CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-082

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW
Division of Pulmonary and Allergy Drug Products (HFD-570)

Application Number:	21-082	**Application Type:**	NDA
Sponsor:	Novartis Consumer Health, Inc.	**Proprietary Name:**	Tavist®Allergy/Sinus/Headache
Category of Drug:	Antihistamine/ decongestant/ analgesic/ antipyretic	**USAN Name:**	Clemastine fumarate/ acetaminophen/ pseudoephedrine HCl
		Route of Administration:	Oral
Medical Reviewer:	Charles E. Lee, M.D.	**Review Date:**	2/14/01

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Application	Document Date:	CDER Stamp Date:	Submission Type, Comments:
NDA 21-082 BL	11/9/00	11/9/00	Correspondence, labeling
NDA 21-082 BL	10/30/00	11/3/00	Facsimile, correspondence

RELATED APPLICATIONS (if applicable):

Document Date:	Application Type:	Application Number:	Comments:
2/25/77	NDA	17-661	Tavist® 2.68 mg tablets
6/28/85	NDA	18-675	Tavist syrup
8/21/92	NDA	20-925	Tavist-1, OTC, 1.34 mg tablets
8/21/92	NDA	18-298	Tavist-D, OTC
8/9/96	NDA	20-640	Tavist-D, [redacted], OTC

REVIEW SUMMARY:

NDA 21-082, Tavist® Allergy/Sinus/Headache (0.335 mg clemastine fumarate/500 mg acetaminophen/ 30 mg pseudoephedrine HCl) was submitted 10/7/99 by Novartis Consumer Health, Inc. The original NDA submission provided adequate evidence of safety and efficacy for the temporary relief of various nasal and ocular symptoms associated with the hay fever, allergic rhinitis, and the common cold. The Division of Pulmonary and Allergy Drug Products took an approvable action on 8/4/00. The sponsor was asked to submit revised product labeling, which was reviewed in the Medical Officer review of NDA 21-082 dated 12/26/00. This reviewer recommended that the Agency's recommended language be retained regarding conditions for which patients should seek advice from a doctor or pharmacist before using the product. The proposed labeling was otherwise acceptable.

The submission of 10/30/00 includes final proposed labeling for the 24-count package. The submission of 11/09/00 includes final proposed labeling for the 48-count package. Final proposed package labeling included in these two submissions includes language regarding conditions for which patients should seek advice from a doctor or pharmacist before using the product for both package sizes. Final proposed labeling is now acceptable.

OUTSTANDING ISSUES:

None

RECOMMENDED REGULATORY ACTION:

N drive location:

New Clinical Studies:	**Clinical Hold:**	**Study May Proceed:**
NDA, Efficacy/Label Supplement is:	**Fileable:**	**Not Fileable:** **Approvable: X**

SIGNED:

Medical Reviewer: **Date:**

Medical Team Leader: **Date:**

MEDICAL OFFICER REVIEW
Division of Pulmonary and Allergy Drug Products (HFD-570)

Application Number:	21-082	**Application Type:**	NDA
Sponsor:	Novartis Consumer Health, Inc.	**Proprietary Name:**	Tavist®Allergy/Sinus/Headache
Category of Drug:	Antihistamine/ decongestant/ analgesic/ antipyretic	**USAN Name:**	Clemastine fumarate/ acetaminophen/ pseudoephedrine HCl
		Route of Administration:	Oral
Medical Reviewer:	Charles E. Lee, M.D.	**Review Date:**	12/26/00

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Application	Document Date:	CDER Stamp Date:	Submission Type, Comments:
NDA 21-082, AZ	9/7/00	9/8/00	Response to IR, Volume 7.1
NDA 21-082	10/25/00	10/25/00	Facsimile, correspondence

RELATED APPLICATIONS (if applicable):

Document Date:	Application Type:	Application Number:	Comments:
2/25/77	NDA	17-661	Tavist® 2.68 mg tablets
6/28/85	NDA	18-675	Tavist syrup
8/21/92	NDA	20-925	Tavist-1, OTC, 1.34 mg tablets
8/21/92	NDA	18-298	Tavist-D, OTC
8/9/96	NDA	20-640	Tavist-D, [redacted], OTC

REVIEW SUMMARY:

NDA 21-082, Tavist® Allergy/Sinus/Headache (0.335 mg clemastine fumarate/500 mg acetaminophen/ 30 mg pseudoephedrine HCl) was submitted 10/7/99 by Novartis Consumer Health, Inc. The original NDA submission provided adequate evidence of safety and efficacy for the temporary relief of various nasal and ocular symptoms associated with the hay fever, allergic rhinitis, and the common cold. The Division of Pulmonary and Allergy Drug Products took an approvable action on 8/4/00. In the approvable letter, the sponsor was advised of various deficiencies in the submission. These deficiencies included CMC issues related to product specifications, purity, and stability, and clinical deficiencies related to proposed product labeling. The sponsor was asked to submit revised product labeling. This document reviews the revised proposed product labeling submitted in the response to approvable letter and amended in a subsequent facsimile. This reviewer recommends that the Agency's recommended language be retained regarding conditions for which patients should seek advice from a doctor or pharmacist before using the product. The proposed labeling is otherwise acceptable.

APPEARS THIS WAY
ON ORIGINAL

OUTSTANDING ISSUES:

None

RECOMMENDED REGULATORY ACTION:

N drive location:

New Clinical Studies:	**Clinical Hold:**	**Study May Proceed:**
NDA, Efficacy/Label Supplement is:	**Fileable:**	**Not Fileable:** **Approvable: X**

SIGNED:

Medical Reviewer: **Date:**

Medical Team Leader: **Date:**

1. BACKGROUND

NDA 21-082, NDA 21-082, Tavist® Allergy/Sinus/Headache (0.335 mg clemastine fumarate/500 mg acetaminophen/ 30 mg pseudoephedrine HCl) was submitted 10/7/99 by Novartis Consumer Health, Inc (NHC). The original NDA submission provided adequate evidence of safety and efficacy for the temporary relief of various nasal and ocular symptoms associated with the hay fever, allergic rhinitis, and the common cold. The Division of Pulmonary and Allergy Drug Products took an approvable action on 8/4/00. In the approvable letter, the sponsor was advised of various deficiencies in the submission that should be addressed before the submission could be considered for approval.

These deficiencies included — CMC issues related to product specifications, purity, and stability and four clinical deficiencies related to the proposed product labeling. The sponsor was asked to make four labeling changes to correct the clinical deficiencies. These four changes are listed below:

1. Add a footnote to the front panel of the carton label that defines caplet as a "capsule-shaped tablet."
2. Remove the seal with the statement " ——— located on the front panel.
3. Remove the statement " ——— " located on the front panel.
4. Revise the carton and blister labels according to prototype labeling included with the approvable letter.

The sponsor was asked to address the — CMC deficiencies and to submit revised draft labeling including correction of the clinical deficiencies. The Division provided the sponsor with recommended changes to be incorporated into the revised draft labeling.

The sponsor submitted a response to approvable letter that included CMC data and revised proposed product labeling. In addition, on 10/25/00, NHC submitted additional information in a facsimile that supplemented the response. This document reviews the sponsor's revised proposed product labeling submitted in the response to approvable letter and the subsequent facsimile.

2. REVIEW OF REVISED DRAFT LABELING

This reviewer comments on the proposed labeling follow numbered entries containing or describing the pertinent sections or recommended changes to the revised product labeling.

1. Add a footnote to the front panel of the carton label that defines caplet as a "capsule-shaped tablet."

   Reviewer comment: The sponsor agreed and added the footnote.

2. Remove the seal with the statement ———" located on the front panel.

   Reviewer comment: The sponsor replied that the seal "———" is supported by data from the clinical studies submitted to the NDA and should remain on the front panel.

Subsequently, NHC proposed alternative language for the seal on the front panel which states "Allergy & Sinus Relief" [Correspondence, N. Nicolaou, NHC, 10/25/00]. The alternative language for the seal on the front panel, "Allergy & Sinus Relief" is acceptable.

3. Remove the statement "————," located on the front panel.

Reviewer comment: The sponsor removed the statement.

4. Revise the carton and blister labels according to prototype labeling included with the approvable letter.

Reviewer comment: In general, the sponsor agreed with the Agency's prototype labeling, with the following exceptions:

a. "Clemastine fumarate 0.335 mg (equivalent to 0.25 mg clemastine), pseudoephedrine HCl 30 mg tablet, and acetaminophen 500 mg"

Reviewer comment: The sponsor proposes not to include this information on the front panel of the label because the statement of identity needs to provide for terms descriptive of the intended actions. The sponsor points out the other existing Tavist D products do not include such labeling. This change is acceptable.

b. The front panel of the label referring to uses:
   - Sinus congestion and pressure
   - Runny nose and sneezing
   - Itchy, watery eyes
   - ————
   - Itchy throat

Reviewer comment: The sponsor proposed to delete "————" from the list of uses on the front panel. This change is acceptable.

c. The "Uses" section of Drug Facts:

[First row, left to right]
- Sinus congestion and pressure
- Headaches
- Sneezing
- Itching of the nose and throat
- Fever

[Second row, left to right]
- Nasal congestion
- Itchy watery eyes
- Runny nose
- Minor aches and pains

Reviewer comment: The sponsor agreed to the Agency's recommended wording, but modified the order of the bulleted items as listed below. The changes are acceptable.

d. "Ask a doctor or pharmacist before use if you are
- Taking sedatives or tranquilizers
- Using another product containing acetaminophen, clemastine fumarate, or pseudoephedrine HCl
- Under a doctor's care for any continuing medical condition
- Taking other drugs on a regular basis"

Reviewer comment: The sponsor proposed deleting the last two bullets, "Under a doctor's care for any continuing medical condition" and "Taking other drugs on a regular basis." These bullets should remain. Patients may be taking other antihistamines for allergic rhinitis, urticaria, or other allergic conditions, or may be using diphenhydramine as nighttime sleep aid. Use of clemastine in patients taking other antihistamines would increase the likelihood of drowsiness and anticholinergic side effects.

3. SUMMARY

In summary, this reviewer recommends that the Agency's recommended language be retained regarding conditions for which patients should seek advice from a doctor or pharmacist before using the product. The proposed labeling is otherwise acceptable.

Reviewed by:

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

Badrul A. Chowdhury, M.D., Ph.D.
Team Leader, Division of Pulmonary and Allergy Drug Products

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA
HFD-570/Division File
HFD-570/Chowdhury/Team Leader
HFD-570/Lee/Medical Reviewer
HFD-560/Hu/OTC/Medical Reviewer
HFD-560/Merritt/OTC/CSO
HFD-570/Hilfiker/CSO

APPEARS THIS WAY
ON ORIGINAL

/s/

Charles Lee
12/27/00 09:11:03 AM
MEDICAL OFFICER

Badrul Chowdhury
12/27/00 09:41:52 AM
MEDICAL OFFICER
I concur

APPEARS THIS WAY
ON ORIGINAL

HJ Ritter
JUL 7 2000

Application Number:	21-082	**Application Type:**	NDA
Sponsor:	Novartis Consumer Health, Inc.	**Proprietary Name:**	Tavist®Allergy/Sinus/Headache
Category of Drug:	antihistamine/ decongestant/ analgesic/ antipyretic	**USAN Name:**	Clemastine fumarate/ acetaminophen/ pseudoephedrine HCl
		Route of Administration:	Oral
Medical Reviewer:	Charles E. Lee, M.D.	**Review Date:**	6/15/00

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Application	Document Date:	CDER Stamp Date:	Submission Type, Comments:
NDA 21-082	10/7/00	10/8/88	NDA, 56 volumes
NDA 21-082, B2	3/1/00	3/2/00	Response to IR 2 volumes
NDA 21-082	6/15/00	6/19/00	Case report forms

RELATED APPLICATIONS (if applicable):

Document Date:	Application Type:	Application Number:	Comments:
2/25/77	NDA	17-661	Tavist® 2.68 mg tablets
6/28/85	NDA	18-675	Tavist syrup
8/21/92	NDA	20-925	Tavist-1, OTC, 1.34 mg tablets
8/21/92	NDA	18-298	Tavist-D, OTC
8/9/96	NDA	20-640	Tavist-D, [redacted], OTC

REVIEW SUMMARY:

This document is a review of an application of a fixed drug combination product containing clemastine base 0.25 mg, acetaminophen 500 mg, and pseudoephedrine HCl 30 mg in a caplet form (Clemastine Triple Combination, CTC). The proposed dose for adults and children 12 years of age and older is 2 caplets every 6 hours as needed. The proposed indications are temporary relief of various nasal and ocular symptoms associated with the following conditions: hay fever, allergic rhinitis, [redacted] and the common cold. The four PK studies included with this application, HSC-151, HSC-152, HSC-153B, and HSC-302 showed no PK interaction among each of the drug product components and linked the CTC product with other dose forms of clemastine. Pivotal studies HSC-305 and HSC-306 support the efficacy of the CTC product. HSC-305 showed that clemastine 0.5 mg QID and clemastine 1.0 mg BID were superior to placebo for the primary efficacy variables at Days 4 and 8, and for some at Visit 15. The primary efficacy variables were physician-assessed rhinorrhea and sneezing scores and patient-assessed instantaneous and reflective rhinorrhea and sneezing scores. The patient-assessed instantaneous individual treatment scores showed that efficacy was maintained to the end of the dosing interval for both treatment regimens. HSC-306 showed CTC was superior to TheraFlu® Sinus (TF Sinus) and placebo in the average reduction from baseline in the Major Symptom Complex (MSC), the primary efficacy variable. Onset of efficacy was at 2 hours after dosing and efficacy was maintained throughout the 6 hour dosing interval. Safety data from pivotal controlled clinical studies, PD and PK studies, data from the Agency's Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS), and the sponsor's review of the published literature support the safety of clemastine and the CTC product. Somnolence, fatigue, dry mouth, dyspepsia, abdominal pain, and nausea were identified as common AEs. There were no SAEs or deaths in any of the clinical studies. The studies in this application demonstrate no PK interaction among each of the components of CTC, that clemastine is effective at the dose and frequency of 0.5 mg PO Q6H, and has a safety profile comparable to that of clemastine at the approved dose of 1 mg PO Q12H. There are no safety concerns that would prohibit approval of this application. This application contains no data to support the clinical use of this product in [redacted]. This reviewer recommends this application for approval for the hay fever, allergic rhinitis, and common cold indications.

OUTSTANDING ISSUES:

None

RECOMMENDED REGULATORY ACTION:

N drive location:

New Clinical Studies:	**Clinical Hold:**	**Study May Proceed:**	
NDA, Efficacy/Label Supplement is:	**Fileable:**	**Not Fileable:**	**Approvable: X**

SIGNED:

Medical Reviewer: /S/ **Date:** 7/7/00

Medical Team Leader: /S/ **Date:** 7/7/00

(See TL Memorandum)

1. TABLE OF CONTENTS

2. EXECUTIVE SUMMARY AND RECOMMENDATIONS

2.1. Background and Administrative Issues

This document is a review of an application for approval of a fixed drug combination product containing clemastine base 0.25 mg (equivalent to 0.335 mg clemastine fumarate), acetaminophen 500 mg, and pseudoephedrine HCl 30 mg in a caplet form (Clemastine Triple Combination, CTC, or proposed trade name TAVIST® ALLERGY/SINUS/HEADACHE). The sponsor is Novartis Consumer Health, Inc.

The proposed dose for adults and children 12 years of age and older is 2 caplets every 6 hours as needed, and not more than 8 caplets in 24 hours unless directed by a doctor. It is not proposed for use in children under 12 years of age.

The proposed indications are:

- Temporary relief of sneezing, runny nose, and itching of the nose or throat and itchy watery eyes due to hay fever (allergic rhinitis), and sneezing and runny nose due to the common cold
- Temporary relief of nasal and sinus congestion due to the common cold, hay fever, or other upper respiratory allergies or ———
- Temporary relief of minor aches, pains, headache, ———, and fever associated with the common cold; temporary relief of minor aches, pains and headache associated with hay fever, allergic rhinitis, and ———

2.2. Clinical Program

The clinical portion of this application includes two pivotal clinical studies, HSC-305 and HSC-306, two PD studies, HSC-303 and HSC-304, and four PK studies, HSC-151, HSC-152, HSC-153B, and HSC-302. The sponsor included a summary of postmarketing adverse events for clemastine and a survey of the literature for articles that included primary safety data for clemastine.

The tentative final monograph for combination cough, cold, and allergy drug products ("Monograph," 53 FR 30522) details combinations of active ingredients permitted for OTC cough, cold, and allergy drug products. Monograph requirements are met for this product by use of pseudoephedrine (PSE) 60 mg immediate release PO Q4-6H in adults and children ages 12 and older. Monograph requirements are met for this product by use of acetaminophen (APAP) 1000 mg immediate release Q6H in adults and children ages 12 years and older. Clemastine is not an antihistamine listed in the Monograph, and clemastine has not been approved for use at a frequency less than Q12H in any other product. A new NDA was therefore required.

2.3. Efficacy

The efficacy of the CTC product is supported by the PK study results and the results of the two pivotal studies. HSC-151 showed that dosing with one 0.5 mg clemastine tablets QID was bioequivalent to dosing with one Tavist-1® 1.0 mg tablet BID. There was no drug accumulation with dosing of clemastine 0.5 mg QID. HSC-152 showed that CTC tablets and TF Sinus tablets were bioequivalent with respect to acetaminophen and pseudoephedrine and that clemastine did not affect the bioavailability of either acetaminophen or pseudoephedrine. HSC-153B showed that CTC tablets and 0.5 mg clemastine tablets administered with TF Sinus tablets were bioequivalent with respect to both acetaminophen and pseudoephedrine.

Pivotal study HSC-305 supports the efficacy of clemastine 0.5 mg QID and clemastine 1.0 mg BID in the treatment of symptoms of SAR. The primary efficacy variables were physician-assessed rhinorrhea and sneezing scores and patient-assessed instantaneous and reflective rhinorrhea and sneezing scores. Clemastine 0.5 mg QID and clemastine 1.0 mg BID were superior to placebo for the primary efficacy variables at Days 4 and 8, and for

some at Day 15. An improvement was seen in the placebo group at Day 15 compared with baseline. An improvement in the placebo group resulted in the lack of difference in the change from baseline at Day 15 between active drug and placebo groups in most of the primary efficacy variables. Results of secondary efficacy variables support the efficacy of clemastine 0.5 mg QID and clemastine 1.0 mg BID. The patient-assessed instantaneous individual treatment scores showed that efficacy was maintained to the end of the dosing interval for both treatment regimens.

Pivotal study HSC-306 supports the efficacy of CTC in the treatment of the symptoms of SAR. CTC decreased Major Symptom Complex (MSC) scores, the primary efficacy variable, over hours 2-5 more than TF Sinus and placebo after both doses of treatment medication. There was a placebo effect noted after both doses. Results of secondary efficacy variables support the efficacy of CTC. Onset of efficacy was 2 hours after Dose 1 and efficacy was maintained throughout the 6 hour dosing interval. Patient global assessment of efficacy showed CTC superior to TF Sinus and placebo.

2.4. Safety

Safety data from pivotal controlled clinical studies, PD and PK studies, data from the Agency's Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS), and the sponsor's review of the published literature support the safety of clemastine and the CTC product. Treatment exposure in the clinical development program for CTC was adequate to assess safety. Somnolence, fatigue, dry mouth, dyspepsia, abdominal pain, and nausea were identified as common AEs. These AEs have previously been noted with clemastine and other first generation antihistamines and represent no new safety signal. There were no SAEs or deaths in any of the clinical studies. Elevated BP and elevated CPK were seen in patients taking clemastine in these clinical trials. There were no ECG changes noted in any of the clinical studies. Review of AEs, SAEs, deaths, and overdose reports from the Agency's SRS database identified elevated BP as a possible safety signal. Review of the sponsor's literature survey identified no new safety concerns for clemastine.

2.5. Special Populations

Very small numbers of patients in studies submitted in this NDA were over the age of 65 years, and none were under the age of 12 years. Small numbers of patients in these age groups preclude a subgroup analysis of efficacy by age. The sponsor believes the CTC product would not be a significant improvement over adequately labeled, currently marketed products, and seeks a waiver of the pediatric study requirement.

Women taking both doses of active drug and placebo in pivotal study HSC-305 showed greater improvement than males in the primary efficacy variables, physician and patient-assessed nasal discharge/runny nose and sneezing scores, but difference in efficacy was not noted in the other pivotal study, HSC-306. The difference in efficacy by gender in HSC-305 may be due to chance.

No consistent difference in efficacy was seen in HSC-305 between Caucasian and non-Caucasian patients. Caucasians had slightly smaller reductions in the primary efficacy variable for CTC, TF Sinus, and placebo in HSC-306. The concordant findings in the active

and placebo arms in HSC-306, and the lack of similar findings in HSC-305 indicate that the decreased efficacy noted in Caucasians in study HSC-306 may be due to chance.

A higher frequency of AEs was seen in women in pivotal studies HSC-305 and HSC-306 in both the active treatment, control, and placebo groups. No particular AE was substantially more frequent in women than in men. An analysis of AEs by race revealed no consistent difference between Caucasian and non-Caucasian patients that could not be explained by the small numbers.

2.6. Recommended Regulatory Action

The studies in this application demonstrate the absence of PK interaction among each of the components of CTC, that clemastine is effective at the dose and frequency of 0.5 mg PO Q6H, and has a safety profile comparable to that of clemastine at the approved dose of 1 mg PO Q12H. There are no safety concerns that would prohibit approval of this application. This application contains no data to support the clinical use of this product in ——— This reviewer recommends this application for approval for the hay fever, allergic rhinitis, and common cold indications.

3. MATERIAL REVIEWED AND CONDUCT OF THE REVIEW

This application includes two pivotal controlled clinical studies, two PD studies, four PK studies, an Integrated Summary of Efficacy (ISE), Integrated Summary of Safety (ISS), and Integrated Summary of Risks and Benefits (ISRB), a literature survey, and a listing of spontaneous AE reports for clemastine.

Efficacy review was performed in the following fashion. Pivotal controlled clinical studies HSC-305 and 306 received a detailed review of efficacy results. PD studies HSC-303 and 304 received a brief efficacy review. PK studies HSC-151, 152, 153B, and 302 were reviewed in depth by the Biopharmacology reviewer, Dr. Wakelkamp-Barnes, and the conclusions will be summarized in this review.

All clinical studies received an detailed review of safety data. The sponsor's summary and listings of spontaneous AE reports and the sponsor's review of the clinical literature for articles related to the safety of clemastine were also reviewed.

4. CHEMISTRY/MANUFACTURING AND CONTROLS

The proposed drug product is a ——— layer, immediate release, capsule-shaped, film-coated tablet which contains 0.25 mg clemastine, 500 mg acetaminophen, and 30 mg pseudoephedrine. The tablet is white and is debossed with "Tavist" on one side and "C-A-S" on the other side.

The sponsor indicates that clemastine fumarate/acetaminophen/pseudoephedrine hydrochloride tablets are to be manufactured, tested, packaged, labeled, and released by Novartis Consumer Health, 10401 Highway 6, Lincoln, Nebraska [Volume 1.1, pages 30-36].

Please see the Chemistry/Manufacturing and Controls (CMC) review prepared by Dr. Kevin Swiss for additional information. The CMC portion of this application has deficiencies related to the quantitation of impurities, regulatory specifications for clemastine, acetaminophen, and pseudoephedrine, and drug product stability. In addition, the sponsor's ——————————, has failed Agency compliance inspections. These CMC deficiencies may prevent approval of this application.

5. ANIMAL PHARMACOLOGY/TOXICOLOGY

No new preclinical pharmacology or toxicology studies were conducted in support of this application [Volume 1.1, page 38].

6. CLINICAL BACKGROUND

This NDA submission is for a fixed drug combination product containing clemastine base 0.25 mg (equivalent to 0.335 mg clemastine fumarate), acetaminophen 500 mg, and pseudoephedrine HCl 30 mg in a caplet form (Clemastine Triple Combination, CTC, or proposed trade name TAVIST® ALLERGY/SINUS/HEADACHE). The sponsor is Novartis Consumer Health, Inc.

The proposed dose for adults and children 12 years of age and older is 2 caplets every 6 hours as needed, and not more than 8 caplets in 24 hours unless directed by a doctor. It is not proposed for use in children under 12 years of age.

The proposed indications are:

- Temporary relief of sneezing, runny nose, and itching of the nose or throat and itchy watery eyes due to hay fever (allergic rhinitis), and sneezing and runny nose due to the common cold
- Temporary relief of nasal and sinus congestion due to the common cold, hay fever, or other upper respiratory allergies or ——————
- Temporary relief of minor aches, pains, headache, ——————— and fever associated with the common cold; temporary relief of minor aches, pains and headache associated with hay fever, allergic rhinitis, and ——————

The tentative final monograph for combination cough, cold, and allergy drug products ("Monograph," 53 FR 30522) details combinations of active ingredients permitted for OTC cough, cold, and allergy drug products. Monograph requirements are met for this product by use of pseudoephedrine (PSE) 60 mg immediate release PO Q4-6H in adults and children ages 12 and older. Monograph requirements are met for this product by use of acetaminophen (APAP) 1000 mg immediate release Q6H in adults and children ages 12 years and older. Clemastine is not an antihistamine listed in the Monograph, and clemastine has not been approved for use at a frequency less than Q12H in any other product. A new NDA is therefore required.

Critical issues for the sponsor to establish for this fixed drug combination were:

- Demonstration of absence of PK interaction among each of the components
- Demonstration that clemastine is effective at the dose and frequency of 0.5 mg PO Q6H

- Demonstration that clemastine at the dose and frequency of 0.5 mg PO Q6H has a safety profile comparable to that of clemastine at the approved dose of 1 mg PO Q12H.

6.1. Relevant Human Experience

Clemastine was approved for use in the US on 2/25/77 as Tavist®, clemastine base 2 mg (NDA 17-661). Tavist® syrup, clemastine base 0.5 mg/5 ml, was approved in the US on 6/28/85 (NDA 18-675). Tavist-1®, clemastine base 1 mg, was approved in the US as an OTC product for symptoms of allergic rhinitis on 8/21/92 (NDA 20-925). In 1996, Tavist-1® was approved for temporary relief of runny nose and sneezing associated with the common cold. Clemastine has also been approved for OTC use as a combination product containing 1 mg clemastine plus 75 mg extended-release phenylpropanolamine (Tavist-D®, NDA 18-298, NDA 20-640) [Volume 1.1, page not numbered and page 5].

6.2. Important Information From Related INDs and NDAs

No additional information from related INDs or NDAs was provided by the sponsor.

6.3. Foreign Experience

Clemastine was first marketed in Europe as a prescription drug in 1966. Clemastine has been approved as AllerEze Plus® (0.5 mg clemastine base and 25 mg phenylpropanolamine) in the UK in 1986 and in Ireland in 1987. Clemastine has been approved in at least one oral dose form in 127 countries worldwide.

6.4. Human Pharmacology, Pharmacokinetics, and Pharmacodynamics

Results of PK studies included with this application are summarized in Section 8.5.1. of this review, PK Results. Please see Dr. Wakelkamp-Barnes' biopharmacology review for detailed information on human pharmacology, pharmacokinetics, and pharmacodynamics.

Pharmacokinetic parameters for clemastine with the CTC product are displayed in Table 6.4.1.

Table 6.4.1 Pharmacokinetic parameters for clemastine, CTC tablets, studies HSC-152 and HSC-153B [Volume 1.1, pages 55-58]

Study	Dose of clemastine	C_{max}, pg/mL	AUC_{0-t}, pg h/mL	AUC_{0-inf}, pg h/mL	T_{max}
HSC-152	0.5 mg (2 tablets)	570.2	7273.6	9798.7	5-6 hours
HSC-153B	1.0 mg (4 tablets)	1005.3	18732.2	23155.8	5-6 hours

6.5. Other Relevant Background Information

No additional relevant background information was provided with this application.

6.6. Directions for Use

The proposed dose for adults and children 12 years of age and older is 2 caplets every 6 hours as needed, and not more than 8 caplets in 24 hours unless directed by a doctor. It is not proposed for use in children under 12 years of age.

7. DESCRIPTION OF CLINICAL DATA SOURCES (IND AND NON-IND)

Please see Section 6.1 of this review, Relevant Human Experience, for a description of previous clemastine NDAs.

8. CLINICAL STUDIES

Review of clinical studies submitted with this application follows. These clinical studies include two pivotal controlled studies, HSC-305 and HSC-306, two PD studies, HSC-303 and HSC-304, and four PK studies, HSC-302, HSC-151, HSC-152, and HSC-153B.

8.1. HSC-305: A multi-center, double-blind, double-dummy, placebo-controlled, randomized , parallel-group study to evaluate the safety and efficacy of clemastine 0.5 mg QID vs. clemastine 1.0 mg BID vs. placebo for allergy symptom relief

8.1.1. Summary and reviewer's conclusion of study results

This was a two-week, multi-center, double-blind, double-dummy, placebo-controlled, randomized, parallel-group, Phase 3 study performed in 12 U.S. centers. The purpose of this study in the sponsor's drug development program was to show that clemastine 0.5 mg QID, a dose lower than that currently approved, is safe and effective. Clemastine is currently approved for OTC use at the dose of 1.0 mg BID.

The primary efficacy variables were not clearly defined. The protocol and statistical methods section indicated that the primary efficacy variables were to be nasal discharge/runny nose and sneezing. However, the sample size determination was based on the total nasal sign/symptom score. This reviewer considered the physician-assessed rhinorrhea and sneezing scores and patient-assessed instantaneous and reflective rhinorrhea and sneezing scores to be primary efficacy variables. Clemastine 0.5 mg QID and clemastine 1.0 mg BID were superior to placebo for the primary efficacy variables at Visits 2 and 3 (Days 4 and 8), and for some at Visit 4 (Day 15). An improvement was seen in the placebo group at Visit 4 compared with baseline. This improvement in the placebo group may represent a placebo effect, or may reflect decrease in patient symptoms due to the lower pollen counts noted at the end of the study. This improvement in the placebo group resulted in the lack of difference in the change from baseline at Visit 4 between active drug and placebo groups in most of the primary efficacy variables. Results of secondary efficacy variables support the efficacy of clemastine 0.5 mg QID and clemastine 1.0 mg BID. The patient-assessed instantaneous individual treatment scores show that efficacy is maintained to the end of the dosing interval for both treatment regimens.

This study supports the safety of clemastine 0.5 mg QID and clemastine 1.0 mg BID in the treatment of the symptoms and signs of SAR. There was adequate exposure to active drug in this study. AEs were frequent and mild to moderate in intensity. Headache, somnolence, fatigue, dry mouth, and dizziness were notable AEs in clemastine-treated patients. These AEs were likely to be due to anticholinergic effects of the drug. There were no deaths or SAEs in this study. Somnolence and fatigue were common reasons for withdrawal from the study in

clemastine-treated patients, and there was a dose ordering effect seen in the number of patients withdrawing from the study for these AEs. There was a small, clinically insignificant increase in pulse of 2 to 3 bpm noted in patients taking clemastine 0.5 mg QID. The increase in pulse was likely to be due to anticholinergic effects of the drug.

8.1.2. Objective/Rationale

The objective of this study was to evaluate the efficacy and safety of clemastine 0.5 mg QID versus clemastine 1.0 mg BID versus placebo in relieving the allergy symptoms and signs of patients with moderate to severe seasonal allergic rhinitis (SAR) [Volume 1.26, page 156].

8.1.3. Protocol

This two-week, multi-center, double-blind, double-dummy, placebo-controlled, randomized, parallel-group, Phase 3 study was performed in 12 U.S. centers [Volume 1.26, pages 16, 156].

Patients were to be recruited 1995 fall pollen season. Patient were to have a history of SAR due to fall seasonal pollens. The first subject was enrolled on 8/14/95 and the last subject completed the study on 12/8/95 [Volume 1.26, pages 5, 156, 157].

An outline of the study design is presented in Table 8.1.1. Patients had screening inclusion and exclusion criteria checked, informed consent, skin tests (if not performed in the last year), history and physical examination, vital signs, and labs collected at screening, which occurred from 0 to 14 days before the baseline visit, Visit 1. Randomization was performed at the baseline visit, Visit 1. Medications were dispensed at Visit 1 and at Visit 3. Visit 0 and Visit 1 could be combined and screening and baseline procedures performed on the same day for patients that met all screening and baseline inclusion and exclusion criteria. Investigator evaluation of signs and symptoms was performed at Visits 1, 2, 3, and 4. Investigator global evaluation and patient global evaluation was performed at Visits 2, 3, and 4 [Volume 1.26, pages 39, 165-168, 237].

Visit number was assigned according to the window of days when the visit occurred. The date of Visit 1 was defined as Study Day 1. Any visit taking place on Study Days 2, 3, 4, or 5 was called Visit 2. Any visit taking place on Study Days 6 through 10 was called Visit 3. Any visit after Study Day 10 was called Visit 4 . There were 29 visits that were affected by this rule [Volume 1.26, pages 29, 487-488]. Line listings for these 29 visits were presented in the list of protocol deviations.

Table 8.1.1 Study outline, HSC-305 [Volume 1.26, pages 39, 237]

Visit Number	Visit 0 Screening	Visit 1 Baseline	Visit 2	Visit 3	Visit 4 Final
Study day	-13 to 1	1	4	8	15
Check screening inclusion/exclusion criteria	X				
Informed consent	X				
Skin test, unless performed ≤ 1 year	X				
Medical History	X				
Physical Exam	X				
Vital signs	X	X	X	X	X
Obtain blood and urine for labs	X				X
Randomization		X			

Visit Number	Visit 0 Screening	Visit 1 Baseline	Visit 2	Visit 3	Visit 4 Final
Study day	-13 to 1	1	4	8	15
Baseline inclusion criteria		X			
Urine pregnancy test in women		X			
Serum pregnancy test in women					X
Dispense medications		X		X	
Retrieve mediations				X	X
Investigator evaluation of signs and symptoms		X	X	X	X
Investigator global evaluation			X	X	X
Patients' global evaluation			X	X	X
Dispense patient diaries		X		X	
Review patient diaries			X	X	X
Check prohibited therapies		X	X	X	X
Check concomitant therapies		X	X	X	X
Check adverse events		X	X	X	X

8.1.3.1. Inclusion criteria [Volume 1.26, pages 158, 160-161]

Inclusion criteria at the screening visit were as follows:

1. Written informed consent
2. History of moderate to severe SAR due to fall seasonal pollens with a positive skin test in the last one year to relevant fall pollens
3. Men and women, any race, ages 12 to 65 years
4. Good health with no clinically significant disease
5. Willing and able to comply with requirements of the study

In addition, patients were to satisfy the following additional inclusion criteria at the baseline visit:

1. Sufficient washout period for prohibited medications as follows:

Medication	Washout period prior to baseline
Astemizole	90 days
Hydroxyzine, loratadine, fexofenadine,	5 days
Other antihistamines, all forms	48 hours
Topical ocular and nasal decongestants	24 hours
Oral and nasal inhaled corticosteroids	2 weeks
Systemic corticosteroids	90 days
Cromolyn sodium, all forms	1 week
Nedocromil	1 week
Intranasal saline	24 hours
Artificial tears and eye drops	24 hours
Lodoxamide ophthalmic drops	1 week
Immunotherapy injections	48 hours
NSAIDS, all forms	24 hours
Diet aids containing medication	24 hours

2. Minimum sign/symptom scores as noted below. Symptom/signs and symptom scales are displayed in Tables 8.1.2 and 8.1.3 of this review.
   - The sum of all eight signs/symptom scores, each rated on a 7-point scale, was to be ≥ 18 on a 7-point (0-6) scale.
   - The sum of the individual signs/symptom scores for rhinorrhea and sneezing was to be ≥ 7, with one ≥ 3 and the other ≥ 4.

Table 8.1.2 HSC-305, nasal and non-nasal symptoms and signs evaluated by investigator [Volume 1.26, page 166]

Nasal symptoms and signs	Non-nasal symptoms and signs
Rhinorrhea	Itchy/burning eyes
Nasal congestion/stuffiness	Tearing/watering eyes
Nasal itching	Redness of eyes
Sneezing	Itching of ears and/or palate

Table 8.1.3 HSC-305, symptom scale used for individual nasal scores and summed to get the total nasal score for the four nasal symptoms. [Volume 1.26, page 166]

Score	Severity of symptoms or signs
0	None
1	Doubtful or trivial
2	Mild–clearly present, but causing little or no discomfort
3	Moderate–annoying, but not causing marked discomfort
4	Moderately severe–causing marked discomfort
5	Severe–some interference with sleep or activities, but not incapacitating
6	Severe and incapacitating

8.1.3.2. Exclusion criteria [Volume 1.26, pages 158-160]

Exclusion criteria at screening were as follows:

1. Women who were pregnant or nursing
2. Women of child-bearing potential who are not practicing a medically acceptable method of contraception
3. Significant renal, hepatic cardiovascular, neurologic, hematologic, gastrointestinal or other medical illness
4. Abnormal vital sign
5. Abnormal lab or PE
6. URI and/or bacterial sinusitis in the preceding 2 weeks
7. Significant pulmonary disease and/or asthma requiring daily drug therapy
8. Patients who have participated in a trial of an investigational drug in the preceding 30 days (90 days if the drug was a steroid)
9. Patients on immunotherapy who were not on a steady dose for at least one month prior to baseline
10. Patients with a clinically significant nasal pathology
11. Patients with a known hypersensitivity to clemastine
12. Patients who are known to be non-responders to antihistamine
13. Patients who are alcohol or drug abusers
14. Patients taking antidepressant pharmacotherapy
15. Patients who have been treated with immunosuppressive or radiation therapy in the preceding 3 months

8.1.3.3. Drug product and placebo [Volume 1.26, pages 162-163]

The sponsor provided investigators with supplies of study drug and placebo. Each patient's supply was packaged in blister packs. Batch numbers for study drug and placebo were as follows:

Treatment	Lot Number
Clemastine 0.5 mg	651-1890.36
Clemastine 1.0 mg	689-1897.49
Placebo matching clemastine 0.5 mg tablet	651-1927.01
Placebo matching clemastine 1.0 mg tablet	689-1897.47

Patients were instructed to take study treatment on the schedule presented in Table 8.1.4:

Table 8.1.4 Dosing of study treatment, active drug and placebo [Volume 1.26, page 163]

	Time of dose			
	12:00 noon	6:00 PM	12:00 Midnight	6:00 AM
Study arm				
Clemastine 0.5 mg QID	C05[1], PL10[2]	C05, PL10	C05, PL10	Co5, PL10
Clemastine 1.0 mg BID	C10[3], PL05[4]	PL10, PL05	C10, PL05	PL10, PL05
Placebo	PL10, PL05	PL10, PL05	PL10, PL05	PL10, PL05

[1]C05: clemastine 0.5 mg,
[2]PL10: placebo to match clemastine 1.0 mg
[3]C10: clemastine 1.0 mg
[4]PL05: placebo to match clemastine 0.5 mg

Each patient was to take two tablets every six hours for 14 treatment cycles. Each treatment cycle was 24 hours. Patients in the clemastine 0.5 mg group were to take one clemastine 0.5 mg tablet and one placebo tablet resembling clemastine 0.5 mg every 6 hours. Patients in the clemastine 1.0 mg group were to take one clemastine 1.0 mg tablet and one placebo tablet resembling clemastine 0.5 mg at 12:00 noon and 12:00 midnight. Patients in the clemastine 1.0 mg group were to take one placebo tablet resembling clemastine 0.5 mg tablet and one placebo tablet resembling clemastine 1.0 mg at 6:00 AM and 6:00 PM. Patients in the placebo group were to take one placebo tablet resembling clemastine 0.5 mg and one placebo tablet resembling clemastine 1.0 mg at each dosing time. All doses of study medication were to be taken within one hour of the prescribed dosing time.

Patients were to be permitted to use 30 mg pseudoephedrine tablets and 500 mg acetaminophen gelcaps as rescue medication if the patient's signs/symptoms of SAR were so uncomfortable as to require additional treatment. Patients were to take rescue medication per package labeling. No pseudoephedrine or acetaminophen was to be taken for 24 hours before scheduled study visits [Volume 1.26, page 157].

Patient compliance with study procedures was assessed by a count of remaining study treatment tablets, review of diary completion and legibility, count of remaining rescue medication, and confirmation that prohibited therapies were not used [Volume 1.26, page 172].

8.1.3.4. Assessment of signs and symptoms

The investigator was to grade the eight individual SAR symptoms/signs at the patient's baseline and subsequent visits. These symptoms/signs are displayed in Table 8.1.2. The symptom scale is displayed in Table 8.1.3.

A total nasal score was also calculated at each visit. The total nasal score was the sum of the four individual nasal scores. The patient's SAR symptoms and signs were to be evaluated by the investigator after 3, 7, and 14 days of treatment. Patients were to record the severity of their symptoms in a diary [Volume 1.26, pages 5, 156-157].

The scale displayed in Table 8.1.3 was used by patients to grade their SAR symptoms in the late morning prior to taking their 12:00 noon dose of study drug. Patients were to record the severity of their symptoms at that moment (instantaneous) and over the preceding 24 hours (reflective) [Volume 1.26, page 167].

The patient and the investigator were to evaluate the global response to treatment at Visits 2, 3, and 4. The scale displayed in Table 8.1.5 was used to assess the global response to treatment.

Table 8.1.5 HSC-305, symptom scale used for investigator- and patient-assessed global response to treatment [Volume 1.26, page 167]

Score	Degree of improvement
3	Markedly better
2	Moderately better
1	Slightly better
0	No change
-1	Slightly worse
-2	Moderately worse
-3	Markedly worse

8.1.3.5. Variables

Efficacy and safety variables for this study are described below.

8.1.3.5.a. Primary efficacy variables

The primary efficacy variables were not clearly defined. The protocol synopsis and the statistics section of the protocol, Appendix D, stated that physician- and patient-assessed rhinorrhea and sneezing scores were to be primary efficacy variables [Volume 1.26, pages 154, 234-235]. However, the sample size determination was based on a 2 tailed-t test comparing the total nasal score for clemastine 0.5 mg versus placebo, which implies that the total nasal score should be the primary efficacy variable. The protocol did not state at which visit efficacy was to be determined, or if patient-assessed scores were to be instantaneous or reflective. Since rhinorrhea and sneezing were explicitly noted as being the primary efficacy variables, this reviewer will consider physician-assessed rhinorrhea and sneezing scores and patient-assessed instantaneous and reflective rhinorrhea and sneezing scores to be co-primary efficacy variables.

8.1.3.5.b. Secondary efficacy variables

Secondary efficacy variables were to include the remaining investigator- and patient-assessed individual symptom scores, investigator- and patient-assessed global response to treatment, and the proportion of patients requiring rescue medication use.

8.1.3.5.c. Safety variables

Adverse events (AEs), vital signs, CBC and differential, blood chemistry, urinalysis were to be safety variables for this study. AEs were to be elicited at each study visit. CBC and differential, blood chemistry, and urinalysis results from the baseline and final visits were to be compared [Volume 1.26, pages 167-169].

8.1.3.6. Statistical Considerations

Even though the protocol indicated that the primary efficacy variables were to be rhinorrhea and sneezing, the sample size was calculated based on a comparison between the total nasal score for clemastine 0.5 mg QID versus placebo. A standard deviation of 5.5 was used for the change from baseline in the total nasal score. One hundred twenty evaluable patients were required to be in each treatment group to be able to detect a change from baseline of 2.0 out of a maximum possible score of 24.0 using a two-tailed t-test with 80% power at a 0.05 level of significance [Volume 1.26, page 234].

Comparisons between treatment groups for efficacy variables were done using Van Elteren's test. The proportion of patients in each treatment group requiring rescue medication was to be analyzed with a Mantel-Haenszel Test.

8.1.4. Results

8.1.4.1. Populations enrolled/analyzed

Although the protocol called for 360 evaluable patients with 120 in each treatment arm, a total of 412 patients were actually randomized to treatment with 408 efficacy evaluable patients. A total of 375 patients completed at least 14 drug treatment cycles and returned for the final visit. Table 8.1.6 summarizes patient disposition.

Table 8.1.6 HSC-305, patient disposition [Volume 1.26, page 31].

	Clemastine, 0.5 mg QID		Clemastine, 1.0 mg BID		Placebo		All patients	
	N	(%)	N	(%)	N	(%)	N	(%)
Number of patients randomized	137		135		140		412	
Number of patients completed	126	(92)	127	(94.1)	122	(87.1)	375	(91.0)
Number of patients discontinued	11	(8.0)	8	(5.9)	18	(12.9)	37	(9.0)
Adverse event	5	(3.6)	6	(4.4)	4	(2.9)	15	(3.6)
Failure to return	4	(2.9)	2	(1.5)	4	(2.9)	10	(2.4)
Did not meet entrance requirements	1	(0.7)	0	(0)	3	(2.1)	4	(1.0)
Treatment failure	0	(0)	0	(0)	6	(4.3)	6	(1.5)
Protocol violation	1	(0.7)	0	(0)	0	(0)	1	(0.2)
Number of patients in efficacy population	136	(99.2)	134	(99.3)	138	(98.6)	408	(99.0)
Number of patients in safety population	136	(99.3)	135	(100)	138	(98.6)	409	(99.3)

The efficacy analysis was performed on 408 patients. Two patients in the placebo group were excluded from the efficacy analysis, Patient 0917 and Patient 1020. Patient 0917 exceeded the age entry criterion and returned for follow-up without the diary record and Patient 1020 failed to return for visits after the baseline visit. One patient in the clemastine 0.5 mg group, Patient 0923, was excluded from the efficacy analysis because of loss to follow-up. One patient in the clemastine 1.0 mg group, Patient 1108, was excluded because no diary or investigator assessments were provided. In this reviewer's opinion, the small number of exclusions from the efficacy evaluable population are not likely to affect the results of the efficacy analysis.

The safety analysis was performed on 409 patients. The safety analysis was performed on the same set of patients as the efficacy analysis, with the exception that Patient 1108 was included because the patient withdrew from the study. In this reviewer's opinion, the small

number of exclusions from the safety evaluable population are not likely to affect the results of the safety analysis.

8.1.4.2. Baseline demographic and background characteristics

The population studied was largely Caucasian. There were more females than males in the study. The mean age was approximately 33 years in all treatment groups. Treatment groups were similar in gender and race. [Volume 1.26, page 51]. These data are displayed in Table 8.1.7.

Table 8.1.7 HSC-305, demographics [Volume 1.26, page 51]

Characteristic	Clemastine 0.5 mg QID N=137		Clemastine 1.0 mg BID N=135		Placebo N=140		Total N=412	
Age, years	N	(%)	N	(%)	N	(%)	N	(%)
<20	12	(8.8)	15	(11.1)	15	(10.7)	42	(10.2)
20-29	45	(32.8)	46	(34.1)	49	(35.0)	140	(10.2)
30-39	48	(35.0)	36	(26.7)	40	(28.6)	124	(30.1)
40-49	25	(18.2)	24	(17.8)	22	(15.7)	71	(17.2)
50-59	7	(5.1)	13	(9.6)	8	(5.7)	28	(6.8)
≥60	0	(0)	1	(0.7)	6	(4.3)	7	(1.7)
Mean age	32.9		33.2		32.9		33	
SD	10.0		11.4		11.9		11.1	
Gender	N	(%)	N	(%)	N	(%)	N	(%)
Male	46	(40.9)	56	(41.5)	61	(43.6)	173	(42.0)
Female	81	(59.1)	79	(58.5)	79	(56.4)	239	(58.0)
Race	N	(%)	N	(%)	N	(%)	N	(%)
Caucasian	113	(82.5)	116	(85.9)	120	(85.7)	349	(84.7)
Black	11	(8.0)	3	(2.2)	10	(7.1)	24	(5.8)
Asian	5	(3.6)	4	(3.0)	4	(2.9)	13	(3.2)
Other	8	(5.8)	12	(8.9)	6	(4.3)	26	(6.3)

8.1.4.3. Protocol deviations

Common protocol deviations included admission to the study without meeting the total symptom score entrance criteria (9 patients, 3 in each treatment group), isolated missed visits, missed doses of medication, and failure to complete diary assessments [Volume 1.26, pages 31-32, 487-488]. The study report also includes a Comments Listing, which provides additional information regarding study conduct. Some of the comments in this section clearly represent protocol violations. It is unclear to this reviewer why these additional data are not included in the list of protocol violations. This could confound and influence the efficacy analysis. It appears that there was low exposure to antihistamines in those that took prohibited medications. Therefore, this reviewer does not believe that the efficacy analysis was likely to have been influenced to a great extent [Volume 1.26, pages 13-32, 447-486].

8.1.4.4. Compliance

There were 111/135 (82.2%) of patients treated with clemastine 0.5 mg that took their study medication (active drug and placebo) QID for at least 13 drug treatment cycles. Each drug treatment cycle was 24 hours and corresponded to one day. There were 119/135 (88.1%) of patients treated with clemastine 1.0 mg that took their study medication (active drug and placebo) QID for at least 13 drug treatment cycles. There were 109/138 (79.0%) of patients

treated with placebo that took their study medication QID for at least 13 drug treatment cycles. There was greater compliance with treatment in both clemastine groups than in the placebo group. This provides some additional support for the efficacy of active drug at both treatment doses. The number of days that study drug was taken and the average number of doses taken per day were similar in clemastine and placebo treatment groups. These data are presented in Table 8.1.8.

Table 8.1.8 HSC-305, patient compliance

	Clemastine 0.5 mg		Clemastine 1.0 mg		Placebo	
Number of treated patients with dosing data	135		135		138	
Number of patients taking study medication QID for at least 13 drug treatment cycles N (%)	111	(82.2)	119	(88.1)	109	(79.0)
Number of days study medication was taken Mean (SD)	13.6	(2.2)	13.6	(2.4)	13.2	(2.7)
Number of doses/day on days medication taken, Mean (SD)	3.9	(0.2)	3.9	(0.2)	3.9	(0.2)

8.1.4.5. Pollen counts

Pollen counts were performed at 11 of the 12 centers. Data was presented in a tabular form for each center. Analysis of pollen counts was not performed. Pollen counts tended to be higher earlier in the study period in most centers. [Volume 1.27, pages 133-153].

8.1.4.6. Efficacy variable outcomes

Efficacy was supported by primary and secondary variables as described below. This study supports the efficacy of clemastine 0.5 mg QID and clemastine 1.0 mg BID in for the treatment of the symptoms and signs of SAR. Review of individual primary and secondary efficacy variables are found in the following sections.

8.1.4.6.a. Primary efficacy variables

Primary efficacy variables included investigator-assessed rhinorrhea and sneezing scores, patient-assessed instantaneous rhinorrhea and sneezing scores, and patient-assessed reflective rhinorrhea and sneezing scores. Clemastine 0.5 mg QID and clemastine 1.0 mg BID were statistically superior to placebo for all primary efficacy variables at Visits 2 and 3, and for some at Visit 4. Patient-assessed instantaneous individual treatment scores indicate that efficacy is maintained to the end of the dosing interval for both treatment regimens. An improvement was seen in the placebo group at Visit 4 compared with baseline. This improvement in the placebo group may represent a placebo effect, or may reflect decrease in patient symptoms due to the lower pollen counts noted at the end of the study. This improvement in the placebo group resulted in the lack of difference in the change from baseline at Visit 4 between active drug and placebo groups in most of the primary efficacy variables. Review of individual primary efficacy variables follows.

Both clemastine 0.5 mg QID and clemastine 1.0 mg BID were statistically superior to placebo at Visit 2 and Visit 3 for investigator-assessed rhinorrhea scores. There was no difference from placebo at Visit 4 for either dose, perhaps due to reasons stated above. These data are presented in Table 8.1.9.

Table 8.1.9 Primary efficacy variable, investigator-assessed symptom score–rhinorrhea [Volume 1.26, pages 53-54]

	Clemastine, 0.5 mg QID		Clemastine, 1.0 mg QD		Placebo	
Visit Number	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Visit 1, Baseline	136	4.33 (0.75)	134	4.31 (0.68)	138	4.27 (0.67)
Visit 2	134	2.84 (1.23)	133	2.78 (1.28)6	137	3.57 (1.11)
Change, Visit 1 to Visit 2		[redacted]		[redacted]		0.70 (1.13)
Visit 3	132	2.87 (1.37)	129	2.81 (1.19)	134	3.25 (1.24)
Change, Visit 1 to Visit 3		[redacted]		[redacted]		1.03 (1.24)
Visit 4	127	2.68 (1.33)	129	2.59 (1.23)	123	2.75 (1.20)
Change, Visit 1 to Visit 4		1.61 (1.55) *p=0.657*		1.73 (1.32) *p=0.228*		1.52 (1.30)

APPEARS THIS WAY ON ORIGINAL

Both clemastine 0.5 mg QID and clemastine 1.0 mg BID were superior to placebo at Visit 2 and Visit 3 and at Visit 4 for clemastine 0.5 mg QID for investigator-assessed sneezing scores. The difference between each of the doses and placebo was statistically significant at Visits 2 and 3. There was no difference from placebo at Visit 4 for either dose. An improvement was seen in the placebo group. These data are presented in Table 8.1.10.

Table 8.1.10 Primary efficacy variable, investigator-assessed symptom score–sneezing [Volume 1.26, pages 65-66]

	Clemastine, 0.5 mg QID		Clemastine, 1.0 mg QD		Placebo	
Visit Number	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Visit 1, Baseline	136	3.90 (0.85)	134	3.91 (0.84)	138	3.97 (0.74)
Visit 2	134	2.05 (1.20)	133	2.02 (1.21)	137	3.11 (1.29)
Change, Visit 1 to Visit 2		[redacted]		[redacted]		0.85 (1.45)
Visit 3	132	1.99 (1.32)	129	2.32 (1.36)	134	2.75 (1.31)
Change, Visit 1 to Visit 3		[redacted]		[redacted]		1.21 (1.43)
Visit 4	127	1.87 (1.41)	129	1.96 (1.33)	123	2.29 (1.32)
Change, Visit 1 to Visit 4		[redacted]		1.94 (1.46) *p=0.141*		1.65 (1.49)

APPEARS THIS WAY ON ORIGINAL

Both clemastine 0.5 mg QID and clemastine 1.0 mg BID were statistically superior to placebo at Visit 2 and at Visit 3 for clemastine 1.0 mg BID for patient-assessed instantaneous rhinorrhea scores. There was no difference from placebo at Visit 4 for either dose. An improvement was seen in the placebo group. These data are presented in Table 8.1.11.

Table 8.1.11 Primary efficacy variable, patient-assessed symptom score–instantaneous rhinorrhea score [Volume 1.26, pages 55]

	Clemastine, 0.5 mg QID		Clemastine, 1.0 mg QD		Placebo	
Visit Number	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Visit 1, Baseline	135	3.52 (1.30)	134	3.46 (1.30)	138	3.49 (1.19)
Visit 2	135	2.55 (1.20)	133	2.45 (1.18)	138	3.03 (1.10)
Change, Visit 1 to Visit 2		[redacted]		[redacted]		0.45 (1.18)
Visit 3	131	2.44 (1.22)	131	2.32 (1.27)	132	2.81 (1.19)
Change, Visit 1 to Visit 3		1.07 (1.60) *p=0.066*		[redacted]		0.67 (1.30)
Visit 4	126	2.43 (1.33)	128	2.23 (1.32)	123	2.44 (1.22)
Change, Visit 1 to Visit 4		1.07 (1.68) *p=0.861*		1.20 (1.65) *p=0.254*		0.98 (1.44)

APPEARS THIS WAY ON ORIGINAL

Both clemastine 0.5 mg QID and clemastine 1.0 mg BID were statistically superior to placebo at Visits 2 and Visit 3 for patient-assessed reflective rhinorrhea scores. There was no difference from placebo at Visit 4 for either dose. An improvement was seen in the placebo group. These data are presented in Table 8.1.12.

Table 8.1.12 Primary efficacy variable, patient-assessed symptom score–reflective rhinorrhea score [Volume 1.26, page 56]

	Clemastine, 0.5 mg QID		Clemastine, 1.0 mg QD		Placebo	
Visit Number	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Visit 1, Baseline	135	4.36 (0.78)	134	4.24 (0.82)	138	4.25 (0.73)
Visit 2	135	2.96 (1.16)	134	2.92 (1.09)	138	3.46 (1.03)
Change, Visit 1 to Visit 2		[redacted]		[redacted]		0.79 (1.02)
Visit 3	131	2.73 (1.25)	131	2.77 (1.20)	132	3.18 (1.18)
Change, Visit 1 to Visit 3		[redacted]		[redacted]		1.08 (1.16)
Visit 4	126	2.68 (1.34)	128	2.61 (1.28)	123	2.84 (1.19)
Change, Visit 1 to Visit 4		1.64 (1.51) *p=0.149*		1.62 (1.46) *p=0.126*		1.38 (1.28)

Both clemastine 0.5 mg QID and clemastine 1.0 mg BID were statistically superior to placebo at Visits 2 and Visit 3 for patient-assessed instantaneous sneezing scores. There was no difference from placebo at Visit 4 for either dose. An improvement was seen in the placebo group. These data are presented in Table 8.1.13.

Table 8.1.13 Primary efficacy variable, patient-assessed symptom score–instantaneous sneezing score [Volume 1.26, page 67]

	Clemastine, 0.5 mg QID		Clemastine, 1.0 mg QD		Placebo	
Visit Number	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Visit 1, Baseline	135	2.74 (1.47)	134	2.84 (1.45)	138	2.89 (1.44)
Visit 2	135	1.78 (1.14)	133	1.78 (1.20)	138	2.56 (1.30)
Change, Visit 1 to Visit 2		[redacted]		[redacted]		0.33 (1.30)
Visit 3	131	1.62 (1.17)	131	1.82 (1.24)	132	2.33 (1.30)
Change, Visit 1 to Visit 3		[redacted]		[redacted]		0.57 (1.50)
Visit 4	126	1.56 (1.23)	128	1.74 (1.27)	123	2.03 (1.31)
Change, Visit 1 to Visit 4		1.16 (1.65) *p=0.188*		1.10 (1.54) *p=0.274*		0.81 (1.55)

Both clemastine 0.5 mg QID and clemastine 1.0 mg BID were statistically superior to placebo at Visits 2 and Visit 3, and clemastine 0.5 mg QID at Visit 4 for patient-assessed reflective sneezing scores. These differences were statistically significant. There was no difference from placebo at Visit 4 for clemastine 1.0 mg BID. An improvement was seen in the placebo group. These data are presented in Table 8.1.14.

Table 8.1.14 Primary efficacy variable, patient-assessed symptom score–reflective sneezing score [Volume 1.26, page 68]

	Clemastine, 0.5 mg QID		Clemastine, 1.0 mg QD		Placebo	
Visit Number	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Visit 1, Baseline	135	3.92 (0.90)	134	3.89 (0.90)	138	4.02 (0.81)
Visit 2	135	2.25 (1.13)	134	2.27 (1.15)	138	3.11 (1.05)
Change, Visit 1 to Visit 2		[redacted]		[redacted]		0.91 (1.14)
Visit 3	131	1.95 (1.14)	131	2.20 (1.27)	132	2.82 (1.26)

	Clemastine, 0.5 mg QID		Clemastine, 1.0 mg QD		Placebo	
Visit Number	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Change, Visit 1 to Visit 3		[redacted]		[redacted]		1.19 (1.34)
Visit 4	126	1.75 (1.22)	128	2.09 (1.23)	123	2.53 (1.24)
Change, Visit 1 to Visit 4		[redacted]		1.78 (1.44) *p=0.059*		1.46 (1.36)

8.1.4.6.b. Secondary efficacy variables

Results of secondary efficacy variables support the efficacy of clemastine 0.5 mg QID and clemastine 1.0 mg BID. The patient-assessed instantaneous individual treatment scores show that efficacy is maintained to the end of the dosing interval for both treatment regimens.

Most individual symptom scores favored clemastine 0.5 mg QID and clemastine 1.0 mg BID over placebo at Visits 2, 3, and 4 when assessed by the investigator, and when assessed by the patient, both instantaneous and reflective. Investigator global response to treatment and patient global response to treatment favored clemastine 0.5 mg BID and clemastine 1.0 mg BID over placebo at Visit 2. There was little change in the global response to treatment for subsequent visits, as the difference was measured from the immediately preceding visit and not from the baseline visit. Patients taking clemastine used less pseudoephedrine as rescue medication than patients taking placebo. This provides some additional evidence of efficacy. There was little difference in the use of acetaminophen between patients taking clemastine and patients taking placebo. Review of results of individual secondary efficacy variables follow.

- Total nasal score

The investigator-assessed total nasal score, the patient-assessed instantaneous total nasal score, and the patient-assessed reflective total nasal score favored clemastine 0.5 mg QID and clemastine 1.0 mg BID over placebo at Visits 2, 3, and 4 [Volume 1.26, pages 85-87].

- Nasal itching

The investigator-assessed nasal itching score, the patient-assessed instantaneous nasal itching score, and the patient-assessed reflective nasal itching score favored clemastine 0.5 mg QID and clemastine 1.0 mg BID over placebo at Visits 2, 3, and 4 [Volume 1.26, pages 61-64].

- Itchy/burning eyes

The investigator-assessed score for itchy/burning eyes, the patient-assessed instantaneous score for itchy/burning eyes, and the patient-assessed reflective score for itchy/burning eyes favored clemastine 0.5 mg QID and clemastine 1.0 mg BID over placebo at Visits 2, 3, and 4 [Volume 1.26, pages 69-72].

- Tearing/watery eyes

The investigator-assessed score for tearing/watery eyes, the patient-assessed instantaneous score for tearing/watery eyes, and the patient-assessed reflective score for tearing/watery eyes favored clemastine 0.5 mg QID and clemastine 1.0 mg BID over placebo at Visits 2, 3, and 4 [Volume 1.26, pages 73-76].

- Ocular redness

The investigator-assessed score for ocular redness favored clemastine 0.5 mg QID and clemastine 1.0 mg BID over placebo at all visits. The patient-assessed instantaneous score for tearing/watery eyes, and the patient-assessed reflective score for tearing/watery eyes favored clemastine 0.5 mg QID and clemastine 1.0 mg BID over placebo at Visits 2, and 3, but not Visit 4 [Volume 1.26, pages 77-80].

- Itching of ears and/or palate

The investigator-assessed score for itching of the ears and/or palate favored clemastine 0.5 mg QID and clemastine 1.0 mg BID over placebo at all visits. The patient-assessed instantaneous score for tearing/watery eyes, and the patient-assessed reflective score for tearing/watery eyes favored clemastine 0.5 mg QID and clemastine 1.0 mg BID over placebo at Visits 2, and 3, but not Visit 4 [Volume 1.26, pages 81-84].

- Nasal congestion

The investigator-assessed nasal congestion score favored clemastine 0.5 mg QID and clemastine 1.0 mg BID over placebo by small amounts at all visits. The patient-assessed instantaneous nasal congestion score and the patient-assessed reflective nasal congestion score favored clemastine 0.5 mg QID and clemastine 1.0 mg BID by small amounts over placebo at Visits 2, and 3, but not Visit 4 [Volume 1.26, pages 57-60].

- Global response to treatment

The investigator-assessed global response to treatment favored clemastine 0.5 mg QID and clemastine 1.0 mg BID over placebo at Visit 2. There was little additional change in subsequent visits. The interval change from the preceding visit was measured, and the largest increase in efficacy was therefore seen between baseline and Visit 2. Little additional change was noted between Visits 2 and 3 and Visits 3 and 4 [Volume 1.26, page 88].

The patient-assessed global response to treatment favored clemastine 0.5 mg QID and clemastine 1.0 mg BID over placebo at Visit 2. There was little additional change in subsequent visits. The interval change from the preceding visit was measured, and the largest increase in efficacy was therefore seen between baseline and Visit 2. Little additional change was noted between Visits 2 and 3 and Visits 3 and 4 [Volume 1.26, page 89].

- Use of rescue medication

Patients taking clemastine 0.5 mg QID and clemastine 1.0 mg BID used less pseudoephedrine as rescue medication between Visits 1-2, Visits 2-3, and Visits 3-4 than patients taking placebo. There was little difference in use of acetaminophen between active and placebo treatment groups between Visits 1-2, Visits 2-3, and Visits 3-4 [Volume 1.26, pages 90-91].

8.1.4.7. Safety outcomes

Safety variables for the study included AEs, SAEs, deaths, withdrawals due to AEs, vital signs, and laboratory studies. Each variable is discussed below. ECGs were not performed in this study. Physical examinations were only performed at screening and therefore were not

safety variables for this study. This study supports the safety of clemastine 0.5 mg QID and clemastine 1.0 mg BID in the treatment of the symptoms and signs of SAR.

There was adequate exposure to active drug in this study. Patients taking clemastine more commonly reported headache, somnolence, fatigue, dry mouth, and dizziness. These AEs are expected due to the sedative and anticholinergic properties of clemastine. A small, 2-3 bpm, increase in pulse rate was also seen in patients taking clemastine. There were no deaths or SAEs in this study. A more detailed discussion of safety data follows below.

8.1.4.7.a. Total drug exposure

Total exposure to study treatment may be estimated from compliance data. Compliance was good and exposure was adequate to assess drug safety. A total of 135 patients were exposed to clemastine 0.5 mg QID. A total of 135 patients were exposed to clemastine 1.0 mg BID. A total of 111 patients (82.2%) treated with clemastine 0.5 mg took study medication QID for at least 13 of the 14 drug treatment cycles. A total of 119 patients (88.1%) of patients treated with clemastine 1.0 mg took study medication QID for at least 13 of the 14 drug treatment cycles. These data are presented in Table 8.1.8.

8.1.4.7.b. Adverse events (AEs)

AEs were frequent in this study and were more common in clemastine-treated patients than in placebo-treated patients. AEs were generally mild to moderate in severity. AEs occurring in ≥2.0% of patients taking either clemastine 0.5 mg QID or clemastine 1.0 mg BID and occurring more frequently than placebo are listed in Table 8.1.15 [Volume 1.26, pages 38, 39, 106-135].

Total AEs showed a small dose response effect with active drug. AEs were reported in 70.6% (96/136) of patients treated with clemastine 0.5 mg QID, in 74.1% (100/136) of patients treated with clemastine 1.0 mg BID, and in 65.9% (91/138) of patients treated with placebo.

The most common AE occurring more frequently in clemastine-treated patients than in placebo was headache. Notable AEs occurring in clemastine-treated patients more frequently than placebo were somnolence, fatigue, dry mouth, and dizziness. These AEs are likely due to the anticholinergic effect of the drug. All of these AEs showed a dose response effect. Somnolence was noted in 17.6% (24/136) of patients taking clemastine 0.5 mg QID, in 25.2% (34/135) of patients taking clemastine 1.0 mg BID, and in 5.8% (8/138) of patients taking placebo. Fatigue (which may not be completely independent of somnolence) was noted in 8.8% (12/136) of patients taking clemastine 0.5 mg QID, in 11.1% (15/135) of patients taking clemastine 1.0 mg BID, and in 0.7% (1/138) of patients taking placebo.

Table 8.1.15 HSC-305, adverse events occurring in ≥2% of patients taking clemastine and more frequently than placebo [Volume 1.26, pages 38, 39]

Adverse Event	Clemastine 0.5 mg QID, n=136		Clemastine 1.0 mg BID, n=135		Placebo, n=138	
	n	(%)	n	(%)	n	(%)
Headache	66	(48.5)	67	(49.6)	63	(45.7)
Somnolence	24	(17.6)	34	(25.2)	8	(5.8)
Fatigue	12	(8.8)	15	(11.1)	1	(0.7)
Pain (general)	6	(4.4)	4	(3.0)	5	(3.6)
Pharyngitis	5	(3.7)	2	(1.5)	4	(2.9)

Adverse Event	Clemastine 0.5 mg QID, n=136		Clemastine 1.0 mg BID, n=135		Placebo, n=138	
	n	(%)	n	(%)	n	(%)
Dry mouth	3	(2.2)	5	(3.7)	2	(1.4)
Sinusitis	4	(2.9)	3	(2.2)	3	(2.2)
Dyspepsia	5	(3.7)	3	(2.2)	1	(0.7)
Influenza-like symptoms	6	(4.4)	2	(1.5)	0	(0)
Fever	3	(2.2)	1	(0.7)	2	(1.4)
Abdominal pain	4	(2.9)	2	(1.5)	0	(0)
Epistaxis	4	(2.9)	1	(0.7)	1	(0.7)
Rash	3	(2.2)	1	(0.7)	2	(1.4)
Dizziness	1	(0.7)	4	(3.0)	0	(0)
Tooth disorder	3	(2.2)	2	(1.5)	0	(0)
Vomiting	4	(2.9)	0	(0)	0	(0)
Arthralgia	0	(0)	3	(2.2)	0	(0)
All events	96	(70.6)	100	(74.1)	91	(65.9)

8.1.4.7.c. Deaths and serious adverse events (SAEs)

There were no deaths or SAEs reported in this study [Volume 1.26, page 41].

8.1.4.7.d. Withdrawals due to AEs

Somnolence and fatigue were common reasons for withdrawal from the study in clemastine-treated patients, and there was a dose response effect seen in the number of patients withdrawing from the study for these AEs. This is consistent with the frequent AE reports of somnolence and fatigue in clemastine-treated patients. There was one patient who withdrew because of somnolence in the placebo group, three patients who withdrew because of somnolence in the clemastine 0.5 mg QID group, and six patients who withdrew because of somnolence, fatigue, or asthenia in the clemastine 1.0 mg BID group. There was one patient treated with clemastine 0.5 mg QID who withdrew because of palpitation and nervousness, and one patient treated with clemastine 0.5 mg QID who withdrew because of a URI and fever [Volume 1.26, pages 40-41].

8.1.4.7.e. Vital signs

The data summarizing the change in vital signs in treatment groups were reviewed. There was a small, clinically insignificant increase in mean pulse of 2 to 3 bpm noted in patients taking clemastine 0.5 mg QID. Other vital signs showed no difference between treatment groups. Review of these data follow.

A small mean increase in pulse of 2 to 3 bpm was noted in patients treated with clemastine 0.5 mg QID. This increase was present at Visits 2, 3, and 4, and was greater than that seen in patients treated with clemastine 1.0 mg QID or placebo. This increase in pulse may be due to the anticholinergic effects of the drug. This small increase in pulse is not clinically significant in this reviewer's opinion. These data are presented in Table 8.1.16 [Volume 1.26, page 94].

Table 8.1.16 HSC-305, vital signs, change in pulse [Volume 1.26, page 94]

	Clemastine, 0.5 mg QID		Clemastine, 1.0 mg QD		Placebo	
Visit Number	N	Pulse, bpm Mean (SD)	N	Pulse, bpm Mean (SD)	N	Pulse, bpm Mean (SD)
Visit 1, Baseline	136	71.0 (8.1)	135	72.5 (9.6)	138	71.9 (9.7)

	Clemastine, 0.5 mg QID		Clemastine, 1.0 mg QD		Placebo	
Visit Number	N	Pulse, bpm Mean (SD)	N	Pulse, bpm Mean (SD)	N	Pulse, bpm Mean (SD)
Visit 2	134	74.4 (9.8)	133	72.9 (8.7)	137	73.3 (8.3)
Change, Visit 1 to Visit 2		[redacted]		0.3 (9.7)		1.5 (9.9)
Visit 3	132	73.5 (9.2)	129	73.5 (9.1)	133	72.1 (9.0)
Change, Visit 1 to Visit 3		[redacted]		0.6 (10.4)		0.2 (9.7)
Visit 4	127	73.0 (8.7)	129	72.7 (8.5)	123	72.9 (9.2)
Change, Visit 1 to Visit 4		[redacted]		0.0 (10.6)		0.7 (10.3)

The change in mean systolic and diastolic blood pressures, respiratory rate, and body temperature were similar in patients treated with clemastine 0.5 mg QID, clemastine 1.0 mg BID, and placebo.

8.1.4.7.f. Laboratory studies

Data summarizing the proportion of patients with change from normal to abnormal in hematology, urinalysis, and chemistry results were reviewed. There was a higher frequency of change from normal to low urine specific gravity in patients treated with clemastine 0.5 mg QID and clemastine 1.0 mg BID than placebo. There was a higher frequency of change in serum glucose from normal to abnormal in patients treated with clemastine 0.5 mg QID and clemastine 1.0 mg BID than placebo. There were more patients treated with clemastine 0.5 mg QID with an abnormal decrease in serum calcium than patients treated with clemastine 1.0 mg BID or placebo. These changes were small and not likely to be clinically significant. Other laboratory studies showed no difference between patients treated with active drug or placebo.

The percent of patients with change in hematology study results from normal to abnormal were reviewed. These data were similar in patients treated with clemastine 0.5 mg QID, clemastine 1.0 mg BID, and placebo [Volume 1.26, page 97].

The percent of patients with change in urinalysis study results from normal to abnormal were reviewed. These data showed a higher frequency of change from normal to low specific gravity in patients treated with clemastine 0.5 mg QID and clemastine 1.0 mg BID than placebo. It is possible that this may be related to the higher frequency of dry mouth in clemastine-treated patients, which could result in greater thirst and fluid intake. There was no dose response effect seen, however, and changes were small and not clinically significant. These data are displayed in Table 8.1.17 [Volume 1.26, pages 98, Volume 1.28, pages 305-331].

Table 8.1.17 Urine specific gravity, change from baseline to follow-up [Volume 1.26, pages 98, Volume 1.28, pages 305-331]

Treatment group	Urine specific gravity					
	Normal->low n	(%)	Normal->high n	(%)	Normal->abnormal n	(%)
Clemastine 0.5 mg QID, 114/136 patients with urine specific gravity performed	13	(11)	2	(2)	15	(13)
Clemastine 1.0 mg BID, 119/135 patients with urine specific gravity performed	12	(10)	2	(2)	14	(12)

Treatment group	Urine specific gravity					
	Normal->low		Normal->high		Normal->abnormal	
	n	(%)	n	(%)	n	(%)
Placebo, 120/138 patients with urine specific gravity performed	9	(8)	1	(1)	10	(8)

The percent of patients with change in serum chemistry results from normal to abnormal were reviewed. These data showed a higher frequency of change in serum glucose from normal to abnormal in patients treated with clemastine 0.5 mg QID and clemastine 1.0 mg BID than placebo. The direction of change in serum glucose was not consistent in clemastine-treated patients and was not consistent with a drug effect. There were more patients treated with clemastine 0.5 mg QID with an abnormal decrease in serum glucose. There were more patients treated with clemastine 1.0 mg BID with an abnormal increase in serum glucose. These changes were small and not likely to be clinically significant. These data are displayed in Table 8.1.18 [Volume 1.26, pages 99, Volume 1.28, pages 359-388].

Table 8.1.18 Serum glucose, change from baseline to follow-up [Volume 1.26, pages 99, Volume 1.28, pages 359-388]

Treatment group	Change in serum glucose					
	Normal->low		Normal->high		Normal->abnormal	
	n	(%)	n	(%)	n	(%)
Clemastine 0.5 mg QID, 129/136 patients with serum glucose performed	10	(8)	5	(4)	15	(12)
Clemastine 1.0 mg BID, 130/135 patients with serum glucose performed	6	(5)	9	(7)	15	(12)
Placebo, 127/138 patients with serum glucose performed	4	(3)	4	(3)	8	(6)

There was a higher frequency of change in serum calcium from normal to abnormal in patients treated with clemastine 0.5 mg QID and clemastine 1.0 mg BID than placebo. There were more patients treated with clemastine 0.5 mg QID with an abnormal decrease in serum calcium than patients treated with clemastine 1.0 mg BID or placebo. There was no dose response effect. These changes were small and were not likely to be clinically significant. These data are displayed in Table 8.1.19 [Volume 1.26, pages 99, Volume 1.28, pages 359-388].

Table 8.1.19 Serum calcium, change from baseline to follow-up [Volume 1.26, pages 99, Volume 1.28, pages 359-388]

Treatment group	Change in serum calcium					
	Normal->low		Normal->high		Normal->abnormal	
	n	(%)	n	(%)	n	(%)
Clemastine 0.5 mg QID, 134/136 patients with serum calcium performed	7	(5)	0	(0)	7	(5)
Clemastine 1.0 mg BID, 133/135 patients with serum calcium performed	3	(2)	0	(0)	3	(2)
Placebo, 134/138 patients with serum calcium performed	0	(0)	1	(1)	1	(1)

8.2. HSC-306: A one-day, multicenter, randomized, double blind, double-dummy, placebo-controlled, parallel-group, study to assess the efficacy and safety of Clemastine Triple Combination (CTC), TheraFlu® Sinus, and placebo in the treatment of seasonal allergic rhinitis.

8.2.1. Summary and reviewer's conclusion of study results

This one-day, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group study was performed at two US centers. The study was performed during the 1997 Fall pollen season. The first patient was enrolled on 9/6/97 and the last patient completed the study on 9/14/97. The objective of this study was to evaluate the efficacy and safety of clemastine in Clemastine Triple Combination (CTC, clemastine base 0.25 mg, acetaminophen 500 mg, and pseudoephedrine HCl 30 mg per tablet) versus TheraFlu® Sinus (TF Sinus, acetaminophen 500 mg, and pseudoephedrine HCl 30 mg per tablet) in patients with moderate to severe symptoms of seasonal allergic rhinitis (SAR). The purpose of this study in the sponsor's drug development plan was to show that clemastine in the combination product in the QID dosing form would provide symptom relief with the first dose and that efficacy is maintained throughout the entire 6-hour dosing interval.

Baseline demographics and background characteristics were equally represented in all treatment groups with the exception of gender. There were proportionately more women in the TF Sinus group. Patients were largely Caucasian. Baseline symptom scores were slightly higher in the TF Sinus group than the CTC and placebo groups, but not to an extent to significantly affect the efficacy analysis.

This study supports the efficacy of CTC in the treatment of the symptoms of SAR. The primary efficacy variable was the average reduction from baseline in the Major Symptom Complex (MSC) at hours 2-5. The MSC was composed of the sum of individual scores for sneezing, itchy nose, runny nose, watery eyes, itchy eyes/ears, and itchy throat. Acetaminophen and pseudoephedrine are OTC cough and cold monograph drugs, but clemastine is not. Therefore, the primary comparison was CTC versus TF Sinus, to assess whether any efficacy is added by clemastine in the combination product. CTC decreased MSC scores over hours 2-5 more than TF Sinus and placebo after both doses of treatment medication. The effect size for CTC after Dose 1 was 5.2% of the maximum possible MSC of 33 and the effect size for CTC after Dose 2 was 7.2% of the maximum possible MSC of 33 compared with TF Sinus. There was a placebo effect noted after both doses.

Results of secondary efficacy variables support the efficacy of CTC. Onset of efficacy was 2 hours after Dose 1 and efficacy was maintained throughout the 6 hour dosing interval. CTC decreased MSC and Total Symptom Complex (TSC) scores over hours 1 to 6 and TSC over hours 2 to 5 more than TF Sinus and placebo after both doses of treatment medication. Patient global assessment of efficacy showed CTC superior to TF Sinus and placebo.

This study supports the safety of CTC in the treatment of the symptoms of SAR. AEs were fairly frequent in this study and were more frequent in CTC-treated patients than in TF Sinus-treated patients and placebo-treated patients. Somnolence and fatigue were the most common AEs in CTC treated patients. AEs occurring in CTC-treated patients were generally

moderate in severity, except for somnolence and fatigue, for which some severe AEs were noted. There were no deaths or SAEs in this study and there were no withdrawals from this study due to AEs. Vital signs and physical examination were performed only at screening and were therefore not safety variables for this study. There were no laboratory studies performed as safety variables for this study. Pregnancy tests were performed as inclusion/exclusion criteria and ECGs were not performed in this study.

8.2.2. Objective/Rationale

The objective of this study was to evaluate the efficacy and safety of clemastine in Clemastine Triple Combination (CTC) versus TheraFlu® Sinus (TF Sinus) in patients with moderate to severe symptoms of seasonal allergic rhinitis (SAR). [Volume 1.30, page 10]

8.2.3. Protocol

This one-day, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group study was performed at two US centers. The study was performed during the 1997 Fall pollen season. The first subject was enrolled on 9/6/97 and the last patient completed the study on 9/14/97. [Volume 1.29, page 13, Volume 1.30, page 10]

Table 8.2.1 displays an outline of the study. The first study visit (Visit 1/Screening) was to be completed no more than four weeks prior to dosing with the study medication. Patients were to complete an informed consent form and were to be assigned a screening number. Patients then were to provide information concerning their medical history and their use of medications during the preceding two weeks. Patients then were to have a limited physical examination with vital signs. A urine pregnancy test was to be obtained in women, and skin testing to prevalent allergens was to be performed.

Pollen counts were to be performed daily starting one week before Visit 1 until two days after Visit 1. Patients selected for the study were to arrive at the study site at 6:30 AM on the day of the study (Visit 2). They were to have their inclusion and exclusion criteria verified, and any changes to their current medications were to be checked. Women were to have a repeat urine pregnancy test before receiving study medication at Visit 2.

Patients were to complete three pretreatment symptom evaluations 30 minutes apart prior to dosing with study medication and were to record the results on a symptom evaluation form. The symptom evaluation forms were to be reviewed by study staff prior to patient randomization and administration of Dose 1 of study medication. Dose 1 of study medication was to be given at 9:30 AM. Symptom evaluations were to be completed by patients at 9:30 AM, 10:00 AM, and hourly until 3:00 PM. Dose 2 of study medication was to be given after the 3:00 PM symptom evaluation. Symptom evaluations were to be completed in the park at 4:00 PM and 5:00 PM. Patients were to be allowed to leave the park after the 5:00 symptom evaluation and were to complete symptom evaluations at home at 6:00 PM and hourly until 9:00 PM.

Table 8.2.1 Study outline, HSC-306 [compiled from Volume 1.30, pages 17-21]

Visit Number	Visit 1 Screening	Visit 2														Visit 3
Study day	-28 to -1	0 Base line														1
Time		6:30 AM	9:00	9:30	10:00	11:00	12:00 Noon	1:00 PM	2:00	3:00	4:00	5:00	6:00	7:00	8:00	9:00	8:00 to 10:00 AM
Study medication given			Dose 1							Dose 2[1]							
Informed consent	X																
Skin test, unless performed in the last 1 year	X																
Medical History	X																
Physical Exam	X																
Vital signs	X																
Urine pregnancy test in women	X	X															
Randomization		X															
Baseline inclusion criteria		X															
Symptom evaluation		X[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Location	OFFICE[3]	[redacted] PARK [redacted]															OFFICE[3]
Adverse events monitored		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patients' global assessment																	X

[1]Medication given after symptom evaluation performed
[2]Baseline symptom evaluation performed three times–at 7:30, 8:00, and 8:30 AM
[3]Investigator's office

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Patients were to return to the investigator's office on the next day between 8:00 AM and 10:00 AM for Visit 3. Symptom evaluations completed at home were to be returned and patients were to be questioned about adverse events. Each patient was to make a global assessment of efficacy at that time.

8.2.3.1. Inclusion criteria

Patients were to meet the following inclusion criteria at the screening visit (Visit 1) [Volume 1.30, page 12]:

- Completed informed consent
- History of moderate to severe seasonal allergic rhinitis (SAR) due to fall seasonal pollens and skin test sensitive to relevant fall pollens
- Ages 12 to 65 years, male or female, any race
- Good health, free of any clinically significant disease
- Able to comply with requirements of the study
- The following washout periods were required before the screening visit:

Drug	Washout period
Hydroxyzine, loratadine, terfenadine, cetirizine	5 days
All other antihistamines, all forms	48 hours

The inclusion criteria called for patients to have a history of moderate to severe SAR. Patients were required to have a sum of 18 for the three baseline MSC evaluations before they were given study medication. The maximum MSC was 33, and the maximum sum for the three baseline symptom evaluation was therefore 99. It should be noted that a sum of 18 out of a maximum of 99 on this score would tend to allow participation of patients who were having rather mild symptoms of SAR, even though they may have had a past history of moderate to severe SAR. The scoring is covered in section 8.2.3.4 of this review.

Patients were to meet the following additional inclusion criteria at the baseline visit (Visit 2) [Volume 1.30, page 14]:

- Patients must not have violated any of the following drug washout periods before the baseline visit:

Drug	Washout period
Astemizole	90 days
Systemic corticosteroids	30 days
Inhaled (oral and nasal) corticosteroids	2 weeks
Ocular corticosteroids	2 weeks
Lodoxamide (Acular) ocular drops	1 week
Cromolyn sodium, all forms	1 week
Nedocromil	1 week
Hydroxyzine, loratadine, terfenadine, cetirizine	5 days
All other antihistamines, all forms	48 hours
Oral decongestants	48 hours
Topically applied ocular and nasal decongestants	48 hours
Artificial tears and eye drops	24 hours
Diet aids containing medication	24 hours
Intranasal saline	24 hours
NSAIDS	24 hours
Alcohol	24 hours

8.2.3.2. Exclusion criteria

Patients were to be excluded from the study if they had any of the following exclusion criteria:

- Women who were pregnant or nursing
- Women of child-bearing potential who were not practicing a medically acceptable method of contraception
- Clinically significant medical illness
- Clinically significant abnormal vital sign
- Clinically significant abnormality on physical examination
- Upper respiratory tract infection and/or bacterial sinusitis within the preceding two weeks
- Patients with pulmonary disease and/or asthma requiring daily maintenance therapy
- Patients who had participated in a trial of an investigational drug within 30 days
- Patients who were initiating or advancing on an immunotherapy regimen during the course of the study or who had been on maintenance therapy for less than one month
- Patients with known nasal abnormality or pathology such as significantly obstructing deviated septum, obstructive nasal polyps, significant nasal tract structural malformations.
- Patients with a known hypersensitivity to or idiosyncratic reaction to antihistamines, sympathomimetic agents, or analgesics
- Patients who were known or suspected non-responders to antihistamines sympathomimetic agents, analgesics or known or suspected placebo responders
- Patients who had already been enrolled in this study
- Patients who were alcohol or drug abusers
- Patients using antidepressant therapy
- Patients who had been treated with immunosuppressive or radiation therapy over the preceding three months and/or required such therapy during the course of the study

8.2.3.3. Drug product and placebo

There was less than a 1% difference in the amount of maltodextrin [redacted] between the Clemastine Triple Combination (CTC) drug product used in this study and the to be marketed formulation. All other components were the same as the to be marketed formulation. This difference is not likely to be clinically significant since this is an immediate release drug product and the difference in maltodextrin between the two formulations is small. The following medications and batches were to be used in this study:

- Clemastine Triple Combination tablets (CTC, [redacted] mg clemastine fumarate, 30 mg pseudoephedrine hydrochloride, 500 mg acetaminophen per tablet), batch number 690-1999.35.
- Placebo for CTC tablets, batch number 690-1999.10.
- TheraFlu® Sinus tablets (TF Sinus, 30 mg pseudoephedrine hydrochloride, 500 mg acetaminophen per tablet), batch number 754-2097.03.
- Placebo for TF Sinus tablets, batch number 754-2097.04.

Placebos were to be used to blind the study medication. Each dose of study medication was to consist of four tablets. Patients assigned to the CTC group were to receive two CTC tablets and two placebo tablets resembling TF Sinus. Patients assigned to the TF Sinus group were

to receive two TF Sinus tablets and two placebo tablets resembling CTC. Patients assigned to the placebo group were to receive two placebo tablets resembling CTC and two placebo tablets resembling TF Sinus [Volume 1.30, pages 15-16].

Study staff were to assess patient compliance by observing and questioning of the patients. The proper use of medication was to be determined by a count of remaining medication at the end of the study. Study staff were to verify that symptom evaluation forms were properly completed and were to question patients about the use of prohibited therapies [Volume 1.30, page 23]. There was no plan for analysis of compliance.

8.2.3.4. Assessment of symptoms

The symptoms used for patient scoring are displayed in Table 8.2.2. The Major Symptom Complex (MSC) was composed of the sum of the scores for sneezing, itchy nose, runny nose, watery eyes, itchy eyes/ears, and itchy throat. The Total Symptom Complex (TSC) was composed of the MSC plus the scores for nose blows, sniffles, postnasal drip, and cough. Stuffy nose and headache were scored as individual symptoms and were not part of the MSC or TSC.

Table 8.2.2 HSC-306, nasal and non-nasal symptoms and signs evaluated by patients [Volume 1.30, pages 18-19]

Nasal and non-nasal symptoms, MSC and TSC	Symptom complex
Sneezing	MSC, TSC[1]
Itchy nose, average of right and left	MSC, TSC
Runny nose, average of right and left	MSC, TSC
Watery eyes	MSC, TSC
Itchy eyes/ears	MSC, TSC
Itchy throat	MSC, TSC
Nasal and non-nasal symptoms, TSC	**Symptom complex**
Nose blows	TSC[2]
Sniffles	TSC
Postnasal drip	TSC
Cough	TSC
Nasal and non-nasal symptoms, not part of MSC or TSC	**Symptom complex**
Stuffy nose, average of right and left	None[3]
Headache	None

[1]Symptom is part of Major Symptom Complex and Total Symptom Complex
[2]Symptom is part of Total Symptom Complex
[3]None: not applicable, symptom not part of MSC or TSC

There was a discrepancy between the protocol synopsis [Volume 1.30, page 10-11] and the statistics appendix to the protocol, Appendix E [Volume 1.30, page 81], in the method the symptom scores for stuffy nose, itchy nose, and runny nose were to be calculated. The protocol synopsis called for calculating the average of the right and left scores for stuffy nose, itchy nose, and runny nose before calculating the MSC, TSC, or analyzing the individual symptom. The statistics appendix of the protocol called for the individual right and left scores for stuffy nose, itchy nose, and runny nose to be used in the calculation of the MSC, TSC, and for the analysis of the individual symptoms. The data presented in this study were calculated as defined in the protocol synopsis, using the average of the right and left side scores for these symptoms. Using this method, the maximum possible score for the MSC was 33, with 8 points for sneezing and 5 points each for itchy nose (average of right and left), runny nose (average of right and left), watery eyes, itchy eyes/ears, and itchy throat. Using

this method, the maximum possible TSC was 56, with 8 points each for nose blows and sneezing and 5 points each for itchy nose (average of right and left), runny nose (average of right and left), sniffles, postnasal drip, watery eyes, itchy eyes/ears, itchy throat and cough. The effect of averaging right and left for itchy nose and runny nose is discussed in a later section of this review, Section 8.2.3.5.a., Primary efficacy variable.

The symptom scale used for assessing the severity of symptoms displayed below in Table 8.2.3. Stuffy nose was not part of either the MSC or the TSC. The 8-point symptom scale used for nose blows and sneezing is also displayed below in Table 8.2.3. Zero to five nose blows or sneezes were to be scored as the exact number. Six to nine nose blows or sneezes was to be scored as 6. Ten to 15 nose blows or sneezes was to be scored as a 7. More than 15 nose blows or sneezes was to be scored as an 8.

Table 8.2.3 Scales for evaluation of nasal and non-nasal symptoms of SAR [Volume 1.30, page 18-20]

Scale 1:	**Scale 2:**	**Scale 3:**
0 = clear, fully open, no obstruction of air passage 1 = slightly stuffy 2 = stuffy 3 = very stuffy 4 = blocked 5 = completely blocked, cannot move any air through nostril	0 = 0 instances 1 = 1 instance 2 = 2 instances 3 = 3 instances 4 = 4 instances 5 = 5 instances 6 = 6 to 9 instances 7 = 10 to 15 instances 8 = >15 instances	0 = none, no symptoms whatsoever 1 = a little 2 = moderate 3 = quite a bit 4 = severe 5 = very severe, symptoms which are very bothersome and disabling
Symptoms rated on this scale: Stuffy nose, left[1] Stuffy nose, right[1]	**Symptoms rated on this scale:** Nose blows[3] Sneezing[2]	**Symptoms rated on this scale:** Itchy nose, left[2] Itchy nose, right[2] Runny nose, left[2] Runny nose, right[2] Sniffles[3] Postnasal drip[3] Watery eyes[2] Itchy eyes/ears[2] Itchy throat[2] Cough[3] Headache[1]

[1]Symptom not part of MSC or TSC
[2] Symptom is part of Major Symptom Complex and Total Symptom Complex
[3] Symptom is part of Total Symptom Complex

Patients were to provide an assessment of the efficacy of the treatment using the five point scale displayed in Table 8.2.4 when they returned to the investigator's facility at Visit 3.

Table 8.2.4 Symptom scale used for remaining symptoms, HSC-306 [Volume 1.30, page 20-21]

Score	Global assessment of efficacy
4	Excellent
3	Very good
2	Good
1	Fair
0	Poor

8.2.3.5. Variables

Efficacy and safety variables for this study are described below.

8.2.3.5.a. Primary efficacy variable

The primary efficacy variable was the average reduction from baseline in the MSC score at hours 2-5. This was to be calculated as an absolute value and as a percentage of the baseline MSC score after each of the two doses [Volume 1.30, pages 11, 81]. The baseline score was assessed 1.5, 1, and 0.5 hours before the first dose of study medication (see Table 8.2.1). The sample size calculation was made based on the average percent reduction from baseline, and not the absolute values, as noted in this review, Section 8.2.3.6., Statistical considerations. Therefore the percent reduction in symptom scores will be the primary focus for analysis in this review. Acetaminophen and pseudoephedrine are OTC cough and cold monograph drugs, but clemastine is not. Therefore, the primary comparison was CTC versus TF Sinus, to assess whether any efficacy was added by clemastine in the combination product.

8.2.3.5.b. Secondary efficacy variables

Secondary efficacy variables for this study are listed below:

- Average reduction from baseline in MSC over hours 1 to 6 after each dose
- Average reduction from baseline in TSC over hours 2 to 6 and hours 2 to 6 after each dose
- Time point by time point comparisons of MSC and TSC
- Time point by time point comparisons of individual symptoms
- Patient global assessment of efficacy at Visit 3

All comparisons were to be made as a percentage of baseline and absolute values. The average reduction from baseline for hours 1 to 6 did not include the results for 30 minute post-dose assessment.

8.2.3.5.c. Safety variables

The safety variable for this study was adverse events (AEs). Vital signs and physical examination were performed only at screening and were therefore not safety variables for this study. There were no laboratory studies performed as safety variables for this study. Pregnancy tests were performed as an inclusion/exclusion criterion for this study. ECGs were not performed in this study.

8.2.3.6. Statistical Considerations

The sample size was calculated based on a comparison between the MSC for CTC versus TF Sinus. A standard deviation of 35% was used for the reduction from baseline in the MSC. The sponsor assumed that TF Sinus would reduce MSC scores 30% below baseline for hours 2 to 5. The maximum possible MSC was 33. One hundred twenty evaluable patients were required to be in each active treatment group to be able to detect a change from baseline of 12.8% of a maximum possible score of 33 using a two-tailed t-test with 80% power at a 0.05 level of significance [Volume 1.30, pages 81-82]. Enrollment of 340 was planned to allow for 60 patients assigned to the placebo arm and to allow for dropouts.

Each analysis was to be run on the intent-to-treat (ITT) population. All average reduction from baseline analyses and all time point by time point analyses were to be conducted as analyses of covariance (ANCOVA) with main effects of treatment and center, a baseline covariate and all two-way interactions.

The patient global assessment of efficacy was to be analyzed with analyses of variance (ANOVA) having main effects treatment and center and the treatment by center interaction. [Volume 1.30, pages 81-82]

8.2.4. Results

8.2.4.1. Populations enrolled/analyzed

The protocol called for enrollment of 340 patients to allow for 300 evaluable patients. There were actually 353 patients enrolled and 298 patients randomized. A summary of patient disposition is found in Table 8.2.5. The 55 patients that were enrolled but not randomized did not have scores of ≥18 for the 3 baseline allergy symptom assessments. Four patients withdrew from the study. Two patients in the CTC group did not return for Visit 3, one patient in the CTC group withdrew consent, and one patient in the TF Sinus group could not swallow the study medication [Volume 1.29, pages 46, 67].

Table 8.2.5 Patient disposition, HSC-306 [Volume 1.29, pages 45-46, 66]

Site Investigator, location	Recruited	Randomized			
		CTC	TF Sinus	Placebo	Total Randomized
Site 1 Dr. Meltzer, San Diego, CA	169	62	63	32	157
Site 2 Dr. Casale, Papillion, NE	184	56	56	29	141
TOTAL	353	118	119	61	298

8.2.4.2. Baseline demographics and background characteristics

Gender was evenly represented in the CTC and placebo groups. There were proportionately more women in the TF Sinus group. The mean age was similar in all treatment groups. Patients were largely Caucasian. The proportion of patients in each treatment group was similar with regards to race. These data are displayed in Table 8.2.6.

Table 8.2.6 Demographic characteristics, HSC-306 [Volume 1.29, page 70]

Characteristic	CTC N = 118		TF Sinus N = 119		Placebo N = 61		Total N = 298	
Gender, n (%)								
Male	58	(49.2)	47	(39.5)	30	(49.2)	135	(45.3)
Female	60	(50.8)	72	(60.5)	31	(50.8)	163	(54.7)
Age, years								
Mean	28.1		27.5		29.3		NA*	
SD	14.25		13.16		13.45		NA	
Range	12-62		12-56		12-62		12-62	
Race, n (%)								
Caucasian	92	(78.0)	100	(84.0)	50	(82.0)	242	(81.2)
Black	11	(9.3)	9	(7.6)	2	(3.3)	22	(7.4)
Asian	4	(3.4)	4	(3.4)	3	(4.9)	11	(3.7)
Other	11	(9.3)	6	(5.0)	6	(9.8)	23	(7.7)

*NA: Mean, SD was not performed for age.

8.2.4.3. Protocol deviations

At Center 2, 36 patients received their first dose of study medication 15 to 30 minutes late. Of these 36 patients, 14 were in the CTC group, 14 were in the TF Sinus group, and 8 were in the placebo group. The sponsor did not perform an exclusion or subset analysis because the relative proportions of patients in the group receiving their medication late was comparable to the proportion of patients in each group that were randomized [Volume 1.29, page 47]. For the same reason, this reviewer concurs with the sponsor that no additional analyses are necessary.

One patient in the CTC group was found to be participating in another clinical study of allergic rhinitis at the same time as this study. This patient was not excluded from the statistical analysis [Volume 1.29, page 47].

8.2.4.4. Compliance

All patients were in compliance with the prohibited medications with the exception of the patient that was participating in another clinical study. More than 97% of patients in each treatment group completed their symptom assessments at each of the time points [Volume 1.29, pages 47, 82-83]. Patient 2024 could not swallow the TF Sinus tablet and had no study medication and Patient 2064 had one only one dose of CTC [Volume 1.29, page 67].

8.2.4.5. Pollen counts

Pollen counts were performed at each of the centers on most days of the 1-week period before the study day, on the study day, and on the two days following the study day. These data are displayed in Table 8.2.7. It should be noted that the National Allergy Bureau (NAB) classification for pollen and mold levels is specific for each type of aeroallergen–trees, grasses, weeds, and molds. As a result, the grass pollens reach the "high" level at 20 particles/m^3, weed pollens reach the "high" level at 50 particles/m^3, and molds reach the "high" level at 2500 particles/m^3. More information on the classification of pollen and mold counts may be found at the NAB web site, http://www.aaaai.org/nab/reading.stm.

Fall weed pollen counts for Center 1 were low on the day of the study, and were generally low before and after the study. Grass pollen levels were in the moderate range on the day of

the study and for the preceding and following days. It is possible that patients sensitive to both weed and grass pollen at Center 1 would be more likely to be symptomatic from their grass pollen sensitivity than from their weed pollen sensitivity. This would not affect the efficacy analysis, however, because a similar response to drug would be expected regardless of the pollen type.

Fall weed pollen counts for Center 2 were in the high range on the study day and the days preceding and following the study. Grass pollen and weed counts were in the high range on the study day and the days preceding and following the study. High levels of pollen and molds would tend to create a level of exposure favorable to producing SAR symptoms.

Table 8.2.7 Pollen counts, HSC-306 [Volume 1.29, page 48]

[illegible]	[illegible]		[illegible]		[illegible]	
Center 1, Dr. Meltzer, San Diego, CA	Grains/m³	NAB[1] Classification for weed pollen	Grains/m³	NAB Classification for grass pollen	Grains/m³	NAB Classification for molds
8/30/97	7	low	3	low	700	low
8/31/97	7	low	3	low	700	low
9/1/97	7	low	3	low	700	low
9/2/97	14	moderate	17	moderate	587	low
9/3/97	12	moderate	15	moderate	687	low
9/4/97	4	low	6	moderate	403	low
9/5/97	2	low	6	moderate	681	low
9/6/97-Day of study	2	low	6	moderate	681	low
9/7/97	2	low	6	moderate	681	low
9/8/97	1	low	4	low	706	low
[illegible]	[illegible]		[illegible]		[illegible]	
Center 2, Dr. Casale, Papillion, NE	Ragweed	NAB Classification for weed pollen[2]	Total Weed	NAB Classification for weed pollen	Total Molds	NAB Classification for molds
9/6/97	202	high	260	high	2631	high
9/7/97	ND[3]		ND		ND	
9/8/97	ND		ND		ND	
9/9/97	ND		ND		ND	
9/10/97	52	high	88	high	7824	high
9/11/97	87	high	147	high	3861	high
9/12/97	98	high	141	high	2252	moderate
9/13/97-Day of study	105	high	156	high	3358	high
9/14/97	74	high	90	high	2654	high
9/15/97	58	high	89	high	ND	

[1]NAB: National Allergy Bureau, http://www.aaaai.org/nab/reading.stm
[2]Ragweed pollen is classified with the weed pollen classification.
[3]ND: Not done because of power outage

8.2.4.6. Baseline symptom scores

Baseline symptom scores at both centers were slightly higher in the TF Sinus group than the CTC and placebo groups. Despite the higher pollen and mold counts at Center 2, patients at Center 1 had greater baseline MSC scores for all treatment groups. This implies that the patients at Center 1 were more sensitive and had more severe SAR than the patients at Center 2. These data are displayed in Table 8.2.8.

Table 8.2.8 Baseline MSC scores, HSC-306 [Volume 1.29, page 49]

Treatment	Center 1 Dr. Reiter San Diego, CA	Center 2 Dr. Casale Papillion, NE
CTC	14.3	11.0
TF Sinus	15.6	12.2
Placebo	15.5	10.3

8.2.4.7. Efficacy variable outcomes

Efficacy was supported by primary and secondary variables as described below. This study supports the efficacy of CTC in the treatment of the symptoms of SAR. The results of the primary and secondary efficacy variables are reviewed in the following sections.

8.2.4.7.a. Primary efficacy variables

The primary efficacy variable was the average reduction from baseline in the MSC score at hours 2-5 after each of the two doses [Volume 1.30, pages 11, 81]. These data are displayed in Table 8.2.9. The primary comparison was CTC versus TF Sinus, to assess whether any efficacy is added by clemastine in the combination product. Sample size calculations were based on the percentage of the baseline MSC score, and therefore the primary focus of the statistical analysis in this review was the percentage reduction in the MSC. CTC decreased MSC scores over hours 2-5 for CTC more than TF Sinus and placebo after both doses of treatment medication. There was no decrease in MSC scores over hours 2-5 for TF Sinus vs. placebo for either dose of treatment medication. After both doses, there was a decrease of the MSC in the placebo group. This decrease may be a result of the placebo effect or because of abatement of symptoms for other reasons, such as lower pollen counts later in the day, as may be expected with ragweed pollen.

After Dose 1 of study medication, the CTC group had a statistically significant percent reduction in the MSC at hours 2-5 compared with the TF Sinus group (p=0.002) and compared with the placebo group (p=0.023). The effect size for CTC after Dose 1 was 5.2% of the maximum possible MSC of 33 compared with TF Sinus. The effect size was calculated using the following formula:

$$\text{Effect Size} = \frac{\text{(change from baseline in MSC score, CTC) minus (change from baseline in MSC score, placebo or TF Sinus)} \times 100}{\text{Maximum possible change=33}}$$

There was no significant difference in the reduction in the MSC at hours 2-5 between the TF Sinus group and the placebo group (p=0.720). Statistical analysis based on the absolute reduction in the MSC at hours 2-5 showed similar results with a statistically significant reduction in MSC between CTC vs. TF Sinus (p = 0.002), CTC vs. placebo (p = 0.013), and no difference between TF Sinus and placebo (p=0.971).

After Dose 2 of study medication, the CTC group had a statistically significant percent reduction in the MSC at hours 2-5 compared with the TF Sinus group (p<0.001) and compared with the placebo group (p<0.001). The effect size for CTC after Dose 2 was 7.2% of the maximum possible MSC of 33 compared with TF Sinus. There was no significant difference in the reduction in the MSC at hours 2-5 between the TF Sinus group and the placebo group (p=0.871). Statistical analysis based on the absolute reduction in the MSC at