ 66	100/ 96	80	80
10	118/ 94	120/ 82	74	72
15	140/ 90	138/ 92	80	76
17	104/ 80	110/ 80	72	72
24	110/ 80	100/ 70	66	68
26	122/ 70	120/ 78	74	66
27	90/ 60	100/ 70	70	74
32	150/110	146/106	74	84
40	120/ 80	130/ 90	76	76
44	122/ 80	118/ 72	68	70

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S T A T I S T I C A L A N A L Y S I S S Y S T E M

STUDY = 405 TREATMENT = D-PROPRANOLOL

PATIENT		BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
47		140/ 64	128/ 66	98	88
54		120/ 92	120/ 78	76	68
	MEAN	120.2/ 79.2	119.5/ 79.6	79.1	75.6
	STD ERR	4.8/ 6.8	4.8/ 3.1	2.8	2.6

STUDY = 405 TREATMENT = D-PROPRANOLOL

PATIENT		BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
1		120/ 76	124/ 82	88	86
14		140/ 68	110/ 60	86	92
18		122/ 80	126/ 80	74	72
19		126/ 92	124/ 90	88	86
20		112/ 86	110/ 84	72	76
22		130/ 80	120/ 90	76	68
25		120/ 98	100/ 72	68	82
28		118/ 94	122/ 84	68	72
34		130/ 82	136/ 76	88	84
35		130/ 88	142/ 96	68	64
45		130/ 86	138/102	72	80
48		122/ 90	124/ 88	88	86
49		110/ 80	122/ 90	90	88
51		120/ 80	148/ 76	76	90
	MEAN	122.1/ 84.1	123.9/ 83.6	78.7	80.6
	STD ERR	2.3/ 2.1	4.2/ 2.8	2.4	2.4

STUDY = 405 TREATMENT = COMBINATION

PATIENT		BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
1		132/ 82	130/ 80	74	74
6		98/ 60	118/ 70	68	68
9		110/ 80	112/ 82	72	76
11		102/ 78	140/ 70	64	80
26		134/ 84	134/ 86	86	86
29		114/ 68	140/ 88	76	96
32		120/ 80	122/ 82	76	76
33		120/ 90	116/ 88	80	80
38		150/ 98	164/ 96	62	86
39		138/ 92	130/ 76	90	84
42		140/ 80	./ .	80	.
44		132/ 86	120/ 80	86	80
	MEAN	124.0/ 84.0	128.2/ 81.0	81.	82.0

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S T A T I S T I C A L A N A L Y S I S S Y S T E M

STUDY = 405 TREATMENT = COMBINATION

PATIENT		BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
	STD ERR	6.1/ 2.9	3.0/ 2.4	2.4	2.1

STUDY = 406 TREATMENT = PLACEBO

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
5	110/ 78	112/ 80	58	64
6	126/ 76	140/ 70	120	84
8	120/ 80	124/ 84	60	66
9	100/ 60	98/ 60	80	68
15	140/ 92	114/ 70	72	76
20	130/ 92	120/ 90	80	76
25	108/ 80	120/ 70	84	84
29	100/ 60	112/ 68	68	72
38	128/ 78	118/ 78	84	80
39	122/ 76	110/ 78	80	64
40	110/ 70	126/ 90	78	72
45	102/ 64	90/ 50	84	56
51	100/ 70	100/ 80	72	88
MEAN	115.1/ 76.9	113.2/ 73.1	78.5	72.9
STD ERR	3.7/ 2.9	3.1/ 3.7	4.2	2.6

STUDY = 406 TREATMENT = P-PROPANOLAMINE

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
1	134/ 80	130/ 80	88	76
4	100/ 70	100/ 68	80	88
13	120/ 90	100/ 80	72	80
14	120/ 80	110/ 80	84	76
16	110/ 70	120/ 80	72	68
22	100/ 74	100/ 60	72	76
26	116/ 70	120/ 70	100	80
35	112/ 68	110/ 76	82	88
36	100/ 74	100/ 76	80	72
43	136/ 86	130/ 80	84	80
46	136/ 96	140/ 92	96	72
47	120/ 72	110/ 80	100	80
48	104/ 70	120/ 76	64	76
50	130/ 90	116/ 82	100	96
MEAN	117.9/ 77.0	116.6/ 79.1	83.4	77.9
STD ERR	3.2/ 2.1	3.0/ 2.2	2.0	1.9

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S T A T I S T I C A L A N A L Y S I S S Y S T E M

STUDY = 406 TREATMENT = D-EPINEPHRINE

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
3	108/ 60	90/ 56	76	60
12	128/ 70	114/ 70	64	60
18	110/ 80	112/ 70	72	88
19	110/ 90	120/ 82	88	80
21	128/ 88	110/ 80	88	84
24	130/ 82	130/ 90	100	88
30	100/ 58	110/ 70	80	80
31	114/ 78	110/ 70	84	78
32	102/ 60	102/ 60	66	72
33	104/ 66	104/ 60	68	72
42	110/ 70	126/ 82	76	68
44	126/ 80	120/ 70	72	80
MEAN	114.3/ 78.5	112.4/ 71.7	77.8	76.8
STD ERR	3.1/ 3.2	3.1/ 3.0	4.1	3.3

STUDY = 406 TREATMENT = COMBINATION

PATIENT	BLOOD PRESSURE BASELINE	BLOOD PRESSURE 72 HOURS	PULSE RATE BASELINE	PULSE RATE 72 HOURS
2	110/ 80	110/ 60	80	80
7	126/ 82	120/ 88	76	60
10	110/ 80	110/ 76	80	76
11	122/ 66	110/ 70	80	88
17	100/ 70	104/ 66	68	80
23	110/ 60	./ .	80	
27	100/ 60	102/ 60	68	72
28	130/ 80	114/ 68	108	78
34	128/ 80	130/ 80	80	84
37	124/ 72	112/ 68	72	76
41	120/ 70	126/ 72	72	68
48	144/ 88	120/ 88	88	76
52	122/ 78	120/ 70	76	56
MEAN	118.9/ 74.3	114.9/ 72.2	78.2	76.0
STD ERR	3.6/ 2.6	2.6/ 2.7	2.9	2.8

(5)

STUDY EVALUATION REPORT

STUDY NO. 7032

Willem S. Frederik, M.D., Ph.D.
106 Suffolk Road
Wellesley, Massachusetts
Formerly: Pharmatech Inc.
223 Crescent Street
Waltham, Massachusetts

Reference to raw data
Vol. _____
Pages _____

1. Drug, Dosage Form and Phase

Dimetapp Elixir, each component, every combination, and vehicle, Afrin Nasal spray. Phase II.

2. Protocol Number

No number

3. Dates of Initiation and Completion

Initiated: March 1, 1967
Completed: July 31, 1967

4. Materials Used in Study

Commercial stock bottles of:
1. Dimetapp Elixir
2. Dimetane Elixir
3. Elixir Propadrine
4. Elixir Neosynephrine
5. Dimetapp vehicle
6. Afrin nasal spray

Study Objective

To investigate the use of the Respiron* under controlled conditions, as an instrument to evaluate and compare the nasal decongestant effects of Dimetapp Elixir and related formulations and provide data and other information upon which to base the design of definitive studies in this and related areas in the future.

6. Study Description

a. General Study Design

Single-blind, crossover, randomized study in which each subject received one of 8 treatments on 8 separate days.

b. Description of Subjects

Adults with stable or chronic nasal congestion (etiology not of primary importance). Prior to each treatment nasal resistance as determined by the Respiron was at least 10 mm. H_2O.

* See brochure attached to protocol

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c. Dosage Schedule

See Randomization Schedule and Drug Code attached to protocol.

d. Observations

1. Nasal resistance as measured by Respiron (in mm. H_2O at a flow rate of 0.5 L/sec.) - 5 readings at each observation time.
2. Pulse
3. Blood pressure
4. Adverse effects

e. Schedule for Observations

Pre-treatment
30 minutes
1 hour
2 hours

Nasal resistance was again measured after Afrin spray at 3 minutes and 5 minutes the objectives in this procedure were two:

1. to obtain a check on the instrument and techniques
2. to obtain an indication of the possible maximum response for a given subject on a particular day.

7. Findings

a. Effect on Nasal Resistance

Please refer to Mr. Preston's memo. Statistical Analysis of Dimetapp Elixir Study No. 7032, dated September 6, 1967, attached to this report.

b. Description of Subjects

Age Group (Years)	Sex		Total
	Male	Female	
10-19	1	2	3
20-39	3	1	4
40-60	1		1
Total	5	3	8

All subjects had a diagnosis of perennial allergic rhinitis of 2 to 6 years duration.

c. Blood Pressure and Pulse

There was no clinically significant effect of any treatment on blood pressure or pulse in any subject. Raw tabulations of individual blood pressure readings may be found in the file.

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d. Adverse Effects

None were reported

8. Conclusions and/or Comments

See Mr. Preston's memo. Statistical Analysis of Dimetapp Elixir Study No. 7032, dated September 6, 1967, attached to this report.

Ellen J. Preston M.D.

11-22-67
EJP:pcj

AHP4-REG-310-0104292

A·H·ROBINS

date September 6, 1967

memo to Dr. Ellen J. Preston

SUBJECT: Statistical Analysis of Dimetapp Elixir Study No. 7032
(Dr. W. Frederik's Respiron Nasal Resistance Study)

A. Basis for Statistical Analysis

1. The design was a "Randomized Block" one in which each of the 8 subjects received, on a randomized schedule, each of the 8 drug treatments.

2. The 8 drug treatments were selected to form a "2x2x2 Factorial" experiment as follows:

		Phenylpropanolamine (P)			
		0 mg.		10 mg.	
		Phenylephrine (N)		Phenylephrine (N)	
		0 mg.	10 mg.	0 mg.	10 mg.
Dimetane (D)	0 mg.	"Placebo"	"N"	"P"	"N+P"
	8 mg.	"D"	"N+D"	"P+D"	"N+P+D"

(These "treatment codes" are used throughout this memo.)

3. All analyses are based on the arithmetic means of the 5 replicate determinations of nasal resistance that were made at each observation period.

4. Separate analyses have been made for each time period (i.e. ½, 1 and 2 hours) for "inspiration" and, similarly, for "expiration."

5. In order to be more nearly consonant with statistical requirements for the analysis of variance (i.e. homoscedasticity and normality), the data have been transformed as follows:

$$\ln(\text{observation}) / \ln(\text{pre-drug})$$

B. Interpretation of the Statistical Analysis

The following points are largely implicit, or should be, in the interpretation of any statistical analysis, but it is most important, I feel, that due consideration and weight be given to them in the interpretation of these findings and any decisions predicated on them.

1. The restrictions necessarily placed on the selection of subjects for the study, the mixtures of drugs used, conditions of tests, etc., may or may not limit unduly the population to which you might wish

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to project the findings.

2. A finding of "statistical significance" says, in effect, that the differences observed in the experiment (i.e. sample) are of such magnitude, as compared with the inherent variability of the data, that you can reasonably ascribe these differences to "real" population differences rather than to chance. Furthermore, it is clearly desirable to be able to demonstrate "significant" findings in replicates of the experiment, but economic and other factors must also be considered.

3. "Statistically significant" (i.e. "real") differences of objective data may or may not be of "clinical significance":

   a. The objective parameter may or may not be relevant (or totally relevant) to the basic clinical effect desired.

   b. Even if relevant, the magnitude of the "real" difference may or may not be "clinically significant."

4. A statistical finding of "not significant" implies only that the information available from the data is inadequate to support a finding of a "real" difference. A more sensitive experiment (i.e. more information) might well result in a given "not significant" difference becoming "significant."

   Parenthetically, it should be recalled that this experiment was set up as a "pilot" trial with the understanding that additional trials might well be required for more nearly definitive conclusions.

5. It is altogether necessary and proper to consider simultaneously the six separate analyses (viz. "inspiration" and "expiration" at ½, 1 and 2 hours). Cognizance, however, should be taken of the high degree of correlation among the data. While "trends," "clues," etc., are an essential and appealing ingredient of the art of experimentations, the state of statistical theory and methodology largely dictates that any simultaneous consideration be on an intuitive rather than an analytic level.

C. Results and Statistical Analysis

1. The results for the 8 treatments (i.e. non-factorial) are summarized in Table 1 for which the data have been converted to the "% of the pre-drug observation" for each subject and the geometric means calculated for the 8 subjects involved. In none of the 6 sets of data is there a statistically significant difference among the 8 treatments (analysis of variance was performed). The data appear to be highly consistent and are surely of heuristic value and will be referred to in connection with other analyses. [see page 3 for table.]

2. Table 2 shows the direction, magnitude and level of statistical significance for the "main effects" and "interactions" for "2x2x2 factorial" experiment. [see page 4 for table.]

AHP4-REG-310-0104294

TABLE 1

SUMMARY OF RESULTS

	Rank	½ hour	1 hour	2 hours	Over-all
INSPIRATION	1	N+D (54.7)*	N+D (67.4)	D (77.4)	N+D
	2	P (82.6)	P (100.8)	N+D (83.5)	P
	3	N+P+D (91.5)	P+N (109.6)	P (96.8)	D
	4	D (98.9)	D (110.4)	N+P+D (99.1)	N+P+D
	5	N (112.6)	N (113.9)	P+N (113.7)	P+N
	6	P+N (115.2)	N+P+D (115.1)	P+D (152.7)	N
	7	P+D (115.7)	P+D (148.0)	N (172.6)	P+D
	8	Placebo (149.4)	Placebo (174.0)	Placebo (184.8)	Placebo
EXPIRATION	Rank	½ hour	1 hour	2 hours	Over-all
	1	N+D (63.8)	P+N (76.2)	P (76.0)	N+D
	2	P (74.9)	N+D (86.3)	N+D (84.9)	P
	3	N+P+D (85.0)	P (87.2)	N+P+D (85.5)	P+N
	4	P+N (89.9)	N (95.4)	P+N (97.5)	N+P+D
	5	Placebo (100.1)	N+P+D (113.0)	D (104.1)	N
	6	N (100.8)	Placebo (115.0)	Placebo (130.3)	Placebo
	7	P+D (117.0)	D (126.0)	N (132.0)	D
	8	D (123.7)	P+D (155.3)	P+D (145.1)	P+D

* ( ) = Geometric Mean (% of pre-drug observation)
8 subjects pa. mean
Cones (see above)

AHP4-REG-310-0104295

TABLE 2

TABLE OF EFFECTS

(2x2x2 Factorial)

[Data: ln (observation)/ln (pre-drug)]

INSPIRATION

Main Effects	½ hour	1 hour	2 hours
Dimetane (D)	-0.12074✓	-0.07529	-0.15764*
Phenylephrine (N)	-0.09041	-0.12204✓	-0.03764
Phenylpropanolamine (P)	-0.00515	-0.00078	-0.03858
Interactions: NxD	-0.04967	-0.00846	-0.03534
PxD	+0.12142*	+0.14652*	+0.17041**
NxP	+0.10404	+0.08641	+0.00461
NxPxD	-0.03732	-0.04815	-0.09330

EXPIRATION

Main Effects	½ hour	1 hour	2 hours
Dimetane (D)	+0.00458	+0.08020	-0.01748
Phenylephrine (N)	-0.07239	-0.09593✓	-0.05458
Phenylpropanolamine (P)	-0.00823	-0.00678	-0.05475
Interactions: NxD	-0.09160✓	-0.02888	-0.07227
PxD	+0.04763	+0.08459✓	+0.10161*
NxP	+0.04388	+0.01238	-0.00945
NxPxD	+0.02033	-0.00479	-0.04093

** Indicates $p \leq .01$
* Indicates $p \leq .05$
✓ Indicates $p \leq .10$

Negative (-) = decreased nasal resistance
Positive (+) = increased nasal resistance

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3. Table 3 shows the direction, magnitude and level of statistical significance for the "main effects" and the "interaction" for the "2x2 factorial" experiment in which only those treatments in which phenylpropanolamine was at the "zero" level were considered in the analysis.

TABLE 3

TABLE OF EFFECTS

(2x2 Factorial - Phenylpropanolamine at "zero" level)

[Data: ln (observation)/ln (pre-drug)]

	Main Effects	½ hour	1 hour	2 hours
INSPIRATION	Dimetane (D)	-0.2422*	-0.2219√	-0.3280**
	Phenylephrine (N)	-0.1945√	-0.2085√	-0.0422
	Interaction			
	NxD	-0.0124	+0.0397	-0.0580

	Main Effects	½ hour	1 hour	2 hours
EXPIRATION	Dimetane (D)	-0.0431	-0.0044	-0.1191
	Phenylephrine (N)	-0.1163√	-0.1083	-0.0451
	Interaction			
	NxD	-0.1119√	-0.0241	-0.0313

** Indicates $p \leq 0.01$
* Indicates $p \leq 0.05$
√ Indicates $p \leq 0.10$

Negative (-) = decreased nasal resistance
Positive (+) = increased nasal resistance

D. Conclusions and/or Comments

1. The replicated determinations, the consistancy of the mean results and the magnitude and uniformity of the "error mean squares" in the analysis of variance are indicative of the relatively high degree of precision of the data and lend considerable support to their credibility.

2. Perhaps the most definitive (and intriguing) finding is the statistically significant adverse interaction between Dimetane and phenylpropanolamine (Table 2). In 5 of the 6 sets of data, the "PxD" interaction is significant and in all cases the direction is toward increased nasal resistance.

   As an illustration of the "meaning" of a "PxD" interaction, consider Table 4.

AHP4-REG-310-0104297

TABLE 4

ILLUSTRATION OF THE "DxP" INTERACTION

(Inspiration: ½ hour)

	Phenylpropanolamine		Difference
	0 mg.	10 mg.	
Dimetane at 0 mg.	6.57	6.51	0.06 (Decrease)
Dimetane at 8 mg.	6.45	6.51 (.39)	0.06 (Increase)
Difference (effect)	0.12 (Decrease)	0.00 (none)	

"PxD" Interaction = 0.12

Note that when phenylpropanolamine (P) is not present (i.e. at its zero level), 8 mg. of Dimetane (D) has the effect of reducing nasal resistance by 0.12 units. However, when phenylpropanolamine is present at its 10 mg. level, 8 mg. of Dimetane has no effect on the nasal resistance. The interaction is 0.12 units (i.e. 0.12 + 0.00).

Of course, the interaction is symmetric. When Dimetane is absent, 10 mg. of phenylpropanolamine has the effect of decreasing nasal resistance by 0.06 units. With 8 mg. of Dimetane present, 10 mg. of phenylpropanolamine has the effect of increasing nasal resistance by 0.06 units. Again the interaction is 0.12 units (i.e. 0.06 + 0.06).

Perhaps a more cogent way to look at these data is in terms of the "interaction" as a failure of the two treatment effects to be "additive." When given separately the drugs decrease nasal resistance by 0.06 units and 0.12 units for phenylpropanolamine and Dimetane, respectively. The combined effect of the drugs is only 0.06 units (0.57 - 0.51) instead of 0.18 units (0.12 + 0.06). In the absence of interaction, the "anticipated" results for the combination would have been 0.39 units instead of 0.51 units.

This adverse "PxD" interaction is reflected in Table 1 in which the "P+D" combination ranks seventh in "Inspiration" and eighth in "Expiration."

5. Because of the "PxD" interaction, conclusions about the effects of Dimetane are based on the supplementary 2x2 analysis summarized in Table 3. It can be seen that Dimetane is effective in decreasing nasal resistance during inspiration. The effect is not significant during expiration, but "tends" to be in the "right" direction.

   It "appears" also that the Dimetane effect persists, if not increases, during the first 2 treatment hours.

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6. Phenylephrine has the statistically significant effect of reducing nasal resistance for both inspiration and expiration.

   There is some evidence, however, that the effect of phenylephrine does not persist for two hours.

7. There is one statistically significant ($p \leq 0.10$) "NxD" interaction, but all of these interactions "tend" to be "favorable." A "favorable" interaction can be interpreted conversely to the "adverse" "PxD" interaction as discussed above [i.e. not only are the "favorable" separate effects of Dimetane and of phenylephrine additive, but there could be a supplementary favorable effect from the combination (potentiation?)(synergism?)]. Simple additive effects (i.e. no interaction) appear to me to be adequate justification *primae faciae* for the formulation of a drug combination.

8. No definitive statement can be made about the statistical significance of phenylpropanolamine because of the significant "PxD" interaction. The effect, however, appears to be "favorable."

9. Rather surprisingly, as I understand it, there appears to be a tendency toward an "adverse" interaction between phenylephrine and phenylpropanolamine (i.e. "NxP" interaction). None of these interactions, however, is significant. In this connection, note both Tables 1 and 2.

10. It should be pointed out that there is no detrimental data with respect to the Dimetapp ("N+P+D") formulation *per se*. The third order "NxPxD" interaction "tends" toward being "favorable" (Table 2) and this formulation appears to be "superior" to the placebo in all of the sets of data (Table 1). On the other hand, the Dimetapp formulation appears to be "inferior" to the Dimetane-phenylephrine (N+D) combination (Table 1).

Please let me know if you have any comments or questions about these analyses or if you desire any additional analyses.

Lester W. Preston, Jr.

cc: Mr. Bell

LWP/bl

AHP4-REG-310-0104299

A·H·ROBINS

date September 20, 1967

memo to Dr. Ellen J. Preston

SUBJECT: Statistical Analysis of Dimetapp Elixir Study No. 7032 - 11
(Dr. W. Frederik's Respiron Nasal Resistance Study)

Per our recent discussions of the previous analysis and in consideration of the manifold imponderables, I recommend the following points be accepted as working hypotheses for the present:

1) "N+D" better than "N+P+D" better than "Placebo"

2) a) "N+P+D" equivalent to "P+N"; therefore, "D" = ?

b) "N+P+D" better than "P+D"; therefore, "N" = F*

c) "N+P+D" worse than "N+D"; therefore, "P" = A*

3)

	A Priori	Main Effect	Added	Interaction
"D"	F	F	?	? = F
"N"	F	F	F	? = F
"P"	F	?	A	A

4)

	A Priori	Main Effect	Added	Interaction
"D"	F	F	F	? = F
"N"	F	F	F	? = F

*(F = Favorable
*(A = Adverse

Lester W. Preston, Jr.

LWP/bl

CONFIDENTIAL

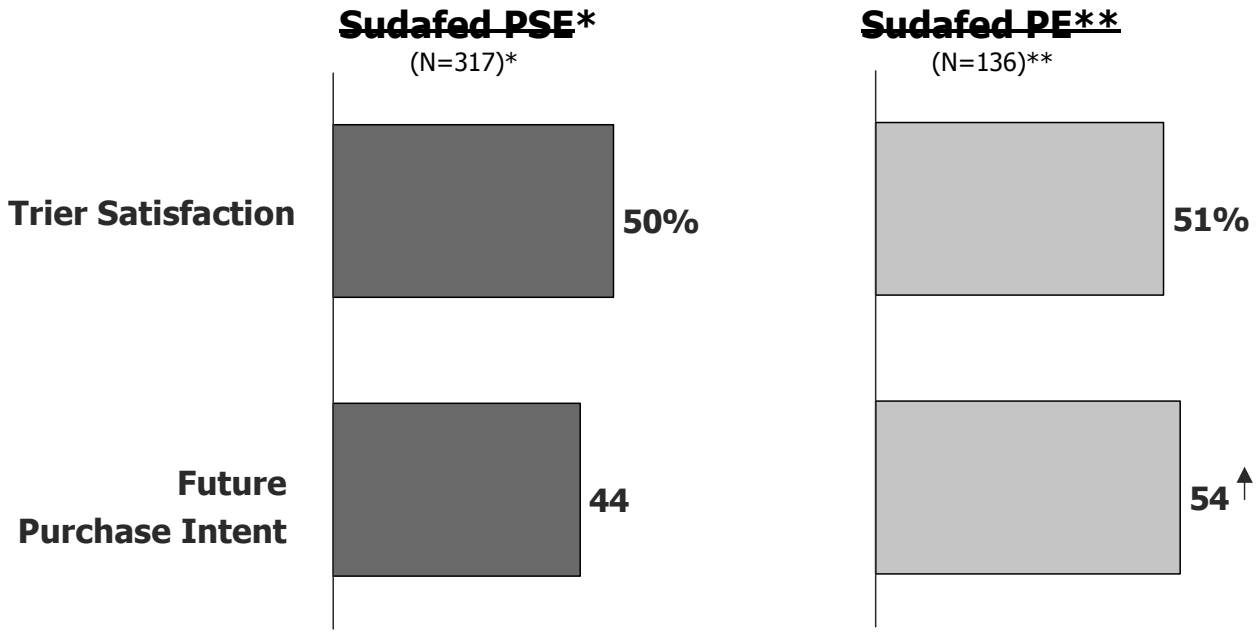
AHP4-REG-310-0104300

AHP4-REG-310-0104300

- Satisfaction levels are equal for the PSE and PE versions of Sudafed.
- Future purchase interest is significantly lower for the PSE Sudafed formula. This may be due to the extra effort needed to purchase it from the pharmacy counter.

Sudafed PSE vs. PE Comparison – 4Q05/1Q06 Cough/Cold Tracker

Based on those who Ever Tried the brand (Top 2 Box Scores)



* Consists of an average across Sudafed Nasal Decongestant, Sinus & Allergy, and Sinus Headache PSE variants.

** Consists of any Sudafed PE (non variant specific).

↑↓ Significantly higher/lower at 90% confidence level than other group

Wyeth Consumer Healthcare

Phenylephrine Review

November 16, 2007

Docket 76N-052N

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The recent series of communications between Representative Waxman and the FDA on the efficacy of phenylephrine prompted us to examine all studies of phenylephrine (PE) conducted by Wyeth Consumer Healthcare (WCH). The purpose of this communication is to submit information on three unpublished studies conducted between 1967 and 1983 that were not previously submitted to the OTC Monograph for Nasal Decongestant Drug Products, Docket 76N-052N. The study reports are appended and the results are summarized in this document. In our opinion, all three studies support the efficacy of 10 mg PE for nasal decongestion.

In addition to the review of the three clinical studies, this report summarizes the studies reviewed in 1976 by the FDA on this subject, as well as other published studies that were not part of the OTC Review. It is our conclusion that the total body of evidence supports the nasal decongestant efficacy of 10 mg of PE.

Furthermore, data are presented to show that there is no evidence that larger doses of PE result in greater efficacy. Therefore, we concur with the FDA's opinion that 10 mg of PE is a safe and effective decongestant.

STUDIES CONDUCTED BY WYETH CONSUMER HEALTHCARE, NOT PREVIOUSLY SUBMITTED TO DOCKET 76N-052N

Wyeth Consumer Healthcare (WCH), formerly AH Robins, conducted three double blind, randomized clinical trials which evaluated the efficacy of PE 10 mg for the treatment of nasal congestion. These are summarized in Table 1. Each study is discussed individually below:

1. **Study AHR-GIA** was a randomized, single-dose, double-blind, partial factorial, parallel group, single-center study conducted in 48 subjects (ages 19-74) with nasal congestion due to an upper respiratory infection (conducted in 1973). Subjects were enrolled within 24-72 hours of the onset of symptoms. The principal investigator was Burton M. Cohen, M.D. Subjects were randomly assigned to one of the following treatment groups: PE 10 mg (n=8), phenylpropanolamine (PPA) 10 mg (n=8), brompheniramine (BR) 8 mg (n=8), or PE+PPA+BR (n=24). Measurements of nasal inspiratory and expiratory resistances (using a Respiron instrument) and subjective assessments of nasal mucosal congestion, nasal mucosal hyperemia, nasal secretion, and ease of nasal breathing were assessed on 0-4 point

scales (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe or 0=normal, 1=mildly impaired, 2=moderately impaired, 3=severely impaired, 4=total obstruction) were completed at baseline and every 30 minutes post-dose for up to 4.5 hours. PE 10 mg alone resulted in statistically significant reductions from baseline in both inspiratory and expiratory resistances from 60 through 150 minutes after dosing ($p<0.05$), and marginally significant reductions in inspiratory resistance at 180-210 minutes after dosing ($p<0.10$). There were no statistically significant differences among the decongestant treatments. Results from the subjective assessments were consistent with those of the objective measures: PE significantly reduced (from baseline) nasal secretions from 30-180 minutes, congestion from 60-120 minutes (differences at 150-210 minutes were marginally significant), hyperemia from 30-180 minutes, and ease of breathing was significantly better at 60-150 minutes after dosing. There were no statistically significant differences between PE and PPA for any of the subjective assessments. WCH believes that this study is supportive of the efficacy of PE 10mg for the treatment of nasal congestion.

2. **Study AHR-4010-3** was a randomized, six-center, multiple-dose, double-blind, parallel group study conducted in subjects with nasal congestion due to an upper respiratory infection conducted in 1983. Subjects were enrolled within 48 hours of the onset of symptoms. Subjects were required to take study medication every 4 hours over a 72-hour period. The study evaluated the following treatments: PE 10 mg, PPA 25 mg, PE 5 mg+PPA 12.5 mg, and placebo (PBO). Using a four-point categorical scale (0=not present, 1=mild, 2=moderate, 3=marked), subjective evaluations of runny nose, stuffy nose, sneezing and headache were provided by the subject at baseline, and at 24, 48 and 72 hours after taking the first dose of study medication, and by the Investigator at baseline and at 72 hours. Also using 4 and 5-point categorical scales (1=marked benefit, 2=moderate benefit, 3=minimal benefit, 4=no benefit, or 5=worse), both the subject and the investigator provided an overall evaluation of therapeutic effect at the end of the evaluation period. In addition to the patient and investigator subjective assessments, only subjects enrolled at one study site (site 0401) underwent objective assessments of nasal inspiratory and expiratory resistance at 15, 30, and 45 minutes, and 1-4 hours after the first dose of medication. The study enrolled a total of 274 subjects (ages 18-77 years) at 6 sites.

Site 0401 enrolled a total of 48 subjects, with 12 subjects randomized to each of the four treatment groups. PE 10 mg was found to be statistically significantly better than PBO for total nasal airway resistance (NAR) at 30-180 minutes after the first dose was administered, and was marginally better at 15 minutes. The total airway resistance improvement for PE

and PPA were similar. PE was also either significantly better, or marginally significantly better than placebo for the following subjective assessments: subjects' assessment of stuffy nose at 72 hours, investigator's assessment of stuffy nose at 72 hours ($p<0.10$), subjects' assessment of sneezing at 24 and 48 hours ($p<0.10$), and the investigator's assessment of sneezing at 72 hours ($p<0.10$). For the most part, both PE and PPA provided similar relief of runny nose, nasal congestion and sneezing, although the severity of the subjects' stuffy nose in those on PE was significantly lower than those on PPA at 72 hours.

There was a statistically significant ($p<0.01$) treatment-by-site interaction for both the subject and investigator's overall evaluations at 72 hours. The interaction became insignificant ($p<0.55$) when site 0401 was excluded from the analysis. The pooled data from the remaining 5 sites failed to show significant differences among the four treatments. Site 0401, other than being the only site to collect objective assessments, tended to have more severe nasal congestion and less severe runny nose at baseline (56% and 15% with severe stuffy nose and runny nose baseline ratings, respectively) compared to those enrolled at the other 5 sites (38% and 34% with severe stuffy nose and runny nose baseline ratings, respectively). Subjects at site 0401 also tended to be older (mean age = 47.7) than those from the other 5 sites (mean age = 33.9 years). It is not clear if any of the baseline differences between site 0401 and the other 5 sites could have contributed to the different outcomes. Nonetheless, WCH believes that this study is supportive of the efficacy of PE 10mg for nasal congestion.

3. **Study #7032** conducted in 1967 was a randomized, single-dose, single-blind, placebo controlled, full-factorial, 8-way crossover, single-center study conducted in 8 subjects (ages 8-60) with stable or chronic nasal congestion due to allergy. Each subject received each of the following treatments in random order on 8 separate treatment days: PE 10 mg, PPA 10 mg, BR 8 mg, PE+PPA, PE+BR, PPA+BR, and PE+PPA+BR and PBO. During each treatment period, NAR was measured at baseline and at 30, 60, and 120 minutes after dosing using a Respiron instrument. Subjects were required to have a NAR reading of at least 10 mm at baseline. PE 10 mg alone produced marginally statistically significant reductions ($p< 0.10$) in inspiratory and expiratory nasal airway resistances at 1 hour after dosing. Readings at 30 minutes and 2 hrs after dosing were numerically better, but not statistically different from placebo. The reductions seen in both inspired and expired nasal resistance at 30 minutes and 1 hour for PE were numerically greater than those seen with PPA. The two treatments were similar at 2 hours post-dose.

Two of these studies (AHR-GIA; AHR-4010-3) demonstrated with objective and subjective measures that in subjects with nasal congestion, PE 10 mg was significantly more effective than PBO or demonstrated significant improvements in NAR from baseline, whereas the third study (#7032) was weakly supportive.

STUDIES REVIEWED BY THE FDA IN 1976

WCH obtained copies of all studies that were cited in the bibliography of the PE section of the 1976 OTC Review of Cough, Cold and Allergy ingredients (Federal Register, vol. 41, no. 176, pages 38396-38400, September 9, 1976). We identified 14 studies reviewed by the FDA in 1976 (these studies are references 5, 6, 7, 8, 9, 10, 19, 20, 21, 22, 23, 24, 25, 26 in the 1976 Federal Register document). Of these, reference 19 was not evaluated further because this was a methodological paper that tested an oral combination product containing a vasoconstrictor, an antihistamine and an analgesic whose specific ingredients were unknown. Additionally, reference 25 was rejected because it was an abstract without any clinical data. Table 2 summarizes the design, pertinent strengths, weaknesses and findings from each of these studies. All studies evaluated objective measures of nasal congestion by measuring reduction of nasal airway resistance (NAR), using rhinometric methods. Furthermore, 11 of these 12 studies measured subjective responses on a 5-point severity scale of nasal congestion.

Five of the studies (references 5, 20, 21, 23, and 24) were negative, i.e., PE at doses ranging from 5 mg to 75 mg did not significantly reduce NAR compared to placebo. On examination of these studies, 3 of them (references 21, 23 and 24) did not include a positive control group which brings into question the sensitivity of the rhinometric assay performed. In another study (reference 5) the author noted that the baseline NAR measurements suggested "the majority of patients did not have baseline nasal congestion". In addition, the positive control failed to separate from placebo again suggesting that the methods used were not sensitive. Finally, another study (reference 20) showed a statistically significant reduction in NAR by the positive control (PPA) and not by 10 and 25 mg PE suggesting a true failure of PE efficacy under the conditions of that study. One would conclude therefore that of these 5 studies, there was <u>one</u> well-conducted study that failed to demonstrate the efficacy of PE. On the other hand, seven double blind (DB), randomized trials (R) [references 6, 7, 8, 9, 10, 22, and 26] were positive, i.e., PE demonstrated a significant reduction in NAR at the doses tested ranging from 5 – 25 mg. Four of the studies (references 7, 10, 22 and 26) included a 10 mg dose of PE and another study included a 5 mg dose (reference 8). In each study a

clinically significant reduction in NAR (20% or greater) was achieved at the 5 and 10 mg doses.

STUDIES NOTED IN HENDELES LETTER-TO-THE-EDITOR

WCH obtained all clinical studies cited in the Hendeles and Hatton letter-to-the-editor and conducted a computerized search for all published articles on the efficacy of PE. This latter search only revealed one completed but unpublished study by Schering Plough (http://clinicaltrials.gov/ct/show/NCT00276016). This study was conducted as a randomized, placebo-controlled, investigator–blind, three-way crossover trial to examine the efficacy of PE 12 mg and pseudoephedrine (PSE) 60 mg in 39 subjects with nasal congestion due to seasonal allergic rhinitis. Although PE failed to separate from PBO in the primary efficacy comparison of subjective nasal congestion scores, the authors believed that possible recall biases inherent in the crossover design may have influenced the result for PE.

Three additional studies were identified from the Hendeles and Hatton's 2006 letter-to-the-editor (Bickerman, 1971, Cohen, 1972 and McLaurin et al, 1961). Bickerman, 1971 corresponds to the FDA's abstract reference 25. The study by McLaurin et al, 1961 was evaluated by FDA for safety but not efficacy in their review. Cohen's study was published in 1972 but was not reviewed by the FDA in their 1976 review for reasons unknown to us. Table 3 summarizes these three studies.

McLaurin's study assessed the oral decongestant efficacy of PE 10 mg, PPA 25 mg, PSE 60 mg and ephedrine (EPH) 25 mg in a mixed population of patients with rhinitis. The quality of this study is questionable for the following reasons. First, the study population consisted of patients with rhinitis of mixed etiologies (common cold, sinusitis, allergy, vasomotor rhinitis, hypothyroidism). Second, the methods of randomization and blinding were not clear. Third, 42 out of 130 enrolled subjects (32%) were discontinued from the study and not included in the analyses, potentially biasing the results. Only one of the active treatment arms, i.e. EPH 25 mg but not PSE 60 mg or PPA 25 mg was found to significantly reduce NAR. Subjective assessment of nasal congestion did not reveal any significant treatment effects in contrast to Dr. Hendeles' conclusion that EPH showed efficacy in subjective endpoints as well. In our opinion this cannot be considered to be a valid study showing the lack of PE efficacy because the model's validity and assay sensitivity were not demonstrated.

Bickerman evaluated the efficacy of oral PE 10 mg, PSE 60 mg and PPA 40 mg compared to placebo in an unknown number of patients with chronic non-seasonal rhinitis in what the author described as a "representative crossover study". This study is generally lacking in details and appears to be more of a description and validation of a rhinometric method where a number of baseline measurements were made in patients with upper respiratory tract infections. The evaluation of pharmacological treatments seems to be a secondary objective. The results showed that PSE and PPA but not PE reduced NAR from 30 min to 4 h post dose. Dr. Hendeles constructed a table from the data in this study and published it in his 2006 letter to the editor citing it as evidence of the lack of effect of PE. He further described the study as a double-blind, placebo-controlled, randomized crossover study in 20 patients with nasal stuffiness. We have been unable to verify this statement given the information in the manuscript. Dr. Hendeles had used the same data in a previous paper he authored in 1993 (Pharmacotherapy 1993;13: 129S-134S). In that paper he noted that "the report did not indicate how many patients were studied". Therefore the robustness of these data cannot be established. The on-line repository cited in his letter to the editor does not contain any additional information about this study.

Cohen, studied the efficacy of PE in 48 subjects with nasal congestion due to colds. This was a double blind, randomized, placebo controlled, crossover study which tested the effects of PE 10 mg, 15 mg and 20 mg on NAR and improvement of subjective assessment of nasal congestion. All doses of PE tested showed a significant reduction in NAR and subjective scores of nasal congestion. Furthermore there was statistically significant greater reduction in NAR produced by PE 25 mg compared to 10 mg and 15 mg doses. This is one of the only studies to demonstrate a significant dose response effect. Hendeles criticizes this paper - "it is noteworthy that in the cohort treated with 10mg, baseline nasal airway resistance was significantly different on the 2 study days, making the results difficult to interpret". He is correct in that there was no apparent adjustment for this baseline imbalance (and the data are unavailable to do it now). However, the PE group was consistently numerically less severe post-baseline compared to placebo despite it starting out as more severe. Also, the PE 15 mg group, which did not differ from placebo at baseline, also showed a significant reduction in NAR compared to placebo treatment. Finally, PE 10mg and placebo subjective symptom scores were comparable at baseline, and the scores in the PE 10mg group improved significantly more than in the placebo group.

In our opinion Dr. Hendeles unduly discredits the positive study (Cohen) while emphasizing the two negative studies (McLaurin, Bickerman). At best it can be argued that the data in his

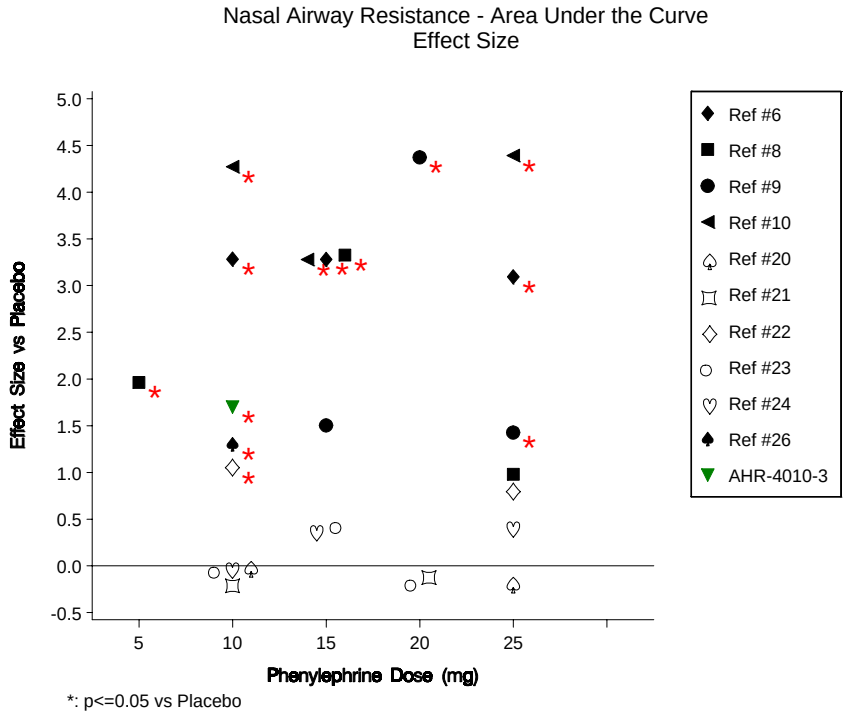
letter-to-the-editor shows one positive (Cohen) and one negative (Bickerman) study with respect to PE. The third study (McLaurin) cannot be relied upon to draw any valid conclusions about PE efficacy.

OVERALL EFFICACY CONCLUSIONS

Of the 19 studies presented above evaluating PE for nasal congestion, 11 studies show benefit of PE in both objective and subjective findings; 3 well conducted studies failed to show the efficacy of PE; and 5 studies demonstrated inadequate model validation and assay sensitivity thereby not allowing efficacy conclusions to be made.

Examination Of Dose-Response Across Studies

We further examined the studies cited above, where data were available, to determine whether a dose-response relationship could be demonstrated for PE. The following figure shows the effect size, which is a measure of the difference between the active treatments and placebo, standardized by the within-study standard deviations (between subjects).



These data show that there is no clear dose response associated with increasing doses of PE. This suggests that doses of PE greater than 10 mg do not produce a larger effect size (or more decongestant effect) than 5-10 mg doses, hence obviating the need to recommend or

further study the efficacy of 25 mg of PE. Given the possibility of increased cardiovascular risks with increasing doses of any sympathomimetic amine and the desire to maximize the benefit risk ratio of these OTC drugs, we disagree with Dr. Hendeles' suggestion that higher doses are warranted.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, WCH concurs with the Agency opinion that 10mg phenylephrine is a safe and efficacious oral nasal decongestant.

We respectfully disagree with Hendeles and Hatton's conclusions regarding the lack of efficacy of PE. The authors suggested that the 1976 US FDA review panel that concluded that PE was safe and effective, reached a "specious conclusion that was not based on a systematic review of the available data". The authors state that the panel reviewed only four studies showing efficacy of the 10mg dose of PE compared with seven studies showing no difference between PE and placebo. As described above, the data reviewed by WCH, which includes all studies that were submitted to the FDA, as well as others published subsequently, along with three unpublished studies conducted by our company, demonstrate that 10mg of PE is effective in both objective and subjective measures of nasal congestion relief.

Drs Hendeles and Hatton also allege that the "poor oral bioavailability" of PE may be a reason that it is unlikely to provide relief of nasal decongestion. It is important to note that bioavailability in itself is not a reason for lack of efficacy. The critical components in this regard are the amount of drug that reaches the appropriate receptor sites and the affinity of the drug for those receptors. There are many examples of highly effective drugs that have "low bioavailability", e.g., the bioavailability of the bisphosphonates is <1%, omeprazole, 30-40% and morphine 40%.

In the final analysis, consumers will decide whether PE is effective for them. As discussed, data from numerous studies suggests that PE is effective. Available market research data also suggests that consumers are as satisfied with PE containing medicines as they were with PSE containing medicines. GfK Group conducted a study comparing consumer satisfaction and future purchase intent for Pfizer's PSE containing Sudafed compared to Sudafed PE. Among approximately 450 users, the satisfaction was similar (50% and 51%) while future purchase intent was higher for Sudafed PE than for the PSE formulation (54% vs. 44%, respectively), (GfK Arbor LLC, 2006).

Consumers have several choices among OTC products for nasal congestion. First, they can select PE products off-the-shelf. If they experience adequate relief, consumers are likely to be satisfied with such products. If they find that they are not experiencing adequate relief, they can seek out PSE-containing medicines, which are available behind the counter. Alternatively, they can seek recommendations for other OTC treatment from the pharmacist with respect to their symptoms.

Abbreviations

AE	Adverse event
BROM	Brompheniramine
DB	Double-blind
EPH	Ephedrine
NAR	Nasal airway resistance
PBO	Placebo
PC	Placebo-controlled
PE	Phenylephrine
PPA	Phenylpropanolamine
R	Randomized
ss	Statistically significant

Table 1. Summary of AH Robins Studies Evaluating Phenylephrine

Study	Basis of Review	Results/Comments
AHR-GIA May, 1973	R, DB, single-dose, partial factorial, parallel group, single-center studying 48 adults with nasal congestion due to URI of 24-72 hrs in duration Treatments PE 10 mg + PPA 10 mg + BROM 8 mg (n=24) PE 10 mg (n=8) PPA 10 mg (n=8) BROM 8 mg (n=8) Assessments Inspiratory and expiratory NAR (electronic posterior rhinometry) at baseline and every 30 minutes post-dose for up to 4.5 hours, Subjective measures (5-point severity scale of nasal congestion, nasal mucosal hyperemia, nasal secretion and ease of nasal breathing)	**Positive study.** NAR (inspiration and expiration): Significant change from baseline* for PE at 60-150 min, and marginally better at 180-210 min PPA numerically better than PE at 120-240 min; the two treatments essentially equal at 30-90 min Subjective Nasal Mucosal Congestion – ss reduced from baseline* for PE sign at 60-120 and marginally better at 150-210 min. Nasal secretions - ss reduced from baseline for PE *30-180 min, hyperemia 30-180 min. Subjective ease of nasal breathing - ss reduced from baseline* for PE sign at 60-150 min. No consistent difference between PE and PPA * within-group comparison

AHR-4010-3 December, 1983	R, DB, parallel, multiple dose (every 4 hours), 3-day study in 48 patients with nasal congestion due to URI of less than 48 hours in duration Treatments PE 5 mg + PPA 12.5 mg (n=12) PE 10 mg (n=12) PPA 25 mg (n=12) PBO (n=12) Assessments NAR (electronic posterior rhinometry) at 15, 30, 45, 60, 120, 180, and 240 min after first dose Subjective symptomatic measures (4-point categorical scale) at 24, 48 and 72 hrs; Investigator symptomatic evaluation at 72 hrs; Overall (global) evaluation by both subject and Investigator at 72 hours	**Positive study.** These data suggest that PE separated from PBO in subjective and NAR assessments and equal to a PPA dose of 25mg. PE significantly reduced NAR at 30-180 minutes compared to PBO and was marginally better at 15 minutes. PE was essentially equal to PPA at all time points PE was either significantly better, or marginally significantly better than PBO for the following subjective assessments: subjects' assessment of stuffy nose at 72 hours, Investigator's assessment of stuffy nose at 72 hours ($p<0.10$), subjects' assessment of sneezing at 24 and 48 hours ($p<0.10$), and the Investigator's assessment of sneezing at 72 hours ($p<0.10$). For the most part, both PE and PPA provided similar relief of runny nose, nasal congestion and sneezing, although the severity of the subjects' stuffy nose for PE was significantly lower than PPA at 72 hours. A WCH re-analysis of the global assessments, based on the data provided in the report, indicates that PE 10mg was significantly better than placebo.
Study 7032 November, 1967	R, PC, SB, single dose, single-center crossover, 2 hr evaluation period in 8 subjects with stable or chronic nasal congestion Treatments PBO, PE 10 mg, PPA 10 mg, BROM 8 mg, PE + PPA, PE + BROM, PPA + BROM, PE + PPA + BROM (n=8) Assessments Inspiratory and expiratory NAR (electronic posterior rhinometry)	**Trending Study (Positive trend)** PE 10 mg alone produced marginally statistically significant reductions ($p< 0.10$) in inspiratory and expiratory nasal airway resistances at 1 hour after dosing. Readings at 30 minutes and 2 hrs after dosing were numerically better, but not statistically different from placebo. The reductions seen in both inspired and expired nasal resistance at 30 minutes and 1 hour for PE were numerically greater than those seen with PPA. The two treatments were similar at 2 hours post-dose.

Table 2. Studies Evaluated by FDA for Efficacy of Oral Phenylephrine

Study Reference #	Basis of Review	Results/Comments
Reference 5 Memo to Lands from Luduena April 23, 1959	DB, PC, incomplete crossover study. Topical PE and PPA and Oral PE dose tested 10, 25, 50, 75 mg and PPA 25, 50 mg. N= 14-15 volunteers/arm	**Negative study.** Actives did not separate from PBO for NAR. Analysis: Inadequate assay sensitivity, no systemic drugs demonstrated any effect.
Reference 6 Memo to Suter from Hulme. June 27, 1967 Elizabeth Biochemical Labs #1	DB, PC, R, incomplete crossover study in 25 subjects with congestion due to colds. Studied oral EPH. 8 mg (n=13) and PE 25mg (n=12)	**Positive study.** Both PE 25 mg and EPH ↓ NAR (peak ↓ ~ 5 units) and subjective scores of nasal congestion significantly ↓ by both treatments compared to PBO.
Referred to in Reference 7 Memo to Wessinger from Hulme. Jan 12, 1968 Elizabeth Biochemical Labs #2	DB, PC, R, incomplete crossover study in 38 subjects with congestion due to colds. Studied oral ephedrine 50 mg (n=6) and PE 10mg (n=16), 15mg (n=10), 25mg (n=6)	**Positive study.** 10 mg, 15mg and 25mg PE separated from PBO. 10 mg PE significantly reduced NAR at all time points from 15 min through 2 hours (p=0.01). Maximal reduction was 5.3 units at 45 and 60 min post dose. All doses ↓ subjective scores of nasal congestion.
Reference 8 Memo to Blackmore from Hulme June 2, 1969 Elizabeth Biochemical Labs #3	DB, PC, R incomplete crossover study in 46 subjects with congestion due to colds for 2 consecutive days. Studied oral PE doses of 5mg (n=16), 15mg (n=10) and 25mg (n=10) and PPA 50mg (n=10)	**Positive study.** All actives ↓'d NAR compared to PBO. No demonstration of dose-response. Only PE 15 mg and PPA 50 mg significantly reduced subjective scores of nasal congestion (p=0.05).
Reference 9 Memo to Blackmore from Hulme. August 11, 1969 Elizabeth Biochemical Labs #4	DB, PC, R incomplete crossover study in 20 subjects with congestion due to colds. PE 15 (n=6), and 20 mg (n=5), PE 25mg (n=9)	**Positive study.** 15 mg, 20 mg and 25 mg PE ↓'d NAR compared to PBO beginning at 45 min post dose. Only 20 mg PE ↓'d subjective scores of nasal congestion.
Reference 10 Memo to Blackmore from Hulme May 27, 1970 Elizabeth Biochemical Labs #5	DB, PC, R incomplete crossover study in 25 subjects with congestion due to colds. Studied oral PE doses of 10mg (n=10), 15mg (n=6) and 25mg (n=9)	**Positive study.** All actives ↓'d NAR compared to PBO as early as 30 minutes after dosing. PE 10 mg duration up to 180 min, peak effect at 60 min (29%↓,P=0.01). Subjective: only 25 mg PE reduced subjective scores of nasal congestion.
Reference 20 Memo to Blackmore from Hulme May 13, 1969 Huntingdon Research Center #1	DB, PC, R, incomplete crossover study in 48 subjects with congestion due to colds. Oral PE 10, and 25 mg, PPA 50mg. N= 16/arm	**Negative study.** No PE doses separated from PBO. PPA positive at 45 and 60 min. Subjective results not reported due to lack of objective effect.

Reference 21 Memo to Blackmore from Hulme. June 26, 1969 Huntingdon Research Center #2	DB, PC, R incomplete crossover study in 50 subjects with congestion due to colds. Oral PE 10, and 20 mg. N= 25/arm	**Negative study.** No doses separated from PBO. Author cited possible reasons for failure: 1) larger variability (compared to other congestion studies), 2) insufficient training of technicians, 3) use of different technicians pre and post-dosing. Subjective results not reported due to lack of effect on NAR.
Reference 22 Memo to Blackmore from Hulme. Apr 10, 1969 Clintest Labs #1	DB, PC, R incomplete crossover study in 48 subjects with congestion due to colds. PE 10, and 25 mg, PPA 50mg. N= 16/arm	**Positive study.** 10, 25 mg PE and PPA ↓'d NAR compared to PBO. PE 10mg effect on NAR seen 90 180 minutes. PE 10 mg and PPA significantly reduced subjective scores for nasal congestion (p=0.05, p=0.01, respectively).
Reference 23 Memo to Blackmore from Hulme. Jan 23, 1970 Clintest Labs #2	DB, PC, R incomplete crossover study in 48 subjects with congestion due to colds. Oral PE 10, 15, and 25 mg. N= 16/arm	**Negative study.** No doses separate from PBO on objective and subjective measures. No positive control.
Reference 24 Memo to Blackmore from Hulme. May 18, 1970 Clintest Labs #3	DB, PC, R incomplete crossover study in 48 subjects with congestion due to colds. Oral PE 10, 15, and 25 mg. N= 16/arm	**Negative study.** 10 mg PE does not separate from PBO. 15mg and 25 mg are marginal. No positive control. PE 15 mg ↓'d subjective scores of nasal congestion (p=0.05).
Reference 26 OTC volume 040288B	DB, PC, parallel group study of 200 patients with nasal congestion due to head cold. PE 10mg administered orally Q4h x 4 doses, versus PBO	**Positive study.** Significant reduction in NAR by PE 10mg from 15-120 min compared to PBO (11-28%, $p \leq 0.05$). Placebo group was somewhat more severe at baseline, for which there was no adjustment. Subjective: PE was significantly better than PBO for sneezing (115%), runny nose (85%) and stuffy nose (57%), $p < 0.05$.

Table 3. Other Studies in the Literature on the Efficacy of Phenylephrine

Study	Basis of Review	Results/Comments
McLaurin, 1961	Cross-over study in 88 subjects with nasal congestion due to a variety of causes, colds, sinusitis, allergy, vasomotor rhinitis and hypothyroidism. Compared oral PBO, PE 10mg, PSE 60mg, PPA 25mg and Eph 25mg. Measured NAR (McLaurin's Rhinometric method) at baseline and 60 minutes post dose. Subjective change of the nasal airway (6 category scale) recorded 60 min post dose and the following a.m. after taking a second dose 1 hr prior to bedtime the previous evening. Vital signs.	**Negative study. PE did not separate from PBO.** Only Ephedrine was found to significantly (p=0.05) lower NAR (38%). No significant differences between PBO and treatment groups at either 2 time points. Significant methodologic issues: Unclear how this study was blinded or randomized. Almost 1/3 of the subjects (42/130) who entered the study dropped out before completion and were excluded from all analyses. This could have severely biased the results as well since, to some extent, only responders were analyzed. Statistical methods were not provided.
Bickerman, 1971	This study was described by the author as a "Representative DB crossover study". An unknown number of subjects with chronic non-seasonal rhinitis received oral PBO, PSE 60mg, PPA 40 mg or PE 10mg.	**Negative Study. PE did not separate from PBO.** PSE and PPA showed significant reduction of NAR compared to PBO at all post-dose time points (30 min – 4 h) whereas PE did not. No subjective assessments of nasal congestion were made.
Cohen, 1972	DB, PC, R incomplete two way crossover study of 48 subjects with nasal congestion due to the common cold. Each subject received oral PBO and PE 10 (n=16) or 15 (n=16) or 25 mg (n=16).	**Positive study.** All active doses reduced NAR compared to PBO. PE 25mg showed greater ↓ in NAR compared to 10mg and 15mg doses. For PE 10 mg, significant reduction was seen from 30-120 min ($p \leq 0.01$- 0.05). Peak reduction of ~40% at 60 min post dose. Mean % reduction in subjective scores paralleled reduction in NAR for each dose. This study clearly demonstrates the efficacy of PE on objective and subjective measures. There is a statistically significant dose-response effect between 25 mg and 10mg doses. A greater number of AEs were seen at the 25 mg dose.

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Memo to Blackmore from Hulme. Neo-synephrine - Elizabeth Biochemical study No. 5. May 27, 1970.

Memo to Blackmore from Hulme. Oral neo-synephrine – Huntingdon Research Center study No. 1. May 13, 1969.

Memo to Blackmore from Hulme. Oral neo-synephrine – Huntingdon Research Center study No. 2. June 26, 1969.

Memo to Blackmore from Hulme. Oral neo-synephrine – Clintest Labs study No. 1. April 10, 1969.

Memo to Blackmore from Hulme. Oral neo-synephrine – Clintest Labs study No. 2. January 23, 1970.

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Study Report: AHR-4010-3. December 14, 1983 (attached).

Study Report: AHR-G1-A. May 10, 1973 (attached).

Study Report 7032. November 22, 1967 (attached).

The study listed may include approved and nonapproved uses, formulations, or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this registry, healthcare professionals should consult prescribing information for the product approved in their country.

Title of Study:	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).
Studied Period:	09 JAN 2006 to 01 FEB 2006
Clinical Phase:	3

Objective(s): The **primary** 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 **secondary** 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.

Methodology: 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.

Number of Subjects: Thirty-nine subjects received at least one dose of treatment; 38 subjects completed treatment, receiving all three treatment sequences.

Diagnosis and Criteria for Inclusion: 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:

- Skin test positive for the grass pollen allergen used in the chamber at Screening or within the prior 12 months.
- A negative urine pregnancy test at Screening and at monthly intervals for female subjects of childbearing potential.
- The following minimum scores at an evaluation time point during each of the 120-minute screening period challenge sessions:
    1. Nasal Congestion Score of at least 2 (moderate);
    2. Total Nasal Symptoms Score (rhinorrhea, nasal congestion, sneezing, nasal itching) of at least 6;
    3. Total Non-nasal Symptoms Score (eye itching/burning, eye tearing, itching of ears/palate) of at least 2.
- Freedom from any clinically significant disease, other than SAR, that would interfere with the study evaluations.

Subjects meeting any of the following **Key Exclusion Criteria** were not eligible for entry into this study:

- An upper or lower respiratory tract infection within 4 weeks before screening.
- Dependence upon nasal, oral, or ocular decongestants, nasal topical antihistamines, or nasal steroids, in the opinion of the investigator.
- A known potential for hypersensitivity, allergy, or idiosyncratic reaction to the study drug or excipients.

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