CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-082

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies

NDA#:	21-082 JUN 2 7 2000
Applicant:	Novartis Consumer Health, Inc.
Name of Drug:	Tavist Allergy/Sinus/Headache (clemastine fumarate — mg / pseudoephedrine hydrochloride 30 mg /acetaminophen 500 mg) Tablets
Indication:	Relief of symptoms due to the common cold and ———
Documents:	10/7/99 Volumes 1.1, 1.35-1.43; 4/3/00, 5/4/00 Responses
Data:	3/1/00
Statistician:	Barbara Elashoff, M.S.
Medical Input:	Charles Lee, M.D.
Keywords:	clinical studies, NDA review, OTC, gender differences and interaction

1 Introduction

Tavist-1 (clemastine, 1 mg) taken every 12 hours is currently marketed over-the-counter (OTC) by Novartis Consumer Health. The current application was submitted to gain approval for a triple combination product taken qid, consisting of the immediate release form of: clemastine — mg, pseudoephedrine 30 mg, and acetaminophen 500 mg. The sponsor claims that Tavist-1 is safe and effective for adults and children age 12 and above.

Since clemastine is not a monographed antihistamine and is not approved for dosing every 6 hours, the proposed combination drug product requires prior FDA approval before marketing. Two of the components in the combination have monograph status (pseudoephedrine and acetaminophen), and the third component (clemastine) is approved for over-the-counter status (bid) at the same total daily dose. Therefore, the current application focuses on two issues:

- Potential pharmacokinetic interaction among the components; and
- Safety and efficacy of 0.5 mg clemastine given every 6 hours.

The sponsor submitted pharmacokinetic studies to demonstrate that there is no pharmacokinetic interaction among the components and two clinical studies (Studies 305 and 306) to demonstrate the safety and efficacy of the 0.5 mg qid dose of clemastine. Study 305 (n=412, 2 weeks) was conducted to prove that a lower than currently available dose of clemastine (0.5 mg) is safe and effective when given qid. Study 306 (n=298) was a one-day park study to determine the safety and efficacy of the triple combination therapy.

Study HSC-305 Summary

Study 305 was a multi-center, double-blind, placebo-controlled, parallel group study that evaluated the safety and efficacy of clemastine 0.5 mg qid vs. clemastine 1.0 mg bid vs. placebo for allergy symptom relief. "The purpose of this study was to prove that a lower than currently available dose of clemastine (0.5 mg) is safe and effective when given qid." (Vol. 36, page 18). This two-week study enrolled 412 patients (ages 12 to 67 years) with seasonal allergic rhinitis (SAR) at 12 centers (all located in the USA) during the fall of 1995. As described in the study report, the primary efficacy variables were nasal discharge and sneezing. The primary efficacy variables (both in terms of endpoint definition and analyses) were not clearly specified in the protocol. Using two different analytical approaches to the physician and patient data, the results consistently demonstrated the efficacy of both the bid and qid dosing regimens during the first week of treatment. The placebo group improved during the second week, reducing the mean differences between the clemastine groups and placebo. There was no evidence that either of the clemastine dosing regimens was effective after one week of treatment. There was also no evidence that the two clemastine dosing regimens provided different levels of efficacy. The results were not internally consistent across genders. The differences across genders, while not clinically meaningful to individual patients, are indicative of potential problems with the study results and reduce confidence in the evidence derived from the study.

Study HSC-306 Summary

Study 306 was a double-blind, placebo-controlled, parallel group one-day park study to determine the safety and efficacy of the triple combination therapy in patients with at least moderate symptoms of seasonal allergic rhinitis. The triple combination product consisted of clemastine, pseudoephedrine hydrochloride and acetaminophen. This study enrolled 298 patients (ages 12 to 62 years) at two centers (located in California and Nebraska). The primary efficacy variable was "Major Symptom Complex", defined as the sum of the patient's assessments of sneezing, itchy nose, runny nose, watery eyes, itchy eyes/ears, and itchy throat. Patients were randomized to one of three treatment groups: triple combination tablets, TheraFlu Sinus Tablets (pseudoephedrine and acetaminophen), or placebo. This study was conducted to demonstrate that clemastine in the combination product (in a qid dosing form) would deliver effective allergy relief with the first dose taken. The TheraFlu Sinus treatment arm contains only pseudoephedrine and acetaminophen. Therefore, the primary comparison was between the combination product and TheraFlu Sinus. The placebo group was added to "validate the clinical model". (Volume 39, page 24). The results of this study supported the efficacy of the first dose of the clemastine triple combination product as compared to TheraFlu Sinus for the relief of the Major Symptom Complex.

2 Study HSC-305

2.1 Study Design

Study HSC-305 was a 12-center, double-blind, double-dummy, placebo-controlled, parallel group study carried out during the 1995 fall pollen allergy season in the United States (Utah, Colorado, California, Illinois,

Pennsylvania, Virginia, and New Jersey). After a screening and baseline evaluation, the patients were randomized to either clemastine 0.5 mg qid, clemastine 1.0 mg bid or to placebo for a 2-week double-blind period. Since the study employed a double-dummy design, all patients took study medication four times daily. The study included 5 visits [Day –14 to 1 (screening), 1 (baseline), 4, 8, and 15].

Table 1: Study Design

Visit	0	1	2	3	4
Day	-14 to 1	1 (Baseline)	2-5	6-10	>10[1]

Patients with a history of moderate to severe seasonal allergic rhinitis due to hypersensitivity to fall seasonal pollens were eligible for enrollment. Randomization took place at Visit 1 (Baseline) and the first dose of study medication was taken the same day at approximately 12:00 pm. All patients took study medication four times daily (within one hour of 12:00 pm, 6:00 pm, 12:00 am and 6:00 am). Each day, before taking the 12:00 pm dose of study medication, patients recorded the severity of their nasal and non-nasal symptoms (see Figure 1, below) in their diary cards on a seven-point scale, reflecting how they felt "right now" and "in the last 24 hours."

Figure 1: Symptoms Assessed

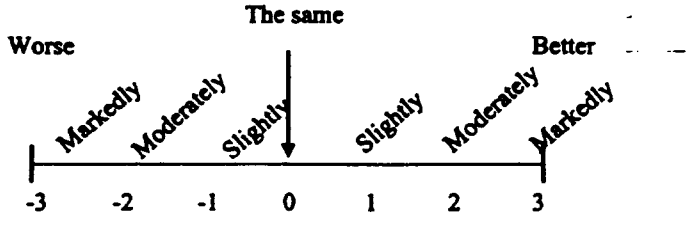
Nasal Symptoms	Non-Nasal Symptoms
Nasal discharge/runny nose	Itchy/burning eyes
Nasal congestion/stuffiness	Tearing/watering eyes
Nasal itching	Redness of eyes
Sneezing	Itching of ears and/or palate

Scale:
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 = Incapacitating

Any rescue medication taken during the previous 24 hours was also recorded on the diary cards.

At each visit, the physician graded the severity of the same symptoms, using the same scale, describing symptoms over the previous 24 hours. Additionally, both the physician and the patient recorded a global evaluation of the patient's response to treatment since the last visit using the scale shown in Figure 2.

Figure 2: Global Evaluation Scale



[1] 109 (90.1%) of patients had 14 days of treatment; 10 (8.3%) had 15 days; 1 (0.8%) had 16 days; and 1 (0.8%) had 17 days.

2.2 *Primary and Secondary Efficacy Endpoints*

2.2.1 Primary Endpoints

The protocol stated that the primary efficacy variables were to be: "nasal discharge/runny nose and sneezing". The sponsor did not specify whether the variables would be compared across groups using a "change" in symptoms or absolute values. Given that there were several different assessments (patient vs. physician, and for the patient: "right now" vs. "over the previous 24 hours"), the description in the protocol of the primary efficacy variables was inadequate. [The sentence specifying the primary variables was located directly beneath the heading "Physician/Patient Assessment", whereas, there was another heading titled "Diary Assessments"; therefore, it is presumed that the diary assessments were not planned to be the primary efficacy assessments.] Further, the sponsor did not state whether the two primary efficacy variables would be totaled, averaged, or treated separately. The description of the *analysis* of the endpoints did not clarify these questions: "each of the efficacy parameters for signs and symptoms, as well as the physician's global evaluation and the patient's global evaluation will be assessed by pairwise comparisons of clemastine 0.5 mg q.i.d. versus clemastine 1.0 mg, and clemastine 0.5 mg versus placebo. For each of the efficacy parameters, pairwise comparisons will be made using Van Elteren's Test," (Volume 36, page 234). The sponsor did not state how missing data would be treated in the analyses.

The planned sample size of the study (n=360) was based on a two-tailed t-test comparing the 0.5 mg qid to the placebo group using the *total nasal symptom score* (sum of the four individual nasal symptom scores). The sponsor did not use the "primary efficacy variables" in determining sample size. One hundred twenty (120) patients per treatment group were needed to have 80% power to detect a difference of 2.0 units in the change from baseline in total nasal symptom score, assuming a standard deviation of 5.5 units and an alpha-level of 0.05.

The sponsor provided the results of the non-parametric Van Elteren tests at each visit, stratified by investigator. Van Elteren's test is a stratified Wilcoxon Rank Sum Test. The ranks within investigative site were calculated, then the results were combined across sites. The sponsor used observed data only for the analysis of each visit. This means that patients who dropped out were excluded from the analyses of the later visits. The numbers and percentages of dropouts across treatment group and the potential impact the missing data had on the results will be investigated in this review.

2.2.2 Secondary Endpoints

Secondary endpoints included:

- physician's and patient's assessments (both "right now" and "over the previous 24 hours") of the individual scores and the total symptom scores;
- physician's and patient's global evaluations at each visit; and
- rescue medication use: percent of patients who took at least 1 dose of Sudafed and percent of patients who took at least 1 dose of Tylenol.

The physician's individual assessments were analyzed using the same methods as the primary efficacy variables. The patient's assessments were averaged in the periods between visits (not explained in protocol) and the average assessments were analyzed using Van Elteren's test. The global evaluations were also analyzed using Van Elteren's Test. Rescue medication use was analyzed using a Cochran-Mantel Haenszel test.

2.3 Results

2.3.1 Study Conduct

Four hundred twelve (Placebo: 140, 0.5 mg qid: 137, 1.0 mg bid: 135) patients were randomized in 12 centers. Of these, 37 (9.0%) discontinued early. The placebo group had the highest percentage of dropouts (12.9%), while the 1.0 mg bid group had the lowest (5.9%), see Table 2, below.

Table 2: Summary of Patient Disposition (Sponsor's Table 9.4-1, Volume 36, page 31)

	Placebo	0.5 mg qid	1.0 mg bid	Combined
Patients Randomized	140	137	140	412
Patients Completed	122 (87%)	126 (92%)	127 (94%)	375 (91%)
Patients Discontinued	18 (13%)	11 (8%)	8 (6%)	37 (9%)
-Adverse event	4	5	6	15
-Failure to return	4	4	2	10
-Did not meet entrance requirements	3	1	0	4
-Treatment failure	6	0	0	6
-Protocol violation	0	1	0	1
Efficacy Population	138	136	134	408
Safety Population	138	136	135	409

2.3.2 Demographics and Baseline Characteristics

The treatment groups were similar with respect to baseline symptom severity and the demographic characteristics: race, age and gender, see Table 3 below.

Table 3: Summary of Patient Demographic and Background Characteristics (Sponsor's Table 9.4-1 Volume 36, page 32)

	Placebo	0.5 mg qid	1.0 mg bid	p-value
Patients Randomized	140	137	135	
Gender, N (%) male	61 (44)	56 (41)	56 (42)	0.91
Race, N (%) Caucasian	120 (86)	113 (83)	116 (86)	0.68
Age, Mean (SD)	33 (12)	33 (10)	33 (11)	0.97
Total Baseline SAR Signs/Symptoms, Mean (SD)				
-Physician's Evaluation	28 (5)	28 (6)	28 (5)	0.59
-Patient's Evaluation, Last 24 hours	28 (6)	29 (6)	28 (6)	0.77
-Patient's Evaluation, Right Now	23 (8)	23 (8)	23 (8)	0.82

2.3.3 Patient Adherence

The sponsor summarized the patient exposure to study medication for the three treatment groups. The study employed a double-dummy design, therefore patients in all three treatment groups took medication four times daily. Compliance to this qid dosing regimen was greatest in the 1.0 mg bid group and least in the placebo group. Summarizing the data in other ways (number of days study medication was taken and average number of doses/day on days taken) demonstrated no differences between the treatment groups, see sponsor's Table 4 below.

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Table 4: Summary of Patient Exposure to Study Medication
(Sponsor's Table 10.1-1, Volume 36, page 33)

	Placebo	0.5 mg qid[1]	1.0 mg bid
Treated Patients with dosing data	138	135	135
N (%) of patients who took study medication qid for at least 13 drug treatment cycles	109 (79.0)	111 (82.2)	119 (88)
Number of days study medication was taken[2], Mean (SD)	13.2 (2.7)	13.6 (2.2)	13.6 (2.4)
Average number of doses/day on days taken, Mean (SD)	3.9 (0.2)	3.9 (0.2)	3.9 (0.2)

[1] Patient #0505 did not return the diary, therefore, only 135 patients from the 0.5 qid group are included in this table.
[2] The days that occurred after a patient dropped out were included in this calculation.

2.3.4 Sponsor's Primary Analysis

The sponsor performed the protocol-specified analysis: Van Elteren's test. The stratification variable (not defined in the protocol) was investigative site. The sponsor performed the test for each visit. Due to dropouts, the sample sizes were smaller and smaller with each subsequent visit. Nine of the 12 analyses yielded p-values < 0.05. Since the sponsor did not specify a primary time point (visit), primary dose comparison, or even a primary symptom (nasal discharge or sneezing), using the usual 0.05 alpha-level to test the significance of the analyses increases the Type I error rate.

Table 5: Sponsor's Analyses of Physician's Assessments of Visit Data
Sneezing and Nasal Discharge Scales: 0-6

		Placebo					0.5 mg qid						1.0 mg bid					
					Mean					Mean						Mean		
Symptom	Visit	N	Mean	SD	Change	SD	N	Mean	SD	Change	SD	p-value	N	Mean	SD	Change	SD	p-value
Nasal	1	138	4.27	0.67			136	4.33	0.75				134	4.31	0.68			
Discharge	2	137	3.57	1.11	**0.70**	1.13	134	2.84	1.23	**1.49**	1.32	<0.001	133	2.78	1.28	**1.53**	1.33	<0.001
	3	134	3.25	1.24	**1.03**	1.24	132	2.87	1.37	**1.45**	1.47	0.022	129	2.81	1.19	**1.51**	1.23	0.002
	4	123	2.75	1.20	**1.52**	1.30	127	2.68	1.33	**1.61**	1.55	0.657	129	2.59	1.23	**1.73**	1.32	0.228
Sneezing	1	138	3.97	0.74			136	3.90	0.85				134	3.91	0.84			
	2	137	3.11	1.29	**0.85**	1.45	134	2.05	1.35	**1.85**	1.35	<0.001	133	2.02	1.21	**1.90**	1.39	<0.001
	3	134	2.75	1.31	**1.21**	1.43	132	1.99	1.39	**1.91**	1.39	<0.001	129	2.32	1.36	**1.60**	1.56	0.028
	4	123	2.29	1.32	**1.65**	1.49	127	1.87	1.45	**2.01**	1.45	0.050	129	1.96	1.33	**1.94**	1.46	0.141

The treatment effects (differences between active treatment and placebo) were between 0.09 and 0.83 units for nasal discharge and 0.29 and 1.05 units for sneezing (both rated on a scale of 0-6). Results were similar for the 0.5 mg qid and 1.0 mg bid groups. The only large differences between clemastine groups were the Visit 4 Nasal Discharge scores (difference with placebo: qid 0.09 vs. bid 0.21) and the Visit 3 Sneezing scores (difference with placebo: qid 0.70 vs. bid 0.39). All of the Visit 2 and 3 clemastine comparisons with placebo had p-values less than or equal to 0.05, while only one of the four Visit 4 analyses did. The sponsor explains the lack of significance for the Visit 4 data using figures of means graphed over time, similar to those provided below.

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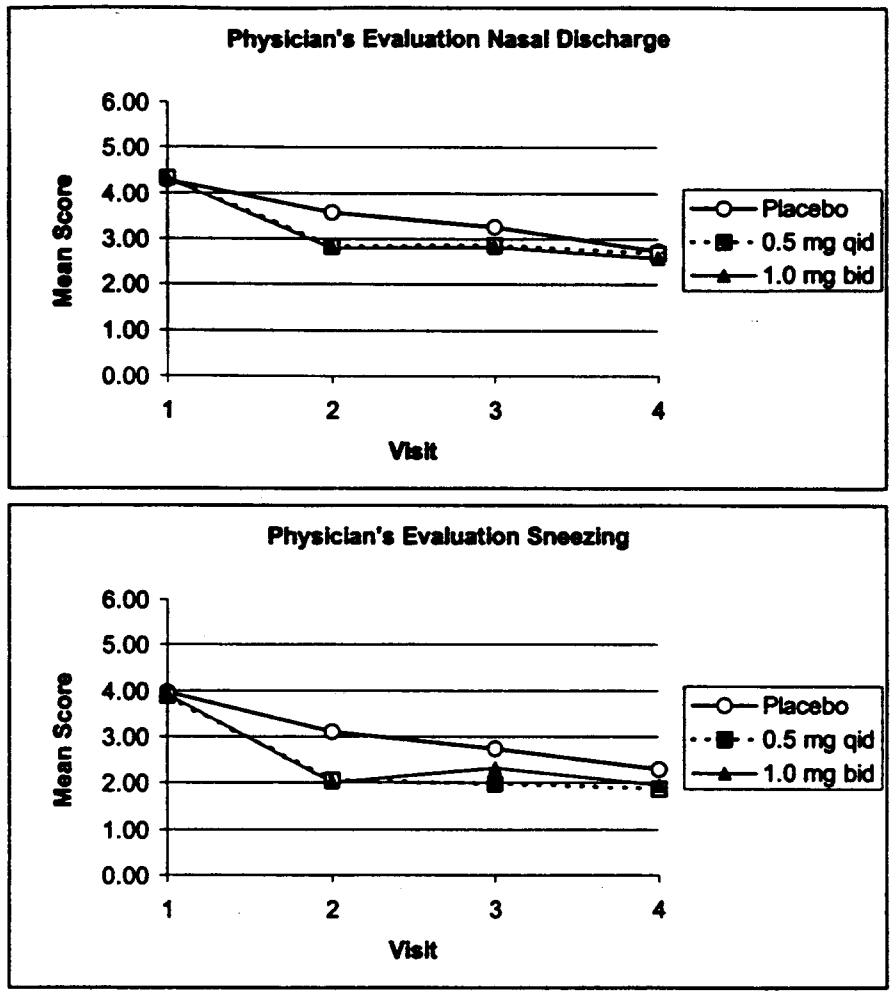
Figure 3: Means of Physician's Evaluation Scores at Each Visit



The sponsor states that, "The figures illustrate the gradual decline of symptoms in the placebo group over the course of 2 weeks. In contrast, the active treatments declined sharply in the first 3 days of treatment, but plateaued [sic] relative to baseline for the remainder of the treatment period. Thus, the lack of statistical significance at Visit 4 is due to the gradual placebo improvement rather than any evident regression in the active groups." -- volume 36, page 34. The improvement of the placebo group is an indication that some unknown factor(s) influenced the symptoms of the placebo patients and may have also influenced the symptoms of the clemastine patients by Visits 3 and 4.

The drug appears to have had an early effect (within 3 days), however, testing the statistical significance of the treatment effect using the usual alpha-level of 0.05 inflates the Type I error rate. The study protocol states that the purpose of the study is to prove that a lower than currently available dose of clemastine (0.5 mg) is safe and effective when given qid. If we assume that the primary dose comparison was 0.5 mg qid versus placebo, the number of possible primary analyses is reduced from twelve to six. If a conservative Bonferroni correction were to be applied, the results would be tested at the 0.0083 level. Of these six analyses, three were statistically significant at the 0.0083 level using the Van Elteren's test: Nasal Discharge Visit 2 and Sneezing Visits 2 and 3.

2.3.5 Sponsor's Secondary Analyses

Individual Symptoms at Visits

The sponsor summarized the results of the physician's assessments of the individual symptoms at each visit, with asterisks (*), unadjusted for multiple comparisons, to signify statistically significant superiority over placebo at the 0.05 level. Both doses were statistically significantly superior to placebo for most symptoms at Visit 2 and for only 3 of the symptoms at Visit 3 (nasal discharge, sneezing, and tearing/watering eyes). There were no consistent statistically significant results at Visit 4. The magnitudes of the treatment differences for the individual symptoms are discussed in more detail in the "Reviewer's Analyses" section (page 12).

Global Evaluations

Both the physician and the patient recorded a global evaluation of the patient's response to treatment since the last visit using the scale [-3 (markedly worse) to +3 (markedly better)]. The sponsor analyzed the results using Van Elteren's Test. The sponsor's results are provided in Table 6 below.

Table 6: Sponsor's Analyses of Physician's and Patient's Global Evaluations

		Placebo			0.5 mg qid				1.0 mg bid			
	Visit	N	Mean	SD	N	Mean	SD	p-value	N	Mean	SD	p-value
Physician	2	137	**0.47**	1.35	134	**1.10**	1.10	<0.001	133	**1.29**	1.19	<0.001
	3	134	**0.57**	1.38	132	**0.58**	1.31	0.764	129	**0.57**	1.32	0.666
	4	123	**0.84**	1.26	127	**0.53**	1.23	0.046	129	**0.85**	1.26	0.873
Patient	2	136	**0.40**	1.37	135	**1.16**	1.15	<0.001	133	**1.18**	1.23	<0.001
	3	134	**0.47**	1.45	132	**0.49**	1.40	0.908	129	**0.50**	1.32	0.739
	4	122	**0.73**	1.33	127	**0.56**	1.28	0.309	128	**0.86**	1.36	0.539

The largest improvements were seen between the first and second visits, for the two clemastine groups. The placebo group improved the most between the third and fourth visits. The greatest treatment differences were seen at the second visit. Using the physician's assessments, the placebo group's improvement between the third and fourth visits was statistically significantly greater than the 0.5 mg qid group's improvement (p=0.046, unadjusted for multiple comparisons). These results correspond well with the results of the sneezing and nasal discharge scores.

Diary Data

The sponsor decided (post-hoc) to summarize all diary data between visits so that the diary scores could be presented in the same format as the physician's scores. Diary data from study Days 2-5 were averaged to yield a value for Visit 2; Days 6-10 were grouped as Visit 3; and all diary data after Day 10 were grouped as Visit 4. The results were similar to those of the physician's assessments, see Tables 7 and 8 below.

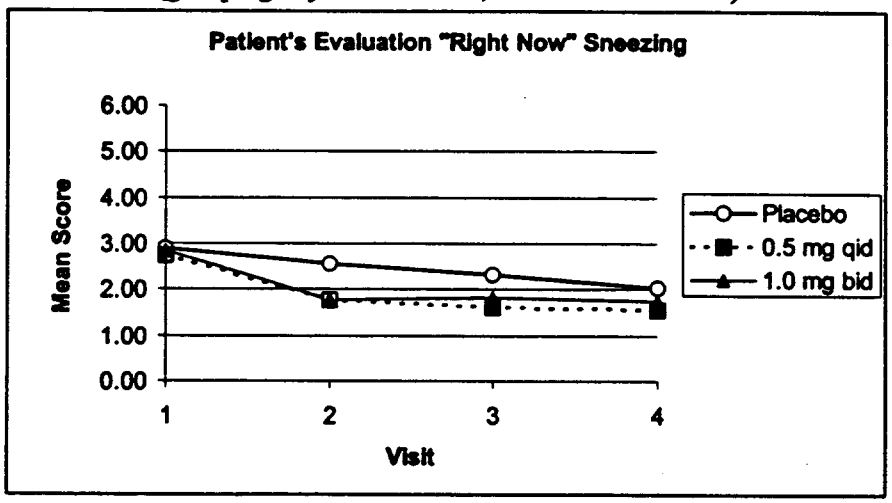
Table 7: Sponsor's Analyses of Patient's Assessments of Visit Data ("Right Now")

"Right Now"		Placebo					0.5 mg qid						1.0 mg bid					
					Mean					Mean						Mean		
Symptom	Visit	N	Mean	SD	Change	SD	N	Mean	SD	Change	SD	p-value	N	Mean	SD	Change	SD	p-value
Nasal	1	138	3.49	1.19			135	3.52	1.30				134	3.46	1.30			
Discharge	2	138	3.03	1.10	**0.45**	1.18	135	2.55	1.20	**0.97**	1.53	0.006	133	2.45	1.18	**1.01**	1.35	<0.001
	3	132	2.81	1.19	**0.67**	1.30	131	2.44	1.22	**1.07**	1.60	0.066	131	2.32	1.27	**1.14**	1.50	0.006
	4	123	2.44	1.22	**0.98**	1.44	126	2.43	1.33	**1.07**	1.68	0.861	128	2.23	1.32	**1.20**	1.65	0.254
Sneezing	1	138	2.89	1.44			135	2.74	1.47				134	2.84	1.45			
	2	138	2.56	1.30	**0.33**	1.30	135	1.78	1.14	**0.96**	1.56	<0.001	133	1.78	1.20	**1.07**	1.42	<0.001
	3	132	2.33	1.30	**0.57**	1.50	131	1.62	1.17	**1.10**	1.68	0.044	131	1.82	1.24	**1.02**	1.46	0.031
	4	123	2.03	1.31	**0.81**	1.55	126	1.56	1.23	**1.16**	1.65	0.188	128	1.74	1.27	**1.10**	1.54	0.274

Table 8: Sponsor's Analyses of Patient's Assessments of Visit Data (Previous 24 Hours)

Previous 24 hrs		Placebo					0.5 mg qid						1.0 mg bid					
					Mean					Mean						Mean		
Symptom	Visit	N	Mean	SD	Change	SD	N	Mean	SD	Change	SD	p-value	N	Mean	SD	Change	SD	p-value
Nasal	1	138	4.25	0.73			135	4.36	0.78				134	4.24	0.82			
Discharge	2	138	3.46	1.03	**0.79**	1.02	135	2.96	1.16	**1.40**	1.32	<0.001	134	2.92	1.09	**1.32**	1.19	<0.001
	3	132	3.18	1.18	**1.08**	1.16	131	2.73	1.25	**1.60**	1.40	0.006	131	2.77	1.20	**1.48**	1.35	0.019
	4	123	2.84	1.19	**1.38**	1.28	126	2.68	1.34	**1.64**	1.51	0.149	128	2.61	1.28	**1.63**	1.46	0.126
Sneezing	1	138	4.02	0.81			135	3.92	0.90				134	3.89	0.90			
	2	138	3.11	1.05	**0.91**	1.14	135	2.25	1.13	**1.67**	1.34	<0.001	134	2.27	1.15	**1.62**	1.28	<0.001
	3	132	2.82	1.26	**1.19**	1.34	131	1.95	1.14	**1.96**	1.33	<0.001	131	2.20	1.27	**1.70**	1.40	0.005
	4	123	2.53	1.24	**1.46**	1.36	126	1.75	1.22	**2.14**	1.33	<0.001	128	2.09	1.23	**1.78**	1.44	0.059

Figure 4: Means of Patient's Evaluations for "Right Now" From Diaries (grouping days into "visits", details in text above)



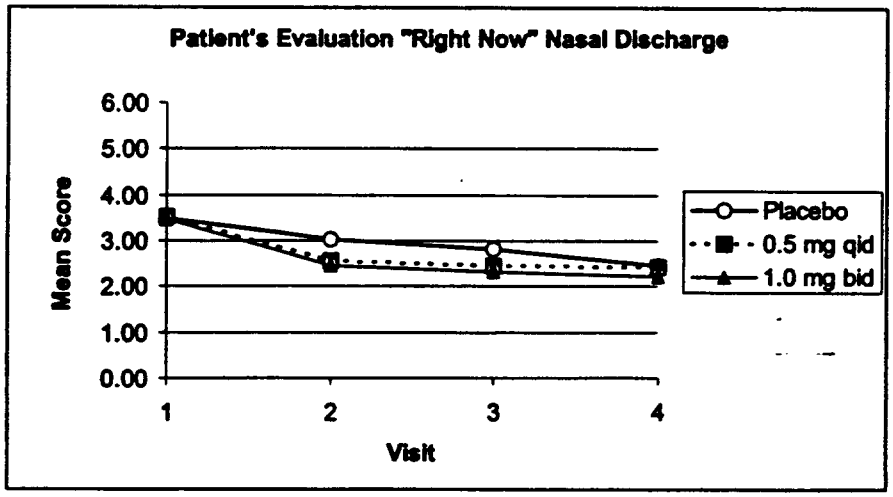
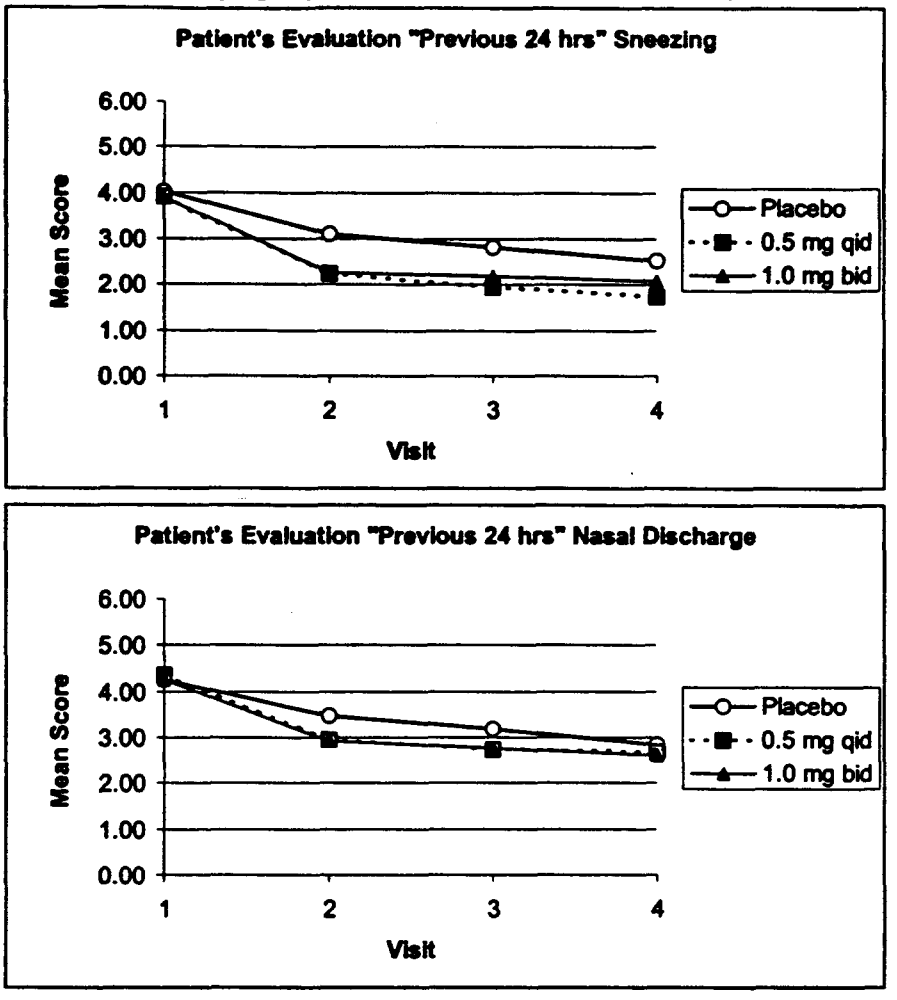


Figure 5: Means of Patient's Evaluations for the Previous 24 Hours From Diaries (grouping days into "visits", details in text above)



2.3.6 Reviewer's Analyses

To investigate the sensitivity of the results to the choice of endpoint and method of analysis used, this reviewer analyzed the diary data using analysis of variance (ANOVA). The diary data were chosen as the endpoint for this reanalysis, because the Division of Pulmonary and Allergy Drug Products (DPADP) typically relies on the analysis of symptom scores in patient diaries to evaluate the efficacy of an SAR drug. The diary data in trials submitted to DPADP are usually analyzed using a parametric method, such as an ANOVA, comparing the mean differences in the change from baseline across treatment groups. For each patient, an average treatment period score is calculated using all the scores the patient recorded while on drug. This average is subtracted from the baseline score to yield a "change from baseline" score. The mean changes are then compared across treatment groups. For the review of this study, if a patient recorded at least one assessment (for a given symptom) during Week 2, the patient was included in the Week 2 analysis. The average of all available data was used.

The results of the total symptom scores (TSS) are provided below; individual symptom score results are in the appendix, Tables A1 and A2, pages 33-34. The results generated using this ANOVA approach support the results and conclusions of the sponsor's analyses. That is, the effect was pronounced in the early part of the trial (Week 1), and deteriorated during Week 2.

Descriptive statistics of the total symptom scores are provided in Tables 9 and 10 below.

Table 9: Diary Data: Sum of all the symptoms (Scale: 0 to 48)

	Baseline					Week 1					Week 2					Weeks 1 & 2				
"Right Now"	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
Placebo	140	23	8			139	19	8			128	16	8			139	18	8		
Clem 0.5 mg qid	135	23	8			135	17	8			128	15	8			135	16	8		
Clem 1.0 mg bid	135	23	8			133	16	8			129	14	9			133	15	8		
"Previous 24 Hours"																				
Placebo	140	28	6			139	22	7			128	19	8			139	20	7		
Clem 0.5 mg qid	135	29	6			135	19	7			128	16	8			135	17	7		
Clem 1.0 mg bid	135	28	6			134	18	8			129	17	8			134	18	8		

Table 10: Diary Data: Mean Changes from Baseline of Sum of all the Symptoms
(Negative values indicate improvement in symptom severity)

	Week 1 Change					Week 2 Change					Weeks 1 & 2 Change				
"Right Now"	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
Placebo	139	-3.6	6			128	-6.4	9			139	-5.0	7		
Clemastine 0.5 mg qid	135	-6.9	9			128	-8.5	10			135	-7.7	9		
Clemastine 1.0 mg bid	133	-7.3	8			129	-8.7	9			133	-8.0	8		
"Previous 24 hours"															
Placebo	139	-6.0	6			128	-9.4	8			139	-7.7	7		
Clemastine 0.5 mg qid	135	-10.0	8			128	-11.9	9			135	-11.1	9		
Clemastine 1.0 mg bid	134	-9.6	8			129	-11.4	9			134	-10.5	8		

As previously observed in the description of the sponsor's results, these results demonstrate that the placebo group continued to improve during Week 2. The qid dosing of clemastine was slightly less effective than the bid dosing for the symptoms "right now," whereas, it was slightly more effective for the symptoms over the "previous 24 hours." The mean differences using the sponsor's analyses of the total symptom scores demonstrated a similar pattern.

This reviewer performed an ANOVA on the mean change from baseline TSS with center and treatment as factors. Six models were run: week 1 average, week 2 average, and weeks 1 and 2 average using the two different assessments ("right now" and "previous 24 hours"). A center-by-treatment interaction term was tested and not found to be statistically significant at the 0.05 level in any of the models. The p-values for the interaction term ranged from 0.12 to 0.19 for 5 of the 6 models, however, the interaction term p-value in one model (Week 2 average "right now") was 0.08, indicating a potential difference in treatment effects across centers. This was investigated and found to be due to three centers with large treatment differences between placebo and the 1.0 mg bid groups (#7 n=14; #3 n=23; #10 n=21), see Figure A1 in the appendix. This reviewer does not consider the differential in treatment effects across centers to be unusual. The results provided below are from models excluding the interaction term.

The results estimated the treatment effect of the qid dosing to be between ——— units, depending on the analysis. The symptom score scale of TSS was 0 to 48. (As stated above, the study was powered to detect a difference of 2.0 units in this score.)

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Table 11: Diary Data ANOVA: Weeks 1 & 2 Average Mean Change from Baseline TSS
Total Symptom Score Scale: 0 to 48
(Treatment and Center as Factors)

"Right Now"	N	LSMean Change	Std Err		(Negative Values indicate Clem qid/bid better) Placebo vs. Clem bid	Placebo vs. Clem qid	(Negative Values indicate Clem qid better) Clem bid vs. Clem qid
Placebo	139	-4.88	0.69	Mean Diff	-3.14	-2.79	0.35
Clem 0.5 mg qid	135	-7.67	0.70	95% CI	(-5.07, -1.21)	(-4.71, -0.87)	(-1.59, 2.30)
Clem 1.0 mg bid	133	-8.03	0.71	p-value	0.0015	0.0046	0.7219
"Previous 24 hours"							
Placebo	139	-7.64	0.65	Mean Diff	-2.84	-3.42	-0.59
Clem 0.5 mg qid	135	-11.06	0.66	95% CI	(-4.67, -1.01)	(-5.25, -1.60)	(-2.43, 1.26)
Clem 1.0 mg bid	134	-10.48	0.67	p-value	0.0024	0.0003	0.5324

Table 12: Diary Data ANOVA: Week 1 Average Mean Change from Baseline TSS
Total Symptom Score Scale: 0 to 48
(Treatment and Center as Factors)

"Right Now"	N	LSMean Change	Std Err		(Negative Values Indicate Clem qid/bid better) Placebo vs. Clem bid	Placebo vs. Clem qid	(Negative Values indicate Clem qid better) Clem bid vs. Clem qid
Placebo	139	-3.54	0.65	Mean Diff	-3.73	-3.31	0.42
Clem 0.5 mg qid	135	-6.85	0.66	95% CI	(-5.54, -1.92)	(-5.12, -1.50)	(-1.41, 2.25)
Clem 1.0 mg bid	133	-7.27	0.66	p-value	0.0001	0.0004	0.652
"Previous 24 hours"							
Placebo	139	-5.98	0.63	Mean Diff	-3.60	-4.02	-0.42
Clem 0.5 mg qid	135	-10.00	0.64	95% CI	(-5.37, -1.83)	(-5.79, -2.26)	(-2.20, 1.36)
Clem 1.0 mg bid	134	-9.58	0.64	p-value	0.0001	0.0001	0.6411

Table 13: Diary Data ANOVA: Week 2 Average Mean Change from Baseline TSS
Total Symptom Score Scale: 0 to 48
(Treatment and Center as Factors)

"Right Now"	N	LSMean Change	Std Err		(Negative Values indicate Clem qid/bid better) Placebo vs. Clem bid	Placebo vs. Clem qid	(Negative Values indicate Clem qid better) Clem bid vs. Clem qid
Placebo	128	-6.34	0.80	Mean Diff	-2.34	-2.11	0.24
Clem 0.5 mg qid	128	-8.45	0.80	95% CI	(-4.56, -0.13)	(-4.32, 0.10)	(-1.97, 2.44)
Clem 1.0 mg bid	129	-8.69	0.80	p-value	0.0378	0.0616	0.8341
"Previous 24 hours"							
Placebo	128	-9.39	0.76	Mean Diff	-1.95	-2.45	-0.50
Clem 0.5 mg qid	128	-11.84	0.75	95% CI	(-4.04, 0.14)	(-4.54, -0.35)	(-2.59, 1.59)
Clem 1.0 mg bid	129	-11.34	0.75	p-value	0.0674	0.0220	0.6408

The results are consistent with those of the sponsor's. The differences between the placebo and clemastine groups were more pronounced during the first week, compared to the second week. There was little difference between the clemastine qid group and the clemastine bid group.

Individual Symptom Score Results

A summary of the results of the analyses on the individual symptom scores is provided in the appendix (Tables A1 and A2). The treatment effects for the qid dosing regimen ranged from ——— units (depending on the symptom and the time period) on a scale of 0 to 6. In general, the treatment effects were larger for the "previous 24 hours" symptom assessments than for the "right now" assessments for the 0.5-qid dosing and

about the same for the 1.0-mg bid dosing. The difference between dosing regimens was small [redacted] units).

The greatest treatment effect was seen for sneezing, then nasal discharge, eye burning and eye tearing. Nasal itching, red eyes and itchy eyes demonstrated smaller treatment effects. The placebo group's nasal itching, eye burning, tearing and red eye symptoms improved greatly during the second week, narrowing the differences between the clemastine groups and placebo.

Clemastine appeared to have had a slightly greater effect on nasal congestion than did placebo. However, the treatment differences for nasal congestion were only significant for the "right now" assessment during the first week for the Clemastine 1.0 bid group.

Gender Analysis

The analysis of variance model was also performed on the two primary efficacy variables to investigate potential differences between genders. There was a statistically significant ($p<0.05$) gender-by-treatment interaction for both Nasal Discharge and Sneezing. The females experienced a greater response to treatment with Clemastine than did the males, and a smaller response to treatment with placebo than did the males. These differences led to statistically significant differences in the treatment effects between males and females for both efficacy variables and both doses, see Table 14 below. Graphs of means over time by treatment group and gender are provided in the Appendix, Figures A2.

Table 14: Gender Differences

	Placebo	*0.5 mg*	*Trt Diff*	*p-value*	*1.0 mg*	*Trt Diff*	*p-value*	*Interaction p-value*
Nasal Discharge								
Male	-0.768	-0.735	**-0.033**	0.8996	-0.782	**0.014**	0.9574	0.0472
Female	-0.575	-1.256	**0.681**	0.0025	-1.367	**0.792**	0.0005	
Overall*			**0.324**			**0.403**		
Sneezing								
Male	-0.744	-0.556	**-0.188**	0.4835	-1.067	**0.323**	0.2310	0.0029
Female	-0.372	-1.396	**1.024**	0.0001	-1.075	**0.703**	0.0026	
Overall*			**0.417**			**0.512**		

* Overall treatment effect with gender-by-treatment interaction in the model

The clinical meaning of these differences across genders is unknown. This internal inconsistency, though potentially due to chance, reduces confidence in the results of this study.

2.3.7 Adverse Events

Safety evaluations included clinical laboratory panels, physical examinations, and adverse event reporting. A greater percentage of patients reported at least one adverse event in the two clemastine groups as compared to the placebo group (0.5 mg bid: 70.6%; 1.0 mg bid: 74.1%; placebo: 65.9%). This was primarily due to two adverse events: somnolence and fatigue (see Table 15 below). Somnolence and fatigue are known side effects of clemastine. After excluding all reports of somnolence and fatigue, the percentages of patients reporting at least one adverse event were similar across treatment groups (0.5 mg bid: 66.1%; 1.0 mg bid 65.9%; placebo: 64.9%).

Table 15: Patients Reporting At Least One Instance of Somnolence or Fatigue

	Placebo	0.5 mg bid	1.0 mg qid
Somnolence	5.8%	17.6%	25.2%
Fatigue	0.7%	8.8%	11.1%

2.4 Conclusions

Study HSC-305 was a double-blind, placebo-controlled, parallel group study that evaluated the safety and efficacy of clemastine 0.5 mg qid vs. clemastine 1.0 mg bid vs. placebo for allergy symptom relief. This two-week study enrolled 412 patients (ages 12 to 67 years) with seasonal allergic rhinitis (SAR), at 12 centers (all located in the USA) during the fall of 1995. The primary efficacy variables were nasal discharge and sneezing. The purpose of the study was to demonstrate the safety and efficacy of the 0.5 mg qid dosing regimen. (The 1.0 mg bid dosing regimen is currently approved and marketed.)

The primary efficacy variables (both in terms of definition and analysis) were not clearly described in the protocol. Using two different analytical approaches to the physician and patient data, the results consistently demonstrated the efficacy of both the bid and qid dosing regimens during the first week of treatment. A mean difference between active treatment groups and placebo of 3.5-4.0 units on a 0-48-point scale was seen during the first week. The placebo group improved during the second week, reducing the mean differences between the clemastine groups and placebo to about 2.0-2.5 units. There was no evidence that either clemastine dosing regimen was more effective than placebo after one week of treatment.

Mean differences across the two clemastine groups were small (-0.10 to 0.13 units) and did not consistently favor one dosing regimen. In general, the mean changes from baseline in the BID dosing regimen group were greater than those in the QID dosing regimen group for the "Right Now" assessments, whereas, the opposite was true for the "Previous 24 hours" assessments.

A statistically significant gender-by-treatment interaction indicated differences in treatment effect across genders. Females experienced large treatment effects, while males had small treatment effects for sneezing and negligible effects for nasal discharge. These gender differences were seen for both dosing regimens. The observed gender differences are puzzling, and may somewhat reduce the confidence that should be placed in the study's results.

3 Study HSC-306

3.1 Study Design

Study HSC-306 was a double-blind, placebo-controlled, parallel group study carried out at two centers during the 1997 fall pollen allergy season in the United States. After a screening visit, the patients were randomized for one day to placebo, the triple combination product, or TheraFlu Sinus Tablets. The triple combination product consisted of: 30 mg pseudoephedrine hydrochloride, 500 mg acetaminophen, and — clemastine fumarate (0.25 mg clemastine) per tablet to be administered as two tablets in a qid dosing regimen. TheraFlu Sinus consists of 30 mg pseudoephedrine hydrochloride and 500 mg acetaminophen per tablet.

The study included three visits (a screening visit, a "day in the park", and a day after the "day in the park"). The screening visit was to be completed no more than 4 weeks prior to the study. Patients between 12 and 65 years of age with a history of moderate to severe seasonal allergic rhinitis due to hypersensitivity to fall seasonal pollens were eligible for enrollment. Patients reported to the outdoor public park facility on a designated day for Visit 2 no later than 6:30 am. The "day in the park" visit for Center #1, Dr. Meltzer (located in San Diego, CA), occurred on 9/6/97. Center #2, Dr. Casale (Papillion, Nebraska), held the "day in the park" visit a week later on 9/13/97. Before being randomized, patients evaluated their symptoms at 7:30 am, 8:00 am, and 8:30 am. A total of fifteen symptoms were evaluated by the patients, using one of three different scales, see Figure 6 below. None of the three scales is the same as the 0-6 scale used in Study 305.

Figure 6: Symptoms and Scoring
(boldface symptoms were those included in the primary efficacy variable "Major Symptom Complex")

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 = 6-9 instances 7 = 10-15 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:	Symptoms rated on this scale:	Symptoms rated on this scale:	
(1) stuffy nose - left (2) stuffy nose - right	(3) nose blows **(4) sneezing**	**(5) itchy nose - left** **(6) itchy nose - right** **(7) runny nose - left** **(8) runny nose - right** (9) sniffles	(10) postnasal drip **(11) watery eyes** **(12) itchy eyes/ears** **(13) itchy throat** (14) cough (15) headache

Eligibility was based on 8 symptoms evaluated at baseline: sneezing, runny nose (right and left), itchy nose (right and left), watery eyes, itchy eyes/ears and itchy throat. The sum of these eight symptoms was called the "Major Symptom Complex" (MSC). The MSC score could range from 0 to 43 units. The sum of the three MSC baseline evaluations (7:30 am, 8:00 am, and 8:30 am) was calculated. This sum could range from 0 to 129 units. The protocol and the study report stated that patients were eligible for enrollment if the *sum of the three MSC baseline evaluations was 18 or more.* The wording in the study report was as follows:

> "Candidates qualified for entry into the study if the sum of the three pretreatment symptom evaluations for the sum of sneezing, runny nose (right and left), itchy nose (right and left), watery eyes, itchy eyes/ears and itchy throat was 18 or more. The three symptom evaluation forms were completed and reviewed by computer for minimum symptom criteria prior to administration of the first dose of study medication."
>
> volume 39, page 36

The cutoff value of 18 seemed low for the sum of the three baseline evaluations and therefore, it was investigated further for this review. The wording in the case report form seemed more indicative of a cutoff of 18 for *each individual evaluation*, not the sum of the three evaluations, "Does the patient have a major symptom complex qualifying score of ≥ 18?" However, in a telecon on March 28, 2000, the sponsor confirmed that the intent of the question was to be the sum of the three evaluations.

Patients eligible for enrollment were randomized to one of the three treatment groups: Clemastine Triple Combination (CTC), TheraFlu Sinus, or placebo. The first dose was to be taken at 9:00 am. Patients evaluated symptoms seven times before the next dose at 3:00 pm - at 30 minutes post dose, 1 hour post-dose and every hour thereafter. A standard meal was provided at noon. At 3:00 pm, patients took the second dose of study medication. Patients completed two more evaluations (at 4:00 pm and 5:00 pm) before leaving the park. Four more evaluations were completed at home (at 6:00 pm, 7:00 pm, 8:00 pm, and 9:00 pm). Figure 7 below is a summary of the schedule of the day.

Figure 7: Schedule of "Day in the Park" Visit (Visit #2)

	Events	Assessments
6:00 AM		
	Patients Arrive	
7:00 AM		
		1st baseline
8:00 AM		2nd baseline
		3rd baseline
9:00 AM	Dose #1 Taken	
		30 min post-dose
10:00 AM		1 hr post-dose
11:00 AM		2 hr post-dose
12:00 PM	Meal served	3 hr post-dose
1:00 PM		4 hr post-dose
2:00 PM		5 hr post-dose
3:00 PM	Dose #2 Taken	6 hr post-dose
4:00 PM		1 hr post-dose
5:00 PM	Patients leave park	2 hr post-dose
6:00 PM		3 hr post-dose
7:00 PM		4 hr post-dose
8:00 PM		5 hr post-dose
9:00 PM		6 hr post-dose

Adverse events or side effects were not recorded on the evaluation forms. At the bottom of each form, there was a question: "Do you have any other problems?", with no room for an answer. Underneath the question, the form stated, "If yes, please tell the study staff."

Patients reported back to the investigator the following day for Visit 3. Patients turned in their symptom evaluation forms for the previous night's assessments. In addition, they answered questions regarding adverse events and the use of any concomitant medications, and rated the global "effectiveness of the treatment" on the following scale (0: Poor, 1: Fair, 2: Good, 3: Very Good, 4: Excellent).

3.2 Primary and Secondary Efficacy Endpoints

3.2.1 Primary Endpoint

The protocol stated that the "pivotal efficacy variable will be the average reduction from baseline in MSC scores over Hours 2-5, as an absolute value and as a percentage of the baseline MSC score". (Volume 40, page 11). This can be interpreted two different ways: Hours 2-5 of the study day, or Hours 2-5 *postdose*. The study report presents the results for "Hours 2-5 postdose". Therefore, the sponsor performed four "primary" analyses:

1. Hours 2-5 after the 9 am dose as an absolute value;
2. Hours 2-5 after the 9 am dose as a percentage;
3. Hours 2-5 after the 3 pm dose as an absolute value; and
4. Hours 2-5 after the 3 pm dose as a percentage.

The protocol defined MSC as the sum of eight symptoms: sneezing, runny nose (right and left), itchy nose (right and left), watery eyes, itchy eyes/ears and itchy throat, counting itchy nose-left separate from itchy nose-right and runny nose-left separate from runny nose-right. The eligibility of the patients was based on MSC counting the right and left symptoms separately. However, the statistical group at Novartis averaged the right and left symptoms for runny nose and itchy nose for a combined total of six symptoms. The impact that this *post-hoc* modification had on the results was negligible (analyses of both definitions are provided in the results section.)

The primary analysis population was to be the intent-to-treat population (ITT). An analysis of covariance (ANCOVA) was the planned primary analysis, with main effects of treatment and center, a baseline covariate and all two-way interactions. The protocol stated that "interactions with treatment may be removed from the model if they are not statistically significant and seriously distort the comparison of the treatment Least Squares Means (LSMeans)", Volume 40, page 82. The sponsor expected TheraFlu Sinus to reduce MSC by an average of 30% below baseline during the hours 2-5 postdose, with a standard deviation of 35%. With 300 patients, the study had 80% power to detect a difference of 12.8% between CTC and TheraFlu Sinus (CTC: 42.8%; TheraFlu Sinus: 30%).

The sponsor provided details in the protocol regarding the actions that would be taken in the event of missing data. A summary of the procedures is as follows (from Volume 40, page 81):

(1) If a missing value is bordered by two non-missing values, the missing assessments will be replaced by the average of the two non-missing assessments.
(2) If a patient is missing data due to early termination of the study then:
    a. If the patient discontinued due to "treatment failure" or if the patient used an antihistamine on the day of the study, all missing values after the final assessment will be imputed using the maximum of the final assessment and the last predosing assessment.
    b. If the patient discontinued due to other reasons, "ad hoc methods will be used to impute all missing assessments after the final assessment, with attention given to the impact on final study results". (The sponsor did not explain what was meant by "ad hoc methods".)

3.2.2 Secondary Endpoints

Secondary endpoints were:

- Average reduction from baseline (ARFB) over hours 1-6 for MSC after each dose;
- ARFB over hours 2-5 for Total Symptom Score (TSC) after each dose (TSC is defined as MSC + nose blows, sniffles, post-nasal drip and cough);
- ARFB over hours 1-6 for TSC after each dose;
- Timepoint-by-timepoint comparisons of MSC;
- Timepoint-by-timepoint comparisons of TSC;
- Timepoint-by-timepoint comparisons of the individual symptoms, as well as headache and stuffy nose (which are not incorporated into MSC or TSC); and
- Global assessment of efficacy

All comparisons were to be done both as absolute values and as percent of baseline. The global assessment of efficacy was to be analyzed with an ANOVA (main effects of treatment, center and treatment-by-center interaction). All of the other secondary endpoints were to be analyzed using the same model as used for the primary endpoint.

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3.3.1 Study Conduct

Two hundred ninety eight patients were randomized (Center #1: 157; Center #2: 141). Only 4 patients (1.3%) did not complete the study. No patients used concomitant antihistamine medication during the study. Although not explicitly stated in the study report or protocol, it appears that the sponsor used a 2:2:1 (CTC: TheraFlu Sinus: Placebo) randomization scheme.

Table 16: Summary of Patient Disposition (Sponsor's Table, Volume 39, page 17)

	Placebo	TheraFlu Sinus	CTC	Total
Patients Entered				
Center 1 (Meltzer: San Diego, CA)	32	63	62	157
Center 2 (Casale: Papillion, NE)	29	56	56	141
Total	61	119	118	298
Discontinuations				
Withdrew Consent			1	1
Uncooperative (failed to return for Visit 3)			2	2
Could not swallow medication		1		1
Completed Study	61	118	115	294

Center #1 Problem

One month after this study ended, it was learned that a patient from Center #1 was participating in another allergic rhinitis clinical study at the same time as this study. This patient was included in all of the sponsor's and reviewer's analyses.

Center #2 Problem

Center #2 experienced delays due to verification of inclusion/exclusion criteria, review of current medications, and collection of baseline allergy symptom evaluations. Consequently, 36 patients received the first dose of their study medication 15-30 minutes late (Placebo: 8; T-F Sinus: 14; CTC: 14). They recorded their assessments on time, regardless of their dose times. The distribution of patients who received the medication late was proportionally comparable to the numbers randomized in each treatment group.

3.3.2 Demographics and Baseline Characteristics

The treatment groups were similar with respect to baseline symptom severity, gender, age and race, see Table 17 below.

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Table 17: Demographic and Baseline Characteristics
MSC Scale: 0-33
TSC Scale: 0-56

Variable	Placebo N=61	T-F Sinus N=119	CTC N=118
N Male (%)	30 (49%)	47 (39%)	58 (49%)
N Caucasian (%)	50 (82%)	100 (84%)	92 (78%)
Age: Mean (Range)	29 (12-62)	28 (12-56)	28 (12-62)
Major Symptom Complex[1,2]: Mean ± SD	13.0 ± 5.9	14.0 ± 6.1	12.7 ± 6.1
Total Symptom Complex[1,3]: Mean ± SD	20.9 ± 9.7	23.7 ± 10.0	21.4 ± 9.9

1. The sponsor stated in a telecon on March 28, 2000 that the means in this table reflect the mean of the average of the three pre-treatment assessments for each patient (not the sum). Eligibility was based on the sum. Further, as stated in the study report, the right and left itchy and runny nose symptoms were averaged to yield one value for itchy nose and one value for runny nose.
2. Major Symptom Complex (MSC), scale 0-33: sum of sneezing, runny nose (right and left), itchy nose (right and left), watery eyes, itchy eyes/ears and itchy throat.
3. Total Symptom Complex (TSC), scale 0-56: MSC + nose blows, sniffles, post-nasal drip and cough.

The baseline symptom scores were greater at Center #1 (Meltzer) than at Center #2 (Casale), see Table 18 and Figure 8, below. The sponsor compared the mean baseline MSC severity scores by investigator and found the difference to be statistically significant ($p<0.001$). However, the treatment-by-center interaction was not statistically significant (reviewer's analysis $p=0.2227$), meaning that differences across treatments were consistent between centers. As mentioned previously, some of the patients at Center #2 received their first dose of study medication late and therefore their baseline symptoms may have reflected more time in the park. However, this extra time should have caused the mean score at Center #2 to be higher, not lower. Pollen and possibly mold counts might help to explain the higher symptoms at Center #1 (although patients with seasonal allergic rhinitis are not necessarily sensitive to mold). Pollen and mold counts were recorded at both sites, beginning one week before and continuing until two days after the study, see Table 19, below. According to a scale used by the National Allergy Bureau (Table 20), the weeds and grasses pollen counts at Center #1 were in the low to moderate range and the mold counts were in the low range. Center #2 had weeds and mold counts in the high range. Center #1 (with the lower counts) had the greater mean baseline symptom scores. Therefore, the pollen and mold counts cannot be used to help explain the statistically significant difference in baseline symptom severity between the two sites.

Table 18: Mean Baseline Scores for Major Symptom Complex (MSC) and Total Symptom Complex (TSC) by Center

	MSC			TSC		
	Placebo	CTC	T-F Sin	Placebo	CTC	T-F Sin
Center #1 (Meltzer: San Diego, CA)	15.5	14.3	15.6	24.4	23.3	25.7
Center #2 (Casale: Papillion, NE)	10.3	11.0	12.2	17.1	19.4	21.4

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Figure 8: Histograms of Baseline MSC Scores by Center and Treatment Group
(Baseline was calculated as an average of the three pre-treatment assessments)

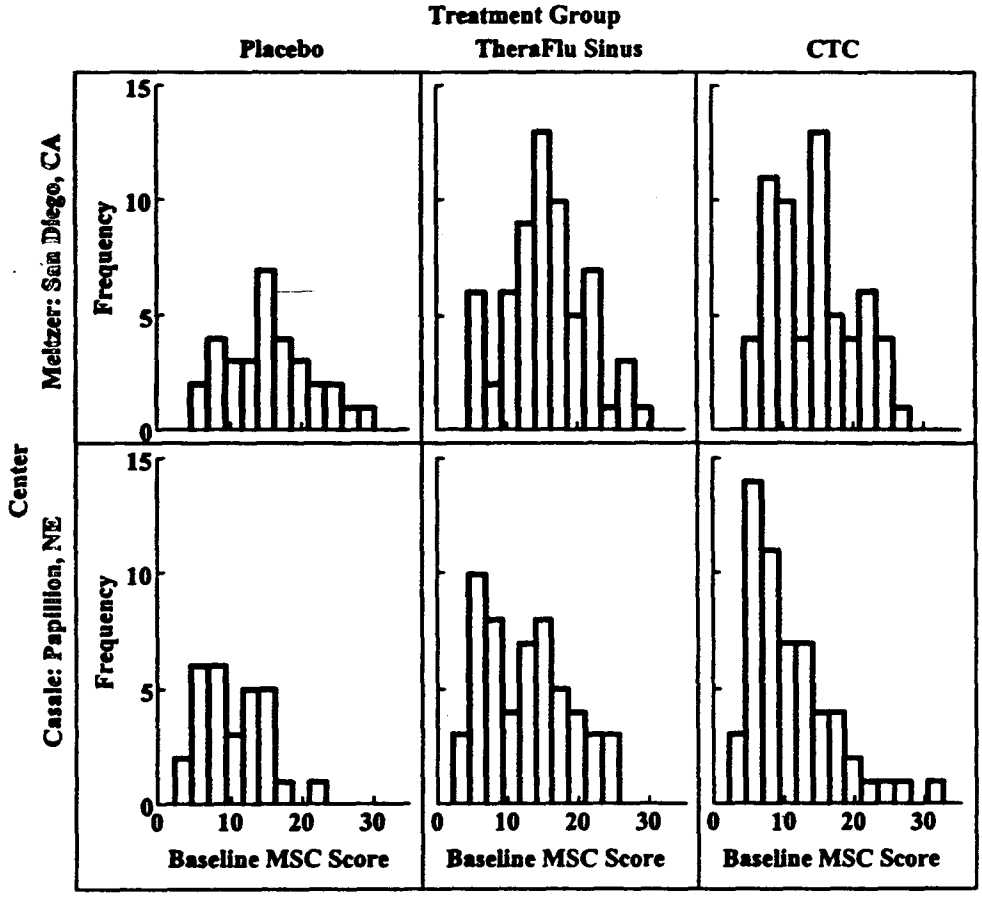

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Table 19: Pollen & Mold Counts (per cubic meter) During Week Before And Two Days After Day in the Park

	Date	Fall Weed	Total Grass	Total Molds
Center #1 (Meltzer: San Diego, CA)	8/30/97	7	3	700
	8/31/97	7	3	700
	9/1/97	7	3	700
	9/2/97	14	17	587
	9/3/97	12	15	687
	9/4/97	4	6	403
	9/5/97	2	6	681
	9/6/97	2	6	681
	9/7/97	2	6	681
	9/8/97	1	4	706
		Ragweed	Total Weed	Total Molds
Center #2 (Casale: Papillion, NE)	9/6/97	202	260	2631
	9/7/97	ND	ND	ND
	9/8/97	ND	ND	ND
	9/9/97	ND	ND	ND
	9/10/97	52	88	7824
	9/11/97	87	147	3861
	9/12/97	98	141	2252
	9/13/97	105	156	3358
	9/14/97	74	90	2654
	9/15/97	58	89	ND

ND: Not Done due to power outage

Table 20: National Allergy Bureau Scale (www.aaaai.og/nab/reading.stm)

Allergen	Category			
	Low	Moderate	High	Very High
Weeds	>0-10	10-50	50-500	>500
Grasses	>0-5	5-20	20-200	>200
Trees	>0-15	15-90	90-1500	>1500
Molds	>0-2500	2500-25000	>25000	

3.3.3 Sponsor's Primary Analysis

The sponsor performed the protocol-specified analyses: ANCOVA on the change from baseline MSC scores over the period of hours 2-5 post-dose using both "absolute value" and "percentage of the baseline MSC score". As mentioned above, the sponsor's calculation of the MSC score in the primary analysis was different from the protocol definition. The sponsor averaged runny nose-right and runny nose-left to form one symptom; the same was done with itchy nose-right and itchy nose-left. The original definition used the right and left symptoms separately, thus the protocol-defined MSC score places more (double) weight on runny nose and itchy nose. The sponsor argues that "itchy nose and runny nose were the most powerful of the symptoms in the MSC for showing the superiority of CTC over T-F Sinus and placebo" and "since CTC has been shown to be significantly superior to T-F Sinus and placebo using MSC as computed by the statistical group, it follows that it would be even more superior if it were computed with the method of the sites," (Volume 39, page 57). The results of the individual symptoms will be discussed in detail in Section 3.3.5 (Reviewer's Analyses). In general, the runny nose and itchy nose scores were not necessarily, as the sponsor states, the "most powerful" of the symptoms for showing the superiority of CTC over T-F Sinus. Further, the variability introduced by the

runny nose and itchy nose scores may have been greater had the sponsor used the protocol definition of MSC. Therefore, DPADP requested that the sponsor re-analyze the data using the protocol definition of the MSC score, fax dated 4/25/00. Both sets of analyses are provided below.

Center and treatment were factors and baseline was a covariate in the model. The sponsor averaged the three baseline assessments to yield one baseline value for each patient. Using the *post-hoc* definition of MSC, with the exception of Baseline-by-Treatment and Baseline-by-Center for the absolute change from baseline over hours 2-5 after *the second dose*, none of the two-way interactions were statistically significant (tested at a conservative alpha-level of 0.25). Using a model with all three two-way interactions, (baseline-by-treatment, baseline-by-center, and treatment-by-center), the p-values of the baseline-by-treatment and baseline-by-center interactions for the second dose (using the absolute change from baseline) were 0.0855 and 0.0375, respectively. A model excluding the baseline-by-treatment interaction still yielded a statistically significant effect for the baseline-by-center interaction term (p=0.0473). The significant baseline-by-*center* interaction means that the influence of baseline on outcome differs between centers. The significant baseline-by-*treatment* interaction means that the influence of baseline on outcome differs between treatment groups. Another way to interpret this second interaction is to say that the treatment effect (difference between groups) differs depending on how severe the symptoms are. The interpretation of these interactions will be discussed further in the reviewer's analysis section.

Since the baseline-by-treatment interaction distorts the estimate of the treatment effect, the sponsor performed the primary analyses excluding this term from the model. As per the protocol, the sponsor kept the remaining two-way interactions in the model (baseline-by-center and treatment-by-center). The primary analysis was performed for this review excluding all 2-way interactions and the results were similar (see Appendix Table A5). The results of the sponsor's analyses are presented in Tables 21-22 below.

As in Study 305, the sponsor calculated change from baseline as baseline minus treatment period, therefore the means of the changes are positive, even though the symptoms decreased.

Table 21: Sponsor's Analyses of MSC Scores Over Hours 2-5 Postdose
MSC: sum of sneezing, runny nose, itchy nose, watery eyes, itchy eyes/ears & itchy throat
Scale: 0 to 33 units
ANCOVA: center and treatment as factors, baseline as a covariate;
and the interactions baseline-by-center & treatment-by-center
Post-hoc Definition of MSC

	Absolute Value Change from Baseline						**Percentage Reduction from Baseline**					
	Dose 1			Dose 2			Dose 1			Dose 2		
	N	LSMean	SE	N	LSMean	SE	N	LSMean	SE	N	LSMean	SE
Placebo	61	4.9	0.6	61	5.7	0.6	61	36.4	5.0	61	42.4	4.8
T-F Sinus	118	4.9	0.4	118	6.0	0.4	118	34.2	3.6	118	43.4	3.5
CTC	118	6.6	0.4	117	8.4	0.4	118	50.0	3.6	117	63.7	3.5
	Difference		p-value	Difference		p-value	Difference		p-value	Difference		p-value
CTC vs. T-F	**1.73**		0.002	**2.39**		<0.001	**15.79**		0.002	**20.35**		<0.001
CTC vs. Placebo	**1.71**		0.013	**2.71**		<0.001	**13.64**		0.023	**21.3**		<0.001
T-F vs. Placebo	**-0.02**		0.971	**0.32**		0.657	**-2.15**		0.72	**0.95**		0.871

Table 22: Sponsor's Analyses of MSC Scores Over Hours 2-5 Postdose
MSC: sum of sneezing, runny nose, itchy nose, watery eyes, itchy eyes/ears & itchy throat
Scale: 0 to 43 units
ANCOVA: center and treatment as factors, baseline as a covariate;
and the interactions baseline-by-center & treatment-by-center
Protocol Definition of MSC*

	Absolute Value Change from Baseline						**Percentage Reduction from Baseline**					
	Dose 1			Dose 2			Dose 1			Dose 2		
	N	LSMean	SE	N	LSMean	SE	N	LSMean	SE	N	LSMean	SE
Placebo	61	6.6	0.8	61	7.6	0.8	61	36.8	4.7	61	42.1	4.8
T-F Sinus	118	6.7	0.5	118	8.3	0.6	118	35.3	3.4	118	44.7	3.4
CTC	118	9.0	0.5	117	11.4	0.6	118	51.3	3.4	117	64.4	3.5
	Difference		p-value	Difference		p-value	Difference		p-value	Difference		p-value
CTC vs. T-F	**2.25**		0.003	**3.09**		<0.001	**15.95**		<0.001	**19.69**		<0.001
CTC vs. Placebo	**2.38**		0.009	**3.79**		<0.001	**14.48**		0.011	**22.34**		<0.001
T-F vs. Placebo	**0.13**		0.891	**0.7**		0.462	**-1.47**		0.797	**2.65**		0.646

* The protocol definition of MSC counted itchy nose-left separate from itchy nose-right and runny nose-left separate from runny nose-right.

The primary comparison was between CTC and TheraFlu Sinus. As mentioned previously, the study was powered to detect a difference of 12.8% between CTC and TheraFlu Sinus (CTC: 42.8%; TheraFlu Sinus: 30%). Using either the protocol-definition or the post-hoc definition of MSC, the study demonstrated a difference of >12.8% for both the 9 am and 3 pm doses. Even with a conservative Bonferroni correction for the four different analyses (adjusted alpha-level = 0.0125), all four analyses yielded statistically significant results. As expected, TheraFlu Sinus had about the same effect as placebo on the MSC score.

3.3.4 Secondary Analyses

TSC and Individual Symptom Scores
The sponsor analyzed the MSC, TSC and individual symptom scores at each timepoint and over hours 2-5 and 1-6. The sponsor used an ANOVA for the individual symptom scores instead of the protocol-defined ANCOVA. (This reviewer performed the ANCOVA and the results are discussed in the reviewer's section.) The sponsor summarized the results of the secondary efficacy variables in a table using symbols (* and #) to signify statistically significant superiority over T-F Sinus and placebo, respectively. In general, the differences between the T-F Sinus and CTC groups were statistically significant at most timepoints for Itchy Nose, Runny Nose, Watery Eyes, Itchy Throat, and Postnasal Drip and at very few timepoints for Sneezing, Cough, Headache, Sniffles and Stuffy Nose. The results using the protocol-specified ANCOVA model in the reviewer's analyses section provide more detail regarding the magnitude of the treatment effects for each individual symptom.

Global Evaluations
At Visit 3, the patients were asked to assess the efficacy of their treatment using a five-point rating scale (0=poor to 4=excellent). The patients answered the question without reference to their allergy symptom evaluation forms. The results are provided in Table 23 below. The mean score for CTC, while statistically significantly different from placebo and TheraFlu Sinus (using alpha=0.05), was only 2.38 units. A score of "2" corresponded to: "Good".

Table 23: Patient Global Evaluations

	Placebo	TheraFlu Sinus	CTC
N	60	118	115
Mean ± SE	1.66 ± 0.15	2.04 ± 0.11	2.38 ± 0.11

Responder Analyses

In addition, the sponsor performed a "responder" analysis (not defined in the protocol). The sponsor calculated the number and percent of patients achieving a 25%, 33% and 50% reduction from baseline in MSC over hours 2-5 following each dose of study medication, see Tables 24-25, below.

Table 24: Percent of Patients Who Achieved at Least a 25%, 33% or 50% Reduction in MSC Scores Over Hours 2-5 After Dose 1

	At least 25% Reduction			At least 33% Reduction			At least 50% Reduction		
	Placebo	T-F Sinus	CTC	Placebo	T-F Sinus	CTC	Placebo	T-F Sinus	CTC
Meltzer	68.8	65.1	83.9	59.4	60.3	74.2	28.1	39.7	61.3
Casale	65.5	63.6	75.0	55.2	56.4	75.0	48.3	41.8	55.4
Total	**67.2**	**64.4**	**79.7**	**57.4**	**58.5**	**74.6**	**37.7**	**40.7**	**58.5**

Table 25: Percent of Patients Who Achieved at Least a 25%, 33% or 50% Reduction in MSC Scores Over Hours 2-5 After Dose 2

	At least 25% Reduction			At least 33% Reduction			At least 50% Reduction		
	Placebo	T-F Sinus	CTC	Placebo	T-F Sinus	CTC	Placebo	T-F Sinus	CTC
Meltzer	75.0	79.4	96.8	65.6	74.6	90.3	50.0	55.6	80.6
Casale	72.4	69.1	80.4	65.5	56.4	75.0	41.4	43.6	62.5
Total	**73.8**	**74.6**	**89.0**	**65.6**	**66.1**	**83.1**	**45.9**	**50.0**	**72.0**

As expected, since symptoms continued to decrease after the second dose, greater percentages of patients met the definition of response after Dose 2 than after Dose 1. Greater percentages of CTC patients than T-F Sinus patients were "responders" after both doses using all three definitions of "responder". In general, the differences between treatment groups in percent of responders were more marked at Dr. Meltzer's clinic (Center #1), see the graphs in Figure 9, below. However, the sizes of the differences do not appear to be unusual for two centers in two different states at two different times.

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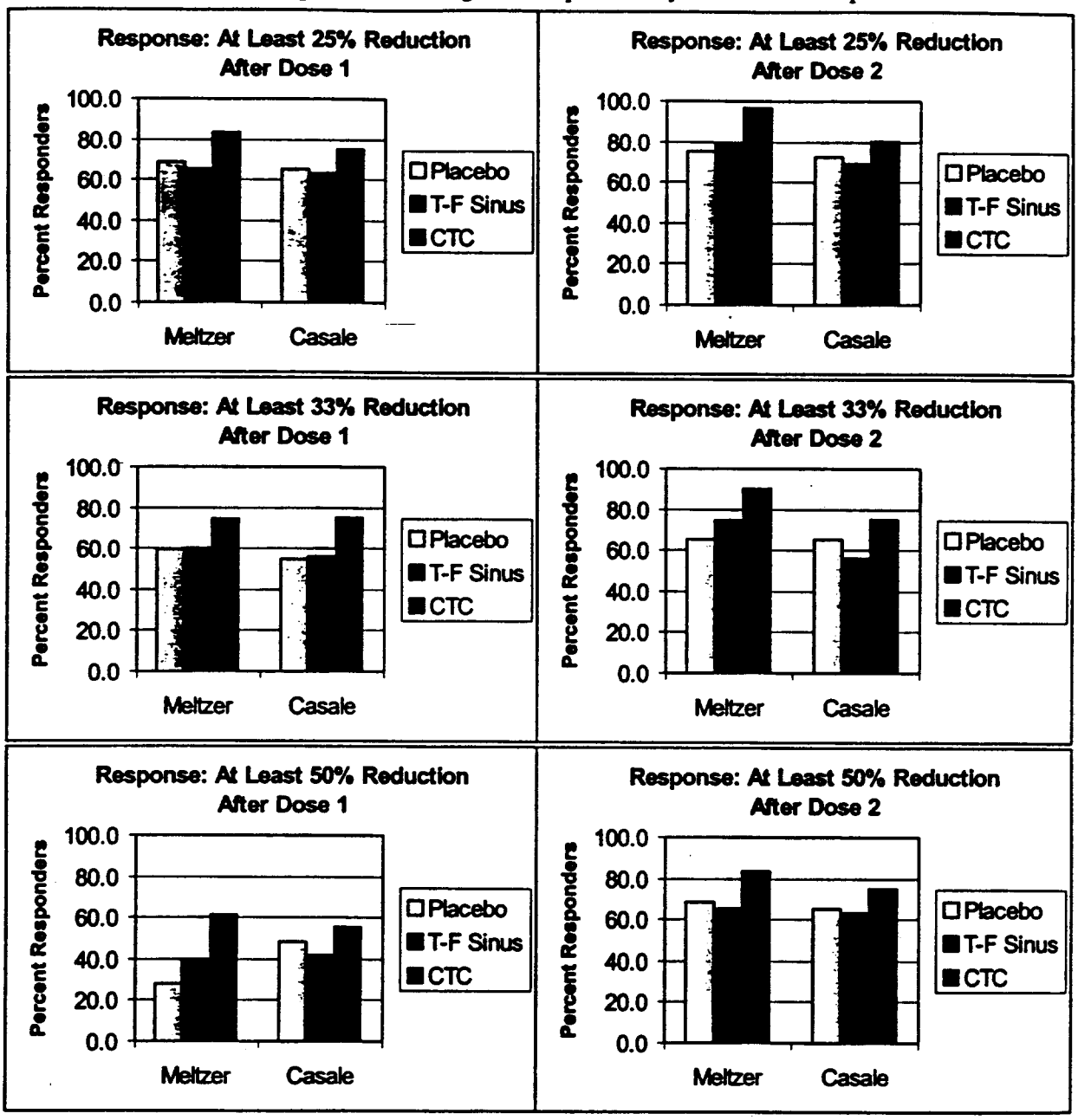
Figure 9: Percentages of Responders By Treatment Group



Onset of Action

The sponsor estimated the onset of action of CTC to be about 2 hours comparing CTC to Placebo and about 30 minutes comparing CTC to TheraFlu Sinus. The results of the ANCOVA models at the early timepoints are presented in the reviewer's section (and Appendix Tables A3-A5) and demonstrate similar findings. The TheraFlu Sinus group performed poorly compared to placebo in the first 2 hours. The placebo group was statistically significantly superior (using alpha=0.05) to TheraFlu Sinus at 30 minutes for several symptoms: sneezing, runny nose, sniffles, and nose blows, and the MSC and TSC scores. The placebo group was also statistically significantly superior (using alpha=0.05) to *CTC* at 30 minutes for one symptom (runny nose), and the symptom complexes MSC and TSC.

The label on the box states that the product provides ——————— " of

- Sinus congestion and pressure;

- Runny nose and sneezing;
- Itchy, watery eyes;
-
- Itchy throat.

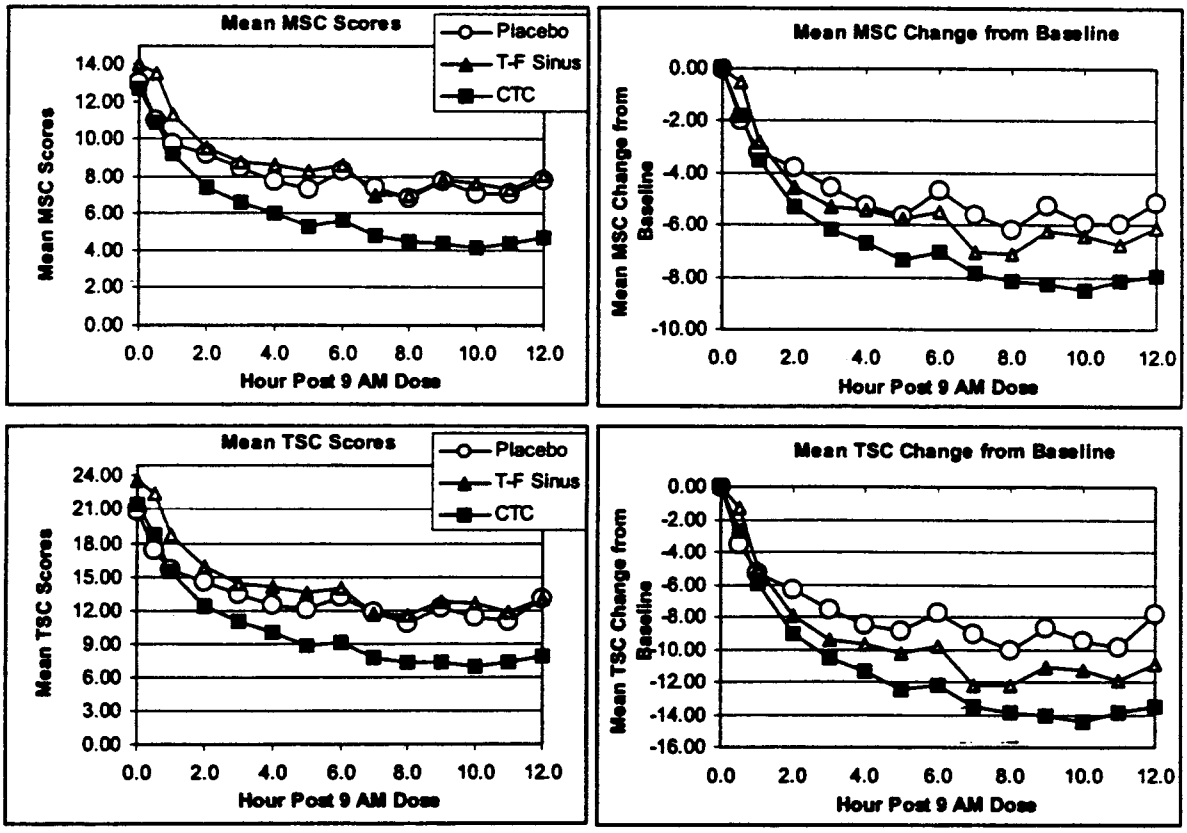
The results of the reviewer's analyses (Appendix Table A3-A5) do not demonstrate statistically significant differences between CTC and placebo (at alpha=0.05) for stuffy nose until after Hour 2. The CTC means of the endpoints: number of sneezes, itchy eyes, and watery eyes were equally slow to improve, as compared to both placebo and TheraFlu Sinus. Statistically significant results were seen for Runny Nose, comparing CTC to placebo and CTC to TheraFlu Sinus at 2 hours post the first dose. Similarly, statistically significant results were seen at 2 hours for Headache, comparing CTC to placebo.

3.3.5 Reviewer's Analyses

Graphs

Mean MSC and TSC scores are graphed in Figure 10 below. Notice that the mean symptoms of the TheraFlu Sinus group were slightly greater at baseline than the other two groups. Over the course of the day, the mean symptom scores of the TheraFlu Sinus group were similar to those of the Placebo group. The CTC group had lower mean symptoms throughout the day.

Figure 10: Mean and Mean Changes in MSC And TSC Scores At Each Hour



Primary Endpoint

This reviewer investigated the significant interaction effects in the primary analysis (MSC scores over hours 2-5 after the 3 pm dose). The two significant interactions were: 1) baseline-by-center; and 2) baseline-by-treatment.

As stated above, the significance of the baseline-by-center interaction means that the influence of baseline on outcome differs between *centers*. The significance of the baseline-by-treatment interaction means that the influence of baseline on outcome differs between *treatment groups*. As the placebo group was only included in the study to "validate the study", these interactions were tested again using only the CTC and T-F Sinus groups. The results were similar. The baseline-by-center interaction was still apparent, but somewhat less significant ($p=0.1226$, in a model with center, treatment, baseline and baseline-by-center). However, the baseline-by-treatment interaction reached a level of significance comparable to the results for the full model that included all three treatment groups ($p=0.0421$, in a model with center, treatment, baseline and baseline-by-treatment). These interactions can be more easily understood using graphs, explained below.

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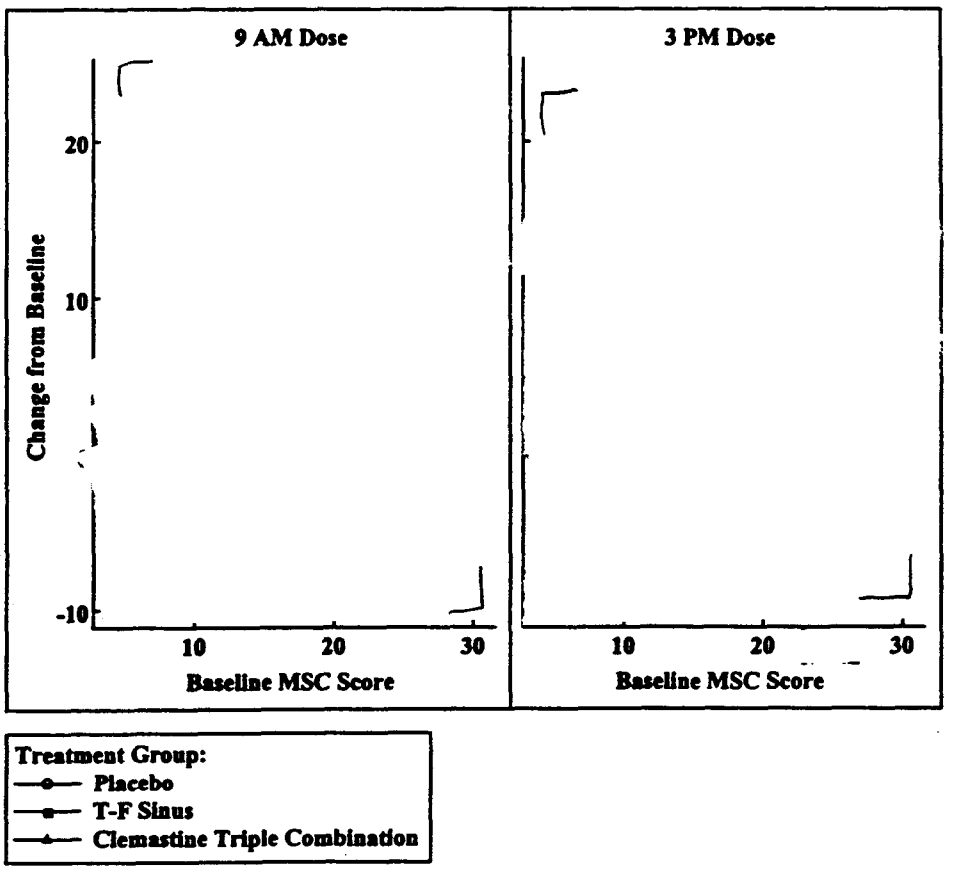
Baseline-By-Treatment Interaction

Figure 11, below, depicts two scatterplots of Average Baseline MSC score vs. Change from Baseline MSC Score averaged over hours 2-5. The data for the two different doses (9 am and 3 pm) are graphed separately. Regression lines for each treatment group are fitted to the data within each graph. To remain consistent with the sponsor's analyses, all change scores were calculated by subtracting the treatment period score from the baseline score. Thus, improvement in symptoms yielded a positive change score. The change from baseline increased with increasing baseline symptom severity. The baseline scores ranged from [redacted] units and the change scores ranged from [redacted] units. The primary comparison is between CTC and T-F Sinus. The CTC fitted line in the graphs is black, and has the steepest slope. The lines in both graphs start close to each other when baseline is low and separate more as baseline increases. The baseline-by-treatment interaction is more pronounced in the graph on the right. For patients with very low baseline severity scores (< 4 units), the CTC patients' symptoms improved little more than the placebo and T-F Sinus groups' symptoms; whereas, for patients with greater baseline symptom severity, the CTC patients' symptoms improved much more than the placebo and T-F Sinus groups' symptoms. Another way of looking at this is to say that all three treatment groups had greater improvement with increasing baseline symptom severity, but the baseline scores in the CTC group had the most profound influence on improvement. This is an example of baseline scores having a different influence on outcome depending on treatment group. One would expect to see this relationship in the presence of an effective drug. There should be little or no difference between groups in patients who have very mild or no symptoms. Therefore, the significant treatment-by-baseline interaction is not a problem. The coefficient for treatment group is not statistically significant when the interaction term is included in the model because (in this model) it is the estimate of the treatment effect at baseline symptom severity equal to zero. Therefore, the sponsor was correct in excluding the interaction terms from the final models.

Figure 11: Scatterplots of Change from Baseline vs. Baseline MSC Score by Treatment



Baseline-by Center Interaction

Figure 12, below, again depicts two scatterplots of Average Baseline MSC score vs. Change from Baseline MSC Score. In these graphs, regression lines for each center are fitted to the data. The lines in the graph on the left (9 AM Dose) are almost parallel, while the lines on the right (3 PM Dose) cross at baseline < 2. The lines separate more as baseline increases. The baseline-by-center interaction is depicted in the graph on the right. The line fitted to Dr. Meltzer's data is steeper. For patients in whom baseline symptom severity was very low (< 4 units), Dr. Meltzer's patients' symptoms improved little more than Dr. Casale's; whereas, for patients with greater baseline symptom severity, Dr. Meltzer's patients' symptoms improved much more than Dr. Casale's. Another way to interpret this is to say that in both centers improvement increased with increasing baseline symptom severity, but this increase was more pronounced at Dr. Meltzer's center. This is an example of the baseline scores having a different influence on outcome between centers. This is interesting, but not germane to the determination of the efficacy demonstrated by the CTC group. Therefore, the baseline-by-center interaction is not a problem.

Figure 12: Scatterplots of Change from Baseline vs. Baseline MSC Score by Center

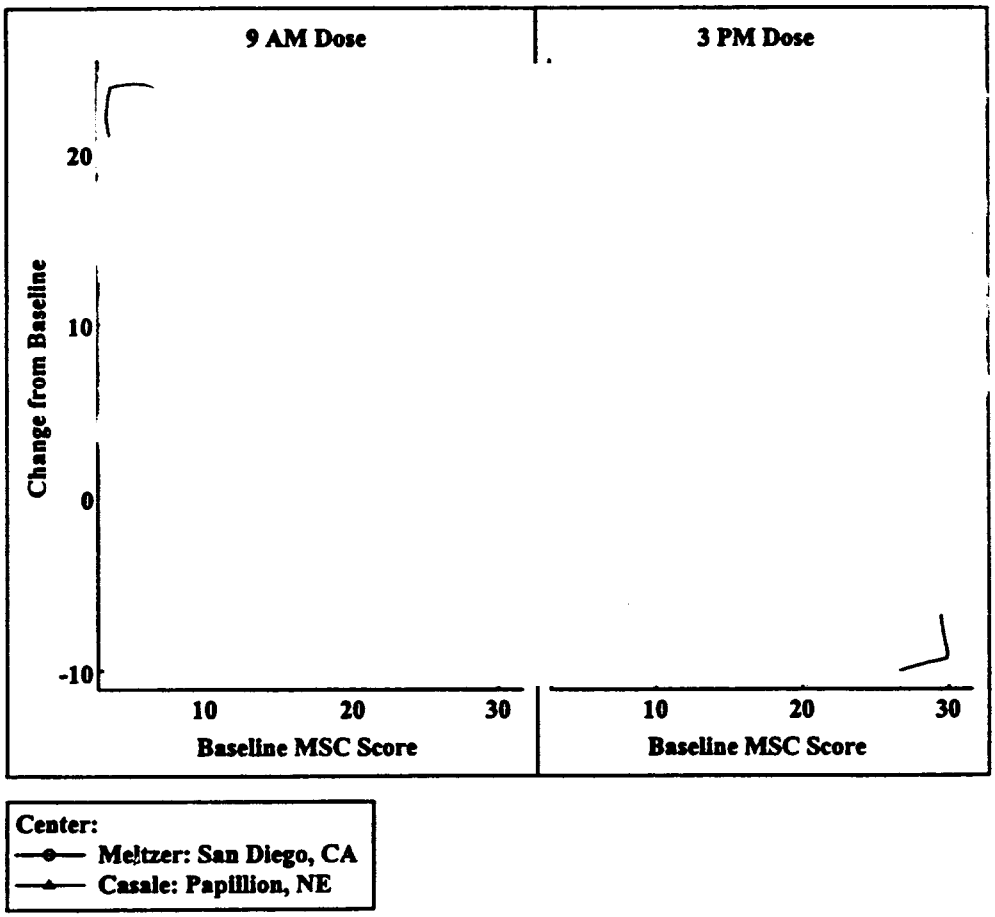
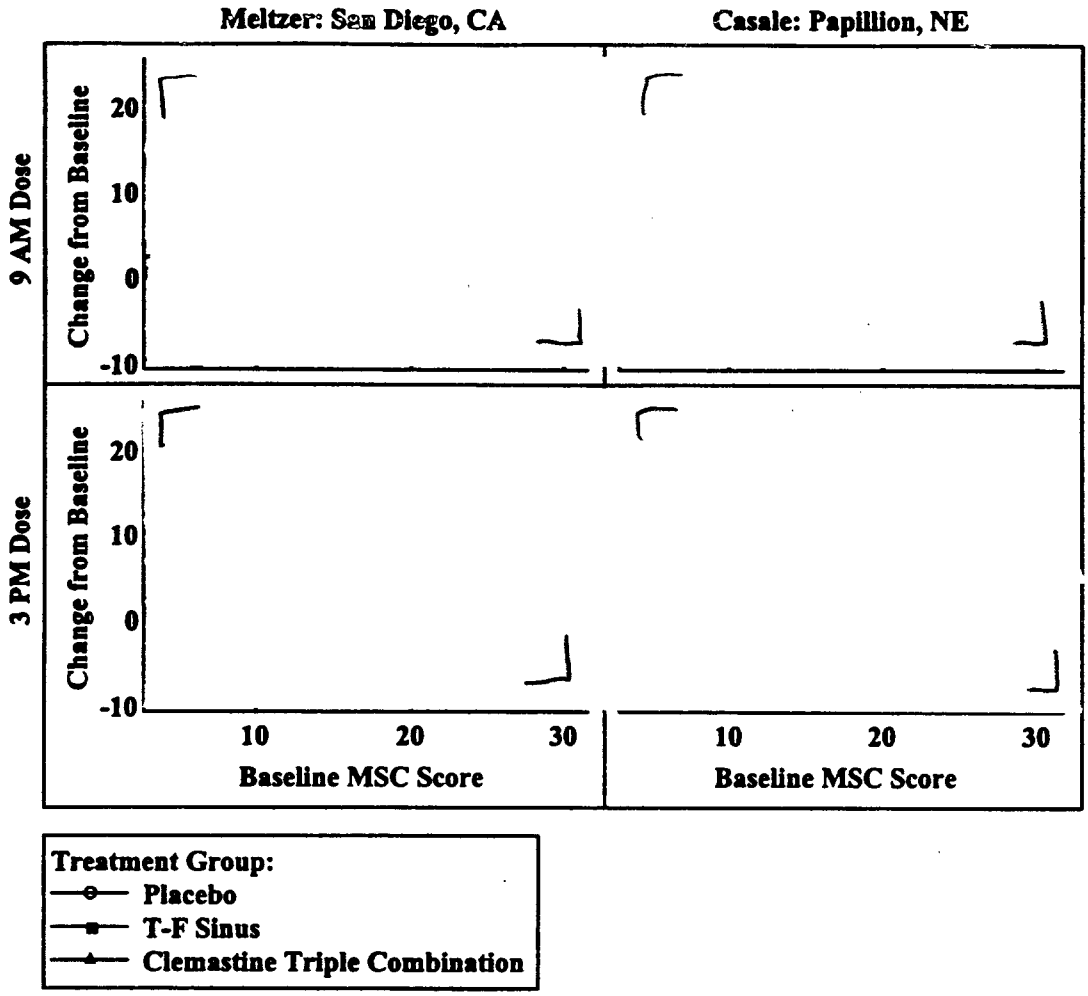


Figure 13 below separates the data by both treatment group and center to demonstrate the differences across centers. Note that in Dr. Casale's center, the placebo and T-F Sinus lines separated, with T-F Sinus providing a greater rate of improvement in symptoms with each increasing unit of baseline symptom severity. In Dr. Meltzer's center, the T-F Sinus and Placebo fitted lines are on top of one another.

Figure 13: Scatterplots of Change from Baseline vs. Baseline MSC Score by Center and Treatment Group



Secondary Endpoints

The sponsor analyzed the secondary endpoints using an ANOVA without baseline as a covariate. This reviewer performed the analyses using an ANCOVA (with baseline). The results of hours 0.5, 1, 2, 1-6, 2-5, 7-12, and 8-11 are presented in the appendix.

The placebo group did remarkably well after the first thirty minutes, as compared to CTC and TheraFlu for several symptoms: sneezes, runny nose, itchy nose, sniffles, and nose blows. Using an unadjusted alpha-level of 0.05, the placebo group was statistically significantly superior to TheraFlu at 30 minutes post the 9 AM dose for sneezes, runny nose, sniffles, nose blows, and the symptom complexes MSC and TSC. The placebo group was also statistically significantly superior to CTC at 30 minutes (using 0.05) for runny nose. The magnitude of these significant differences ranged from ——— units for the individual symptoms and ——— units for the symptom complexes. In general, after the first 30 minutes, the placebo group's mean symptoms continued to decline, but the active treatment group's mean symptoms declined more rapidly – making the active treatment groups' changes from baseline superior to those of the placebo group.

The CTC group performed much better than the T-F Sinus and placebo groups. CTC was numerically superior to both groups at almost all time points for all symptoms. TheraFlu sinus demonstrated superiority over placebo for only one symptom: headache. All other symptoms, including stuffy nose, number of nose blows, sniffles and postnasal drip had similar scores for placebo and T-F Sinus (after 30 minutes – when placebo was superior for sniffles and nose blows).

In general, the treatment differences between CTC and placebo during hours 2-5 were largest for: number of sneezes; itchy nose; sniffles; and number of nose blows. The treatment effects for these symptoms were on the order of ——— units between CTC and placebo. As mentioned above, the scale for sneezes and nose blows was different (see Figure 6, page 15). The variability of the sneeze and nose blow scores was greater than the variability of the other symptoms. The greater variability resulted in fewer timepoints being significant (at the 0.05 level) for sneezes and nose blows than for the other symptoms with the same magnitude of difference between treatment groups.

The results of the individual symptoms demonstrated greater improvement among the CTC group than the TheraFlu group. The treatment differences between CTC and TheraFlu were greatest for sneezes, itchy nose, itchy eyes/ears, watery eyes, and nose blows. The treatment effects for these symptoms were on the order of ——— units between CTC and TheraFlu. As mentioned previously, the sponsor changed the primary endpoint from a sum of 8 symptoms to a sum of 6 symptoms, where averages were used for two sets of symptoms (runny nose-left averaged with runny nose right; itchy nose-left averaged with itchy-nose right). The sponsor argued that the new calculation of the MSC score was actually more conservative because it weighted runny nose and itchy nose symptoms less than the protocol MSC calculation. This was purportedly more conservative because, of the 6 symptoms included in the MSC score (sneezes, itchy nose, runny nose, watery eyes, itchy eyes/ears and itchy throat), runny nose and itchy nose were the "most powerful" for showing the superiority of CTC over T-F Sinus. However, as can be seen in Table 26, below, the differences between treatment groups for itchy nose and runny nose were well within the range of values for all the symptoms. Neither of the symptoms stood out as being the "most powerful". (It should be noted here that the standard deviations for the "number of sneezes" scores were greater than those observed for the other scores. Thus, sneezes may not contribute as much to "showing the superiority of CTC over T-F Sinus" as the other symptoms with similar treatment effect sizes.) The sponsor was asked to perform the protocol-specified analyses (see Table 22 above, page 23).

Table 26: Results from ANCOVA (treatment and center as factors, baseline as a covariate)

	T-F Sinus Least Squares Mean Change from Baseline -CTC Least Squares Mean Change from Baseline	
	Average Over Hours 2-5 After 9 AM Dose	Average Over Hours 8-11 After 9 AM Dose (Hours 2-5 After 3 PM dose)
Sneezes	-0.30	-0.42
Itchy Nose	-0.28	-0.44
Runny Nose	-0.29	-0.52
Watery Eyes	-0.28	-0.46
Itchy Eyes/Ears	-0.25	-0.47
Itchy Throat	-0.36	-0.35

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Gender Analysis

This reviewer performed an ANCOVA on change from baseline MSC over hours 2-5 post-dose with a gender-by-treatment interaction term to investigate potential differences between genders. The differences between genders found in Study 305 were not seen in Study 306. The p-values for the interaction term were >0.50 (Dose 1: p=0.6272; Dose 2: p=0.5934).

3.3.6 Adverse Events

At Visit 3, patients were asked about adverse events that occurred the previous day. A greater percentage of patients reported at least one adverse event in the clemastine group as compared to the placebo and TheraFlu Sinus groups (CTC: 34%; Theraflu Sinus: 26%; placebo: 18%). This was due solely to the adverse events: somnolence and fatigue (see Table 27 below). Somnolence and fatigue are known side effects of clemastine.

After excluding all reports of somnolence and fatigue, the percentages of patients reporting at least one adverse event were similar across treatment groups (CTC: 12.7%; TheraFlu Sinus: 16.8%; placebo: 16.4%).

Table 27: Patients Reporting At Least One Instance of Somnolence or Fatigue

	Placebo	TheraFlu Sinus	CTC
Somnolence	0%	6%	19%
Fatigue	2%	6%	5%

3.4 Conclusions

Study HSC-306 was a double-blind, placebo-controlled, parallel group one-day park study to determine the safety and efficacy of the triple combination therapy in patients with at least moderate symptoms of seasonal allergic rhinitis. This study enrolled 298 patients (ages 12 to 62 years) at two centers (located in California and Nebraska). The primary efficacy variable was "Major Symptom Complex", defined as the sum of the patient's assessments of sneezing, itchy nose, runny nose, watery eyes, itchy eyes/ears, and itchy throat. Patients were randomized to one of three treatment groups: triple combination tablets, TheraFlu Sinus Tablets (pseudoephedrine and acetaminophen), or placebo.

This study was conducted to demonstrate that clemastine in the combination product, in a qid dosing form, would deliver effective allergy relief with the first dose taken. The primary comparison was between the combination product and TheraFlu Sinus. The placebo group was added to "validate the clinical model". (Volume 39, page 24). The primary efficacy variable was Major Symptom Complex score. The protocol defined MSC as the sum of eight symptoms: sneezing, runny nose (right and left), itchy nose (right and left), watery eyes, itchy eyes/ears and itchy throat, counting itchy nose-left separate from itchy nose-right and runny nose-left separate from runny nose-right. The sponsor provided results using the protocol definition of MSC and a post-hoc definition in which the right and left scores of itchy nose and runny nose were averaged to provide one value for itchy nose and one value of runny nose.

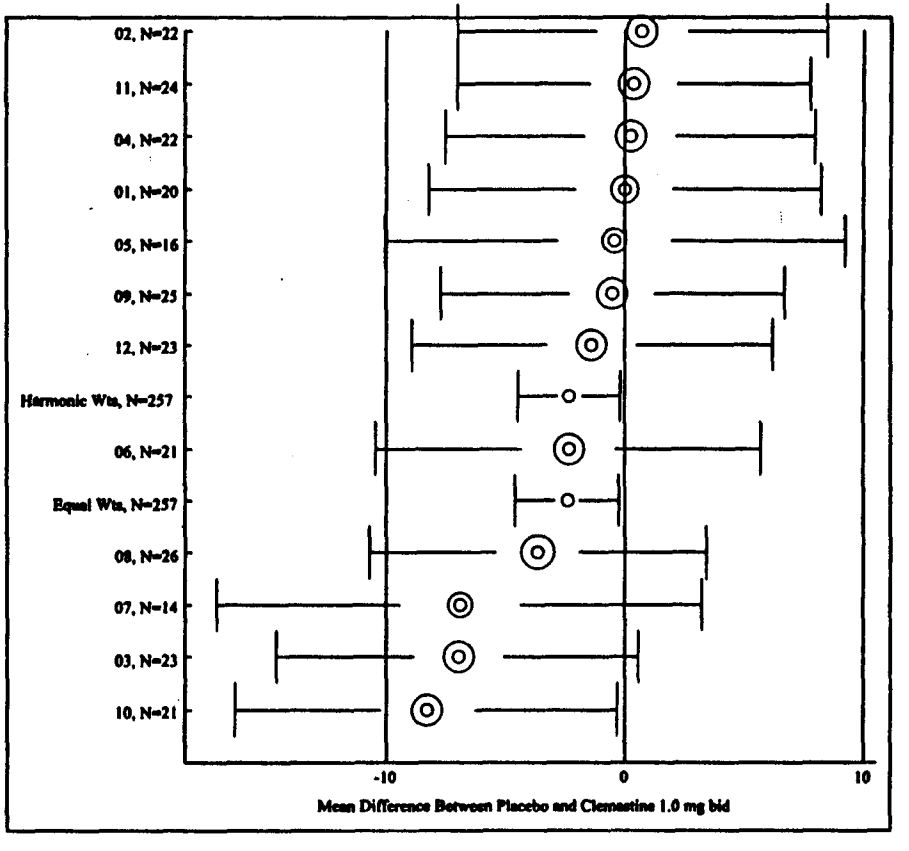
The primary analysis was an ANCOVA on the change from baseline MSC scores over the period of hours 2-5 postdose using both "absolute value" and "percentage of the baseline MSC score". Since there were two doses (9 am and 3 pm), there were four different primary analyses. Even with a conservative Bonferroni correction for the four different analyses (adjusted alpha-level = 0.0125), all four analyses yielded statistically significant results. A mean difference in absolute change from baseline between the triple combination therapy and Thera-Flu Sinus of 2.25 units was seen after the first dose and 3.0 units after the second dose. The differences in percentage reduction from baseline between the two active treatment groups were 16% after the first dose and 20% after the second dose.

The sponsor and this reviewer estimated the onset of action of CTC for the MSC scores to be about 2 hours comparing CTC to Placebo and about 30 minutes comparing CTC to TheraFlu Sinus. The sponsor would like the label to state ——————> of specific individual symptoms, most of which did not demonstrate statistically significant results (at alpha=0.05) at or before 2 hours.

The results of this study support the efficacy of the clemastine triple combination product as compared to TheraFlu Sinus for the relief of the Major Symptom Complex.

4 Appendix

Figure A1: Study 305 Treatment Effects Across Center for Clemastine 1.0 mg bid Treatment Group
Reference text



This graph is from an analysis of variance performed in the program _____. Mean treatment differences and 95% confidence intervals are plotted along the x-axis for each center. Negative values indicate clemastine is superior. The size of the circle represents the sample size of the center. The numbers to the left of the y-axis indicated the center number and the sample size. The confidence intervals identified as "equal wts" and "harmonic wts" are the overall treatment effect sizes weight all centers equally and weighting each center by sample size, respectively. The results from all the analyses of variance and covariance presented in this review weight all centers equally.

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Table A1: Study 305 Reviewer's Analyses of Diary Data "Right Now": Results are from an ANOVA with center and treatment as factors.
All change from baseline means are Least Squares Means, adjusted using the model.

"Right Now" Symptom		Placebo			Clemastine 0.5 qid					Clemastine 1.0 bid					BID vs. QID	
		N	Mean	Std Err	N	Mean	Std Err	Trt Diff	p-value	N	Mean	Std Err	Trt Diff	p-value	Trt Diff	p-value
Nasal Discharge	Baseline	140	3.46	0.10	135	3.52	0.11	0.06		135	3.46	0.11	0.00		0.06	
	Avge Week 1 Change	139	-0.50	0.11	135	-1.00	0.12	-0.51	[illegible]	133	-1.03	0.12	-0.53	[illegible]	0.02	0.8949
	Avge Week 2 Change	128	-0.80	0.14	128	-1.05	0.14	-0.25	0.1829	129	-1.21	0.14	-0.41	[illegible]	0.15	0.4193
	Avge Wks 1 & 2 Change	139	-0.66	0.12	135	-1.05	0.12	-0.38	[illegible]	133	-1.13	0.12	-0.47	[illegible]	0.08	0.6340
Sneezing	Baseline	140	2.88	0.12	135	2.74	0.13	-0.14		135	2.84	0.12	-0.04		-0.10	
	Avge Week 1 Change	139	-0.40	0.12	135	-0.98	0.12	-0.58	[illegible]	133	-1.05	0.12	-0.65	[illegible]	0.07	0.6672
	Avge Week 2 Change	128	-0.75	0.14	128	-1.14	0.14	-0.39	[illegible]	129	-1.09	0.14	-0.34	0.0794	-0.05	0.8104
	Avge Wks 1 & 2 Change	139	-0.54	0.12	135	-1.05	0.12	-0.52	[illegible]	133	-1.07	0.13	-0.54	[illegible]	0.02	0.9182
Nasal Congestion	Baseline	140	3.67	0.10	135	3.79	0.10	0.12		135	3.59	0.11	-0.09		0.21	
	Avge Week 1 Change	139	-0.45	0.10	135	-0.68	0.10	-0.23	0.1156	133	-0.75	0.11	-0.30	[illegible]	0.07	0.6572
	Avge Week 2 Change	128	-0.68	0.12	128	-0.91	0.12	-0.23	0.1740	129	-1.01	0.12	-0.33	0.0515	0.10	0.5545
	Avge Wks 1 & 2 Change	139	-0.58	0.11	135	-0.81	0.11	-0.22	0.1492	133	-0.89	0.11	-0.31	[illegible]	0.09	0.5711
Nasal Itching	Baseline	140	3.26	0.11	135	3.33	0.12	0.08		135	3.30	0.12	0.05		0.03	
	Avge Week 1 Change	139	-0.57	0.11	135	-0.97	0.11	-0.39	[illegible]	133	-1.10	0.11	-0.53	[illegible]	0.14	0.3652
	Avge Week 2 Change	128	-0.96	0.13	128	-1.29	0.13	-0.33	0.0727	129	-1.19	0.13	-0.23	0.2010	-0.10	0.6030
	Avge Wks 1 & 2 Change	139	-0.76	0.11	135	-1.13	0.11	-0.37	[illegible]	133	-1.16	0.11	-0.40	[illegible]	0.03	0.8610
Eye Burning	Baseline	140	2.71	0.13	135	2.81	0.13	0.10		135	2.81	0.14	0.11		-0.01	
	Avge Week 1 Change	139	-0.47	0.11	135	-0.89	0.11	-0.42	[illegible]	133	-0.99	0.11	-0.52	[illegible]	0.10	0.5210
	Avge Week 2 Change	128	-0.87	0.14	128	-1.16	0.14	-0.30	0.1206	129	-1.32	0.14	-0.45	[illegible]	0.16	0.4140
	Avge Wks 1 & 2 Change	139	-0.65	0.12	135	-1.03	0.12	-0.38	[illegible]	133	-1.16	0.12	-0.51	[illegible]	0.13	0.4435
Eye Tearing	Baseline	140	2.36	0.13	135	2.49	0.14	0.13		135	2.44	0.14	0.08		0.05	
	Avge Week 1 Change	139	-0.41	0.11	135	-0.96	0.11	-0.54	[illegible]	133	-0.92	0.11	-0.50	[illegible]	-0.04	0.7878
	Avge Week 2 Change	128	-0.82	0.14	128	-1.19	0.13	-0.37	0.0503	129	-1.13	0.13	-0.31	0.0992	-0.06	0.7552
	Avge Wks 1 & 2 Change	139	-0.59	0.12	135	-1.07	0.12	-0.48	[illegible]	133	-1.03	0.12	-0.44	[illegible]	-0.04	0.8201
Red Eyes	Baseline	140	2.25	0.13	135	2.24	0.13	-0.01		135	2.32	0.14	0.07		-0.08	
	Avge Week 1 Change	139	-0.34	0.10	135	-0.68	0.10	-0.34	[illegible]	133	-0.67	0.10	-0.34	[illegible]	-0.01	0.9560
	Avge Week 2 Change	128	-0.76	0.12	128	-0.81	0.12	-0.05	0.7729	129	-0.85	0.12	-0.09	0.6064	0.04	0.8206
	Avge Wks 1 & 2 Change	139	-0.53	0.11	135	-0.75	0.11	-0.22	0.1478	133	-0.76	0.11	-0.23	0.1293	0.01	0.9402
Itchy Eyes	Baseline	140	2.19	0.15	135	2.48	0.14	0.29		135	2.36	0.14	0.16		0.13	
	Avge Week 1 Change	139	-0.40	0.11	135	-0.69	0.11	-0.29	0.0545	133	-0.76	0.11	-0.36	[illegible]	0.07	0.6585
	Avge Week 2 Change	128	-0.71	0.13	128	-0.89	0.13	-0.18	0.3452	129	-0.87	0.13	-0.16	0.3958	-0.02	0.9239
	Avge Wks 1 & 2 Change	139	-0.57	0.11	135	-0.79	0.12	-0.22	0.1783	133	-0.82	0.12	-0.25	0.1215	0.03	0.8356
Total Symptoms	Baseline	140	22.77	0.69	135	23.40	0.71	0.63		135	23.11	0.72	0.34		0.29	
	Avge Week 1 Change	139	-3.54	0.65	135	-6.85	0.66	-3.31	[illegible]	133	-7.27	0.66	-3.73	[illegible]	0.42	0.6520
	Avge Week 2 Change	128	-6.34	0.80	128	-8.45	0.80	-2.11	0.0616	129	-8.69	0.80	-2.34	[illegible]	0.24	0.8341
	Avge Wks 1 & 2 Change	139	-4.88	0.69	135	-7.67	0.70	-2.79	[illegible]	133	-8.03	0.70	-3.14	[illegible]	0.35	0.7219

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Table A2: Study 305 Reviewer's Analyses of Diary Data "Previous 24 Hours": Results are from an ANOVA with center and treatment as factors.
All change from baseline means are Least Squares Means, adjusted using the model.

Previous 24 hours		Placebo			Clemastine 0.5 qid				Clemastine 1.0 bid				BID vs. QID	
Symptom		N	Mean	Std Err	N	Mean	Std Err	Trt Diff	p-value	N	Mean	Std Err	Trt Diff	p-value	Trt Diff	p-value
Nasal Discharge	Baseline	140	4.24	0.06	135	4.36	0.07	0.12		135	4.24	0.07	0.00		0.12	
	Avge Week 1 Change	139	-0.09	0.13	135	-0.64	0.13	-0.55	[redacted]	134	-0.55	0.13	-0.46	[redacted]	-0.08	0.6414
	Avge Week 2 Change	128	-0.42	0.15	128	-0.77	0.15	-0.35	0.0945	129	-0.83	0.15	-0.41	[redacted]	0.06	0.7719
	Avge Wks 1 & 2 Change	139	-0.28	0.13	135	-0.74	0.13	-0.46	[redacted]	134	-0.70	0.13	-0.42	[redacted]	-0.04	0.8321
Sneezing	Baseline	140	4.02	0.07	135	3.92	0.08	-0.10		135	3.87	0.08	-0.15		0.04	
	Avge Week 1 Change	139	0.17	0.14	135	-0.59	0.14	-0.75	[redacted]	134	-0.60	0.14	-0.76	[redacted]	0.01	0.9594
	Avge Week 2 Change	128	-0.30	0.15	128	-0.87	0.15	-0.56	[redacted]	129	-0.76	0.15	-0.46	[redacted]	-0.11	0.6040
	Avge Wks 1 & 2 Change	139	-0.05	0.13	135	-0.74	0.14	-0.68	[redacted]	134	-0.66	0.14	-0.61	[redacted]	-0.07	0.7145
Nasal Congestion	Baseline	140	4.26	0.07	135	4.26	0.08	0.00		135	4.15	0.08	-0.11		0.11	
	Avge Week 1 Change	139	-0.11	0.12	135	-0.43	0.12	-0.31	0.0572	134	-0.36	0.12	-0.25	0.1282	-0.06	0.7067
	Avge Week 2 Change	128	-0.36	0.13	128	-0.66	0.13	-0.29	0.1038	129	-0.68	0.13	-0.31	0.0820	0.02	0.9104
	Avge Wks 1 & 2 Change	139	-0.25	0.12	135	-0.55	0.12	-0.30	0.0751	134	-0.52	0.12	-0.27	0.1104	-0.03	0.8579
Nasal Itching	Baseline	140	3.61	0.10	135	3.83	0.09	0.22		135	3.71	0.10	0.10		0.12	
	Avge Week 1 Change	139	-0.29	0.11	135	-0.73	0.11	-0.44	[redacted]	134	-0.78	0.11	-0.49	[redacted]	0.05	0.7539
	Avge Week 2 Change	128	-0.67	0.13	128	-1.07	0.13	-0.41	[redacted]	129	-0.95	0.13	-0.28	0.1320	-0.13	0.5039
	Avge Wks 1 & 2 Change	139	-0.47	0.11	135	-0.92	0.12	-0.44	[redacted]	134	-0.87	0.12	-0.40	[redacted]	-0.05	0.7764
Eye Burning	Baseline	140	3.41	0.12	135	3.39	0.12	-0.03		135	3.42	0.13	0.01		-0.04	
	Avge Week 1 Change	139	-0.10	0.12	135	-0.64	0.12	-0.54	[redacted]	134	-0.71	0.12	-0.61	[redacted]	0.07	0.6916
	Avge Week 2 Change	128	-0.64	0.14	128	-1.00	0.14	-0.35	0.0849	129	-1.06	0.14	-0.41	[redacted]	0.06	0.7677
	Avge Wks 1 & 2 Change	139	-0.36	0.12	135	-0.82	0.13	-0.46	[redacted]	134	-0.87	0.13	-0.51	[redacted]	0.04	0.8055
Eye Tearing	Baseline	140	3.06	0.13	135	3.20	0.13	0.14		135	3.05	0.13	-0.01		0.15	
	Avge Week 1 Change	139	-0.04	0.12	135	-0.75	0.12	-0.70	[redacted]	134	-0.64	0.12	-0.60	[redacted]	-0.10	0.5315
	Avge Week 2 Change	128	-0.59	0.14	128	-1.00	0.14	-0.42	[redacted]	129	-0.93	0.14	-0.34	0.0854	-0.07	0.7179
	Avge Wks 1 & 2 Change	139	-0.29	0.12	135	-0.88	0.12	-0.59	[redacted]	134	-0.78	0.13	-0.49	[redacted]	-0.10	0.5785
Red Eyes	Baseline	140	2.82	0.11	135	2.74	0.13	-0.08		135	2.74	0.14	-0.08		0.00	
	Avge Week 1 Change	139	-0.12	0.11	135	-0.60	0.11	-0.47	[redacted]	134	-0.47	0.11	-0.35	[redacted]	-0.13	0.4081
	Avge Week 2 Change	128	-0.61	0.12	128	-0.71	0.12	-0.10	0.5643	129	-0.67	0.12	-0.06	0.7357	-0.04	0.8106
	Avge Wks 1 & 2 Change	139	-0.35	0.11	135	-0.66	0.11	-0.31	[redacted]	134	-0.56	0.11	-0.21	0.1737	-0.10	0.5087
Itchy Eyes	Baseline	140	2.68	0.15	135	2.87	0.15	0.20		135	2.89	0.14	0.21		-0.01	
	Avge Week 1 Change	139	-0.13	0.12	135	-0.49	0.12	-0.36	[redacted]	134	-0.52	0.12	-0.39	[redacted]	0.03	0.8742
	Avge Week 2 Change	128	-0.49	0.14	128	-0.72	0.14	-0.23	0.2302	129	-0.65	0.14	-0.16	0.4056	-0.07	0.7115
	Avge Wks 1 & 2 Change	139	-0.33	0.12	135	-0.61	0.12	-0.28	0.0970	134	-0.57	0.12	-0.24	0.1619	-0.04	0.7976
Total Symptoms	Baseline	140	28.10	0.51	135	28.56	0.54	0.46		135	28.07	0.54	-0.03		0.49	
	Avge Week 1 Change	139	-0.72	0.73	135	-4.86	0.74	-4.14	[redacted]	134	-4.63	0.75	-3.91	[redacted]	-0.22	0.8312
	Avge Week 2 Change	128	-4.09	0.86	128	-6.81	0.85	-2.72	[redacted]	129	-6.53	0.86	-2.44	[redacted]	-0.27	0.8210
	Avge Wks 1 & 2 Change	139	-2.38	0.76	135	-5.92	0.77	-3.54	[redacted]	134	-5.53	0.78	-3.15	[redacted]	-0.39	0.7230

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Figure A2: Study 305 Means of Symptom Scores Over Time by Treatment Group and Gender

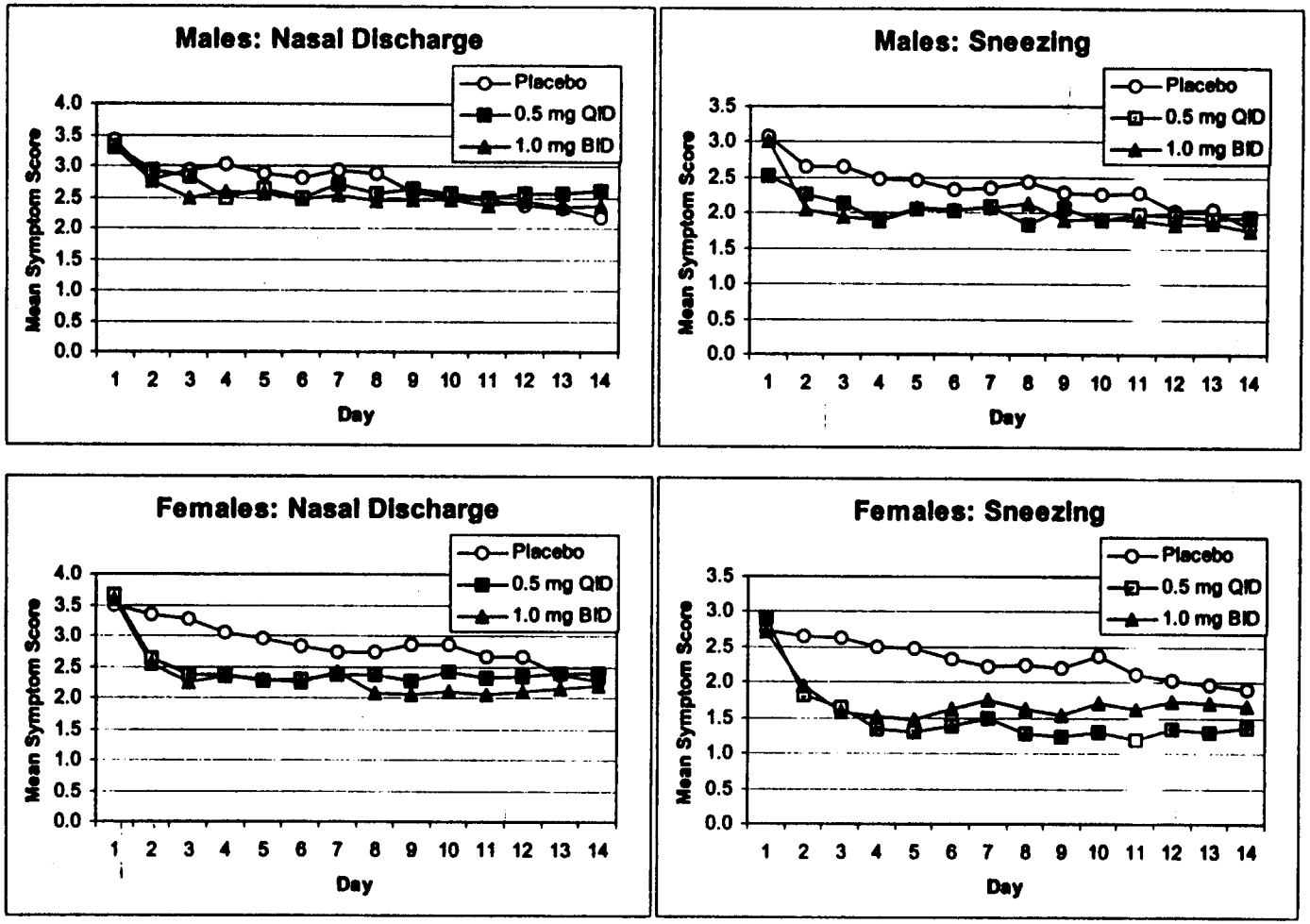

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Table A3: Study 306 Reviewer's Analyses of Covariance: treatment, center as factors, baseline as covariate
All Change from baseline means are Least Squares Means from model
Baseline was calculated as an average of three pre-treatment assessments: 7:30 am; 8:00 am; and 8:30 am.

Symptom	# of Hrs Post 9 am Dose	Placebo N	Placebo Mean	Placebo SE	TheraFlu Sinus N	TheraFlu Sinus Mean	TheraFlu Sinus SE	TheraFlu Sinus Trt Diff	TheraFlu Sinus p-value	Clemastine Triple Combination N	Clemastine Triple Combination Mean	Clemastine Triple Combination SE	Clemastine Triple Combination Trt Diff	Clemastine Triple Combination p-value	CTC vs. T-F Sinus Trt Diff	CTC vs. T-F Sinus p-value
No. of Sneezes	Baseline*	61	2.11	0.23	119	2.38	0.18	0.27		118	2.33	0.19	0.22		-0.05	
	0.5	61	-0.78	0.19	119	-0.18	0.14	0.60	0.0108	118	-0.48	0.14	0.31	0.1933	-0.30	0.1272
	1	61	-0.95	0.19	118	-0.65	0.13	0.30	0.1889	118	-0.94	0.13	0.02	0.9469	-0.29	0.1305
	2	61	-0.72	0.22	118	-0.92	0.16	-0.21	0.4393	118	-0.97	0.16	-0.25	0.3424	-0.05	0.8309
	1-6	61	-0.95	0.17	118	-0.86	0.12	0.09	0.6792	118	-1.15	0.12	-0.20	0.3319	-0.29	0.0940
	2-5	61	-1.01	0.19	118	-0.87	0.13	0.13	0.5667	118	-1.17	0.13	-0.17	0.4637	-0.30	0.1140
	7-12	61	-0.92	0.17	118	-1.13	0.12	-0.21	0.3079	117	-1.54	0.12	-0.62	[redacted]	-0.41	[redacted]
	8-11	61	-0.98	0.17	118	-1.13	0.12	-0.15	0.4709	117	-1.55	0.12	-0.57	[redacted]	-0.42	[redacted]
Runny Nose	Baseline*	61	2.02	0.15	119	2.41	0.11	0.39		118	2.06	0.11	0.04		-0.35	
	0.5	61	-0.44	0.11	119	-0.09	0.08	0.35	0.0100	118	-0.42	0.08	0.02	0.8536	-0.33	[redacted]
	1	61	-0.74	0.12	118	-0.50	0.09	0.23	0.1103	118	-0.65	0.09	0.08	0.5597	-0.15	0.2174
	2	61	-0.85	0.13	118	-0.86	0.10	-0.02	0.9081	118	-1.10	0.09	-0.25	0.1234	-0.23	0.0874
	1-6	61	-0.91	0.10	118	-0.92	0.07	0.00	0.9911	118	-1.19	0.07	-0.27	[redacted]	-0.27	[redacted]
	2-5	61	-0.96	0.11	118	-1.00	0.08	-0.03	0.7979	118	-1.28	0.08	-0.32	[redacted]	-0.29	[redacted]
	7-12	61	-1.09	0.11	118	-1.20	0.08	-0.11	0.4060	117	-1.52	0.08	-0.43	[redacted]	-0.32	[redacted]
	8-11	61	-1.12	0.11	118	-1.22	0.08	-0.10	0.4612	117	-1.54	0.08	-0.42	[redacted]	-0.32	[redacted]
Itchy Nose	Baseline*	61	2.30	0.14	119	2.55	0.10	0.26		118	2.27	0.11	-0.03		-0.28	
	0.5	61	-0.24	0.12	119	0.03	0.08	0.26	0.0641	118	-0.31	0.08	-0.07	0.6269	-0.33	[redacted]
	1	61	-0.35	0.12	118	-0.30	0.09	0.05	0.7238	118	-0.53	0.09	-0.18	0.2280	-0.23	0.0614
	2	61	-0.65	0.13	118	-0.65	0.09	0.00	0.9985	118	-0.80	0.09	-0.15	0.3218	-0.15	0.2332
	1-6	61	-0.67	0.10	118	-0.74	0.07	-0.07	0.5874	118	-1.03	0.07	-0.37	[redacted]	-0.30	[redacted]
	2-5	61	-0.73	0.11	118	-0.81	0.08	-0.08	0.5478	118	-1.09	0.08	-0.36	[redacted]	-0.28	[redacted]
	7-12	61	-0.83	0.12	118	-1.05	0.08	-0.22	0.1361	117	-1.49	0.08	-0.66	<0.0001	-0.45	[redacted]
	8-11	61	-0.84	0.12	118	-1.06	0.09	-0.22	0.1335	117	-1.51	0.09	-0.67	<0.0001	-0.44	[redacted]
Itchy Eyes/ Ears	Baseline*	61	2.49	0.16	119	2.58	0.12	0.09		118	2.38	0.12	-0.11		-0.20	
	0.5	61	-0.22	0.11	119	-0.03	0.08	0.19	0.1815	118	-0.13	0.08	0.09	0.5097	-0.10	0.4128
	1	61	-0.44	0.12	118	-0.35	0.09	0.08	0.5877	118	-0.53	0.09	-0.10	0.5204	-0.18	0.1528
	2	61	-0.63	0.13	118	-0.66	0.09	-0.02	0.8753	118	-0.89	0.09	-0.26	0.0989	-0.24	0.0712
	1-6	61	-0.74	0.10	118	-0.73	0.08	0.01	0.9084	118	-1.00	0.08	-0.26	[redacted]	-0.28	[redacted]
	2-5	61	-0.80	0.11	118	-0.81	0.08	-0.02	0.9015	118	-1.07	0.08	-0.27	0.0575	-0.25	[redacted]
	7-12	61	-1.01	0.12	118	-0.97	0.08	0.04	0.7901	117	-1.42	0.09	-0.41	[redacted]	-0.45	[redacted]
	8-11	61	-1.02	0.12	118	-0.96	0.09	0.06	0.7095	117	-1.43	0.09	-0.42	[redacted]	-0.47	[redacted]
Itchy Throat	Baseline*	61	1.99	0.17	119	2.03	0.12	0.04		118	1.79	0.13	-0.20		-0.24	
	0.5	61	-0.17	0.11	119	-0.05	0.08	0.12	0.3526	118	-0.18	0.08	0.00	0.9795	-0.13	0.2484
	1	61	-0.36	0.12	118	-0.31	0.09	0.05	0.7155	118	-0.51	0.09	-0.15	0.3186	-0.20	0.1003
	2	61	-0.39	0.12	118	-0.52	0.09	-0.13	0.3787	118	-0.90	0.09	-0.51	[redacted]	-0.38	[redacted]
	1-6	61	-0.63	0.10	118	-0.59	0.07	0.04	0.7591	118	-0.94	0.07	-0.31	[redacted]	-0.35	[redacted]
	2-5	61	-0.64	0.11	118	-0.65	0.08	0.00	0.9865	118	-1.01	0.08	-0.37	[redacted]	-0.36	[redacted]
	7-12	61	-0.93	0.11	118	-0.88	0.08	0.05	0.6847	117	-1.21	0.08	-0.28	[redacted]	-0.33	[redacted]
	8-11	61	-0.96	0.11	118	-0.90	0.08	0.06	0.6457	117	-1.25	0.08	-0.29	0.0280	-0.35	[redacted]

[redacted] Active Trt is statistically significantly superior to Placebo
CTC is statistically significantly superior to T-F Sinus
Placebo is statistically significantly superior to Active Trt

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Table A4: Study 306 Reviewer's Analyses of Covariance: treatment, center as factors, baseline as covariate
All Change from baseline means are Least Squares Means from model
* Baseline was calculated as an average of three pre-treatment assessments: 7:30 am; 8:00 am; and 8:30 am.

Symptom	# of Hrs Post 9 am Dose	Placebo N	Placebo Mean	Placebo SE	TheraFlu Sinus N	TheraFlu Sinus Mean	TheraFlu Sinus SE	TheraFlu Sinus Trt Diff	TheraFlu Sinus p-value	Clemastine Triple Combination N	Clemastine Triple Combination Mean	Clemastine Triple Combination SE	Clemastine Triple Combination Trt Diff	Clemastine Triple Combination p-value	CTC vs. T-F Sinus Trt Diff	CTC vs. T-F Sinus p-value
Watery Eyes	Baseline*	61	2.11	0.17	119	2.08	0.12	-0.04		118	1.91	0.11	-0.20		-0.16	
	0.5	61	-0.19	0.12	119	-0.05	0.09	0.14	0.3371	118	-0.42	0.09	-0.23	0.1191	-0.37	[redacted]
	1	61	-0.46	0.12	118	-0.44	0.09	0.03	0.8623	118	-0.53	0.09	-0.07	0.6330	-0.10	0.4307
	2	61	-0.67	0.12	118	-0.62	0.09	0.05	0.7366	118	-0.88	0.09	-0.22	0.1511	-0.27	[redacted]
	1-6	61	-0.74	0.10	118	-0.70	0.07	0.04	0.7432	118	-0.96	0.07	-0.21	0.0790	-0.25	[redacted]
	2-5	61	-0.80	0.10	118	-0.75	0.08	0.05	0.7185	118	-1.03	0.08	-0.23	0.0771	-0.28	[redacted]
	7-12	61	-1.03	0.11	118	-0.89	0.08	0.13	0.3355	117	-1.30	0.08	-0.27	[redacted]	-0.41	[redacted]
	8-11	61	-1.03	0.12	118	-0.87	0.08	0.16	0.2584	117	-1.33	0.08	-0.29	0.045[redacted]	-0.46	[redacted]
Stuffy Nose	Baseline*	61	2.42	0.13	119	2.56	0.10	0.14		118	2.40	0.10	-0.02		-0.16	
	0.5	61	-0.19	0.09	119	-0.03	0.07	0.15	0.1736	118	-0.16	0.07	0.02	0.8452	-0.13	0.1582
	1	61	-0.44	0.10	118	-0.35	0.07	0.09	0.4606	118	-0.45	0.07	-0.01	0.9358	-0.10	0.3224
	2	61	-0.55	0.11	118	-0.72	0.08	-0.17	0.2213	118	-0.79	0.08	-0.24	0.0772	-0.07	0.5103
	1-6	61	-0.65	0.09	118	-0.74	0.07	-0.09	0.4318	118	-0.83	0.07	-0.18	0.1204	-0.09	0.3536
	2-5	61	-0.68	0.10	118	-0.83	0.07	-0.15	0.2461	118	-0.90	0.07	-0.22	0.0805	-0.07	0.4769
	7-12	61	-0.74	0.10	118	-0.92	0.08	-0.18	0.1737	117	-1.11	0.08	-0.37	[redacted]	-0.19	0.0727
	8-11	61	-0.76	0.11	118	-0.95	0.08	-0.20	0.1416	117	-1.14	0.08	-0.38	0.00[redacted]	-0.18	0.0983
Sniffles	Baseline*	61	2.62	0.15	119	2.87	0.11	0.25		118	2.77	0.10	0.15		-0.10	
	0.5	61	-0.50	0.11	119	-0.23	0.08	0.28	0.0493	118	-0.35	0.08	0.16	0.2639	-0.12	0.2994
	1	61	-0.82	0.12	118	-0.63	0.08	0.19	0.1783	118	-0.70	0.08	0.12	0.3895	-0.07	0.5524
	2	61	-0.88	0.13	118	-1.06	0.10	-0.18	0.2768	118	-1.17	0.10	-0.29	0.0724	-0.12	0.3899
	1-6	61	-1.02	0.11	118	-1.09	0.08	-0.07	0.5946	118	-1.25	0.08	-0.23	0.0813	-0.16	0.1421
	2-5	61	-1.06	0.12	118	-1.19	0.08	-0.13	0.3799	118	-1.32	0.08	-0.26	0.0698	-0.14	0.2566
	7-12	61	-1.18	0.12	118	-1.37	0.09	-0.19	0.2077	117	-1.70	0.09	-0.52	[redacted]	-0.33	[redacted]
	8-11	61	-1.23	0.13	118	-1.39	0.09	-0.16	0.3152	117	-1.70	0.09	-0.47	0.00[redacted]	-0.31	[redacted]
No. of Nose Blows	Baseline*	61	1.80	0.21	119	2.65	0.20	0.86		118	2.37	0.19	0.58		-0.28	
	0.5	61	-0.73	0.15	119	-0.23	0.11	0.50	0.0066	118	-0.17	0.11	0.57	0.0021	0.07	0.6596
	1	61	-0.87	0.16	118	-0.50	0.12	0.37	0.0730	118	-0.60	0.12	0.26	0.1948	-0.10	0.5334
	2	61	-0.89	0.19	118	-0.77	0.14	0.12	0.6027	118	-0.94	0.14	-0.05	0.8376	-0.17	0.3758
	1-6	61	-1.01	0.16	118	-0.82	0.11	0.19	0.3215	118	-1.14	0.11	-0.12	0.5263	-0.32	[redacted]
	2-5	61	-1.03	0.17	118	-0.87	0.12	0.17	0.4336	118	-1.19	0.12	-0.16	0.4450	-0.33	0.0599
	7-12	61	-1.05	0.16	118	-1.11	0.11	-0.06	0.7682	117	-1.59	0.11	-0.54	[redacted]	-0.48	[redacted]
	8-11	61	-1.12	0.16	118	-1.11	0.12	0.01	0.9460	117	-1.62	0.12	-0.50	0.01[redacted]	-0.51	[redacted]
Cough	Baseline*	61	1.28	0.17	119	1.50	0.12	0.22		118	1.28	0.11	0.00		-0.22	
	0.5	61	-0.17	0.10	119	-0.11	0.07	0.05	0.6595	118	-0.11	0.07	0.05	0.6743	0.00	0.9800
	1	61	-0.27	0.10	118	-0.39	0.07	-0.12	0.3480	118	-0.49	0.07	-0.21	0.0964	-0.09	0.3815
	2	61	-0.53	0.11	118	-0.49	0.08	0.04	0.7367	118	-0.66	0.08	-0.13	0.3234	-0.17	0.1103
	1-6	61	-0.57	0.08	118	-0.64	0.06	-0.07	0.4830	118	-0.80	0.06	-0.23	[redacted]	-0.16	0.0560
	2-5	61	-0.61	0.09	118	-0.66	0.06	-0.05	0.6218	118	-0.84	0.06	-0.23	[redacted]	-0.18	[redacted]
	7-12	61	-0.82	0.08	118	-0.87	0.06	-0.05	0.6338	117	-1.04	0.06	-0.22	[redacted]	-0.17	[redacted]
	8-11	61	-0.85	0.09	118	-0.87	0.06	-0.02	0.8331	117	-1.07	0.06	-0.23	0.05[redacted]	-0.20	[redacted]

[redacted] Active Trt is statistically significantly superior to Placebo
CTC is statistically significantly superior to T-F Sinus

Placebo is statistically significantly superior to Active Trt

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Table A5: Study 306 Reviewer's Analyses of Covariance: treatment, center as factors, baseline as covariate
All Change from baseline means are Least Squares Means from model
Baseline was calculated as an average of three pre-treatment assessments: 7:30 am; 8:00 am; and 8:30 am.

	# of Hrs Post	Placebo			TheraFlu Sinus					Clemastine Triple Combination					CTC vs. T-F Sinus	
Symptom	9 am Dose	N	Mean	SE	N	Mean	SE	Trt Diff	p-value	N	Mean	SE	Trt Diff	p-value	Trt Diff	p-value
Headache	Baseline*	61	1.19	0.16	119	1.32	0.12	0.13		118	1.29	0.12	0.10		-0.03	
	0.5	61	-0.01	0.09	119	0.09	0.07	0.10	0.3763	118	0.05	0.07	0.06	0.6060	-0.04	0.6546
	1	61	0.02	0.11	118	-0.02	0.08	-0.05	0.7375	118	-0.19	0.08	-0.21	0.1183	-0.17	0.1370
	2	61	0.08	0.11	118	-0.28	0.08	-0.37	[redacted]	118	-0.35	0.08	-0.43	[redacted]	-0.07	0.5685
	1-6	61	-0.07	0.09	118	-0.36	0.07	-0.29	[redacted]	118	-0.47	0.07	-0.40	[redacted]	-0.11	0.2481
	2-5	61	-0.11	0.10	118	-0.41	0.07	-0.31	[redacted]	118	-0.50	0.07	-0.39	[redacted]	-0.09	0.3780
	7-12	61	-0.07	0.12	118	-0.54	0.08	-0.47	[redacted]	117	-0.71	0.08	-0.63	[redacted]	-0.17	0.1640
	8-11	61	-0.08	0.12	118	-0.56	0.09	-0.48	[redacted]	117	-0.72	0.09	-0.64	[redacted]	-0.16	0.1922
Postnasal	Baseline*	61	2.20	0.17	119	2.63	0.13	0.43		118	2.26	0.12	0.06		-0.37	
Drip	0.5	61	-0.26	0.11	119	-0.10	0.08	0.16	0.2378	118	-0.30	0.08	-0.04	0.7415	-0.20	0.0682
	1	61	-0.42	0.12	118	-0.48	0.08	-0.07	0.6375	118	-0.71	0.08	-0.29	[redacted]	-0.23	0.0584
	2	61	-0.65	0.12	118	-0.71	0.09	-0.06	0.6997	118	-1.01	0.09	-0.36	[redacted]	-0.30	[redacted]
	1-6	61	-0.66	0.10	118	-0.91	0.07	-0.24	0.0558	118	-1.16	0.07	-0.49	[redacted]	-0.25	[redacted]
	2-5	61	-0.72	0.11	118	-0.98	0.08	-0.26	0.0560	118	-1.21	0.08	-0.49	[redacted]	-0.23	[redacted]
	7-12	61	-0.96	0.11	118	-1.18	0.08	-0.22	0.1209	117	-1.50	0.08	-0.53	[redacted]	-0.31	[redacted]
	8-11	61	-1.03	0.12	118	-1.18	0.08	-0.15	0.2863	117	-1.51	0.08	-0.48	[redacted]	-0.32	[redacted]
MSC	Baseline*	61	13.02	0.75	119	14.03	0.56	1.01		118	12.74	0.56	-0.28		-1.29	
	0.5	61	-2.04	0.51	119	-0.38	0.36	1.66	0.0082	118	-1.92	0.36	0.12	0.8529	-1.54	[redacted]
	1	61	-3.29	0.53	118	-2.57	0.38	0.73	0.2674	118	-3.67	0.38	-0.38	0.5609	-1.10	[redacted]
	2	61	-3.90	0.60	118	-4.24	0.43	-0.34	0.6431	118	-5.55	0.43	-1.65	[redacted]	-1.31	[redacted]
	1-6	61	-4.63	0.50	118	-4.55	0.36	0.08	0.8914	118	-6.26	0.36	-1.63	[redacted]	-1.71	[redacted]
	2-5	61	-4.93	0.55	118	-4.91	0.40	0.02	0.9754	118	-6.65	0.40	-1.71	[redacted]	-1.73	[redacted]
	7-12	61	-5.78	0.56	118	-6.13	0.40	-0.36	0.6076	117	-8.46	0.41	-2.68	[redacted]	-2.33	[redacted]
	8-11	61	-5.92	0.57	118	-6.16	0.41	-0.24	0.7349	117	-8.59	0.42	-2.66	[redacted]	-2.42	[redacted]
TSC	Baseline*	61	20.91	1.25	119	23.68	0.91	2.77		118	21.42	0.91	0.51		-2.26	
	0.5	61	-3.71	0.77	119	-1.06	0.55	2.66	0.0054	118	-2.82	0.55	0.89	0.3460	-1.77	[redacted]
	1	61	-5.68	0.84	118	-4.59	0.60	1.09	0.2922	118	-6.16	0.60	-0.48	0.6396	-1.57	0.0664
	2	61	-6.83	0.97	118	-7.29	0.70	-0.46	0.6994	118	-9.32	0.69	-2.49	[redacted]	-2.02	[redacted]
	1-6	61	-7.88	0.82	118	-8.03	0.59	-0.15	0.8841	118	-10.58	0.59	-2.70	[redacted]	-2.55	[redacted]
	2-5	61	-8.34	0.90	118	-8.63	0.65	-0.30	0.7893	118	-11.19	0.65	-2.86	[redacted]	-2.56	[redacted]
	7-12	61	-9.77	0.90	118	-10.70	0.65	-0.93	0.4064	117	-14.26	0.65	-4.49	[redacted]	-3.57	[redacted]
	8-11	61	-10.13	0.92	118	-10.74	0.66	-0.61	0.5914	117	-14.47	0.67	-4.33	[redacted]	-3.72	[redacted]

[redacted] Active Trt is statistically significantly superior to Placebo
CTC is statistically significantly superior to T-F Sinus

Placebo is statistically significantly superior to Active Trt

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/S/
for Barbara Elashoff

concur: S. E. Wilson /S/ - 6/27/00

cc:
Orig. NDA 21-082
HFD-570 / Division File
HFD-570 / RMeyer, BChowdhury, CLee, DHilfiker
HFD-715 / Chron, division file
HFD-715 / BElashoff, SWilson

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STATISTICAL REVIEW AND EVALUATION
STABILITY STUDY

NDA Number:	**21-082**
Applicant:	**Novartis Consumer Health, Inc.**
Name of Drug:	**Tavist® Allergy/Sinus/Headache (Clemastine Fumarate /Acetaminophen/Pseudoephedrine)**
Document Reviewed:	**Volume 7.1 - Stability data reports**
Statistical Reviewer:	**Feng Zhou, HFD-715**
Chemistry Reviewer:	**Kevin A. Swiss, Ph.D., HFD-570**

I. Introduction

The sponsor submitted the stability data to support its proposed 30- and 36-month shelf lives for ———— blister package types for Tavist® Allergy/Sinus/Headache. The two package types of the product were stored at 25°C/60%RH condition. The stability data include at least three batches for each package type.

II. Sponsor's Stability Analysis

Sponsor submitted the stability data reports for each testing-parameters of two package types ———— blister) on September 7, 2000 (Volume 7-1) and the electronic stability data (in SAS transport files/CD ROM) on January 02, 2001. The CD-ROM contains stability data through 60 months for the Clemastine Fumarate/Acetaminophen /Pseudoephedrine Hydrochloride Tablets, NDA 21-082. The data were further divided by package type ———— blister) and stability storage condition (25C/60%RH or 30C/60%RH). For the dissolution of Clemastine, Acetaminophen, and Pseudoephedrine at 30 minutes, sponsor submitted only summary variables (minimum, maximum, STD, and average). The individual dissolution data of Clemastine and Acetaminophen at 30 minutes were submitted in a subsequent amendment on February 13, 2001.

There are stability data of three batches through 30 months for each parameter of — blister package type and of more than three batches through 30 to 60 months for some parameters of —— package type. Batches 210451A, 210451B, and 210451C of — package type and batches 210450A, 210450B, and 210450C of —— package type at 25°C/60%RH had the most complete stability data up to 30 months for each parameter. The test times for the parameters of these six batch data were listed in the Tables A and B.

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The sponsor estimated the expiration dating periods based on only data of 25C/60%RH storage condition. Table C lists the specifications for the parameters the sponsor used to establish the stability for Tavist® Allergy/Sinus/Headache. The sponsor didn't submit the details of its estimation analysis. However, the sponsor proposes an expiration dating period of 36 months for the —— blister packaging configuration (p347) and an expiration dating period of 30 months for the — blister packaging configuration when the drug products are stored at room temperature (p352).

Table A
Summary of all Stability Data Points Submitted by the Sponsor for
Tavist® Allergy/Sinus/Headache Stored at 25C/60%RH

			Time Points (Month)								
Test	**Package**	**Batch**	**0**	**1**	**3**	**6**	**9**	**12**	**18**	**24**	**30**
Loss on Drying (Min, Max, Std, Avg.)		210451A, 210451B, 210451C	S	S	S	S	S	S	S	S	S
		210450A, 210450B, 210450C	S	S	S	S	S	S	S	S	S
Hardness (Min, Max, Std, Avg.)		210451A, 210451B, 210451C	S	S	S	S	S	S	S	S	S
		210450A, 210450B, 210450C	S	S	S	S	S	S	S	S	S
Clemastine Fumarate Content		210451A, 210451B, 210451C	S	S	S	S	S	S	S	S	S
		210450A, 210450B, 210450C	S	S	S	S	S	S	S	S	S
Acetaminophen Content		210451A, 210451B, 210451C	S	S	S	S	S	S	S	S	S
		210450A, 210450B, 210450C	S	S	S	S	S	S	S	S	S
Pseudoephedrine HCl Content		210451A, 210451B, 210451C	S	S	S	S	S	S	S	S	S
		210450A, 210450B, 210450C	S	S	S	S	S	S	S	S	S
Degradants of Clemastine Fumarate		210451A, 210451B, 210451C	S	S	S	S	S	S	S	S	S
		210450A, 210450B, 210450C	S	S	S	S	S	S	S	S	S
Total Degradants of Acetaminophen		210451A, 210451B, 210451C	S			S		S		S	
		210450A, 210450B, 210450C	S			S		S		S	S
Total Degradants of Clemastine Fumarate		210451A, 210451B, 210451C	S	S	S	S	S	S	S	S	S
		210450A, 210450B, 210450C	S	S	S	S	S	S	S	S	S
Total Degradants of Pseudoephedrine		210451A, 210451B, 210451C	S			S		S		S	
		210450A, 210450B, 210450C	S			S		S		S	S

S = Submitted in electronic copy (January 02, 2001)

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Table B

Summary of all Stability (dissolution) Data Point Submitted by the Sponsor for Tavist® Allergy/Sinus/Headache Stored at 25C/60%RH

			Time Points (Month)								
Test	**Package**	**Batch**	**0**	**1**	**3**	**6**	**9**	**12**	**18**	**24**	**30**
Acetaminophen	[redacted]	210451A, 210451B, 210451C	S, I					S, I		S, I	S, I
(Min, Max, Std, Avg.)		210450A, 210450B, 210450C	S, I					S, I		S, I	S, I
(Individual)											
Clemastine Fumarate		210451A, 210451B, 210451C	S, I					S, I		S, I	S, I
(Min, Max, Std, Avg.)		210450A, 210450B, 210450C	S, I					S, I		S, I	S, I
(Individual)											
Pseudoephedrine		210451A, 210451B, 210451C	S					S		S	S
(Min, Max, Std, Avg.)		210450A, 210450B, 210450C	S					S		S	S

S = Summary dissolution data submitted in electronic copy (January 02, 2001)

I = Individual dissolution data submitted in electronic copy (February 13, 2001)

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Table C

List of Specifications the Sponsor Used to Establish the Stability for

Tavist® Allergy/Sinus/Headache

Test Parameter	***Acceptance Criteria***
Loss on Drying	
Hardness	
Clemastine Fumarate Content	
Acetaminophen Content	
Pseudoephedrine HCl Content	
Unspecified Individual Degradants of Acetaminophen	
Total Unspecified Degradants of Acetaminophen	
Unspecified Individual Degradants of Clemastine Fumarate	
Degradation of Clemastine Fumarate	
Unspecified Individual Degradants of Pseudoephedrine HCl	
Total Individual Degradants of Pseudoephedrine HCl	
Dissolution Rate at 30 Minutes	Acetaminophen Q = — Pseudoephedrine Q = — Clemastine Q = —

III. Reviewer's Stability Analysis

This reviewer analyzed the data in accordance with FDA's "Guidelines for Submitting Documentation for the Stability of Human Drugs Biologics." Data up to thirty months from three batches (210451A, 210451B, and 210451C) of — package type and three batches (210450A, 210450B, and 210450C) of — package type stored at 25°C/60%RH were analyzed. The data submitted in electronic copy described in Tables A and B were used in the reviewer's analyses.

The results of this reviewer's analysis presented in Tables D-1 and D-2 appear to support a 30-month expiration date for — blister package type and a 36-month expiration date for — blister package type of the product.

In Table D-1, the shortest estimated expiration-dating period, — months, is based on the loss and drying data of the three batches of —blister package type. Figure-A shows the loss and drying data with the fitted line and the estimated expiration-dating period of the package type. In Table D-2, the shortest estimated expiration-dating period, 36 months, is based on Clemastine Fumarate individual vessel dissolution data at 30 minutes of the three batches of — blister package type. Figure B shows the data with the fitted line and the estimated expiration-dating period of the package type.

V. Conclusion

The results of this reviewer's analysis using data of three batches for each package type show that the sponsor's stability data support a 30-month expiration date for product packaged in — blister and a 36-month expiration date for product packaged in — blister.

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Table D-1

Expiry Date Analysis for Tavist® Allergy/Sinus/Headache

—Package Type stored at 25°C/60%RH Condition

Test	Specification	Model Selection	Batch	Fitted Line	Expiry Date
Acetaminophen Content	—	All batches are pooled	POOLED		
Clemastine Fumarate Content	—	The regression lines are Parallel	210451A 210451B 210451C		
Degradation of Clemastine Fumarate	—	All batches are pooled	POOLED		
Hardness Average of Five Tables	—	The regression lines are Parallel	210451A 210451B 210451C		
Hardness Maximum of Five Tables	—	The regression lines are Parallel	210451A 210451B 210451C		
Hardness Minimum of Five Tables	—	The regression lines are Parallel	210451A 210451B 210451C		
Loss on Drying	—	All batches are pooled	POOLED		
Degradation of Clemastine Fumarate	—	All batches are pooled	POOLED		
Degradation of Clemastine Fumarate	—	All batches are pooled	POOLED		
Pseudoephedrine Hydrochloride Content	—	The regression lines are Parallel	210451A 210451B 210451C		
Acetaminophen Dissolution rate at 30 minutes	Q = —	The regression lines are Parallel	210451A 210451B 210451C		
Clemastine Dissolution rate at 30 minutes	Q = —	The regression lines are Parallel	210451A 210451B 210451C		
Pseudoephedrine(Min) Dissolution rate at 30 minutes	Q = —	All batches are pooled	POOLED		

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Table D-2

Expiry Date Analysis for Tavist® Allergy/Sinus/Headache

PVCD Package Type Stored at 25°C/60%RH Condition

Test	Specification	Model Selection	Batch	Fitted Line	Expiry Date
Acetaminophen Content		All batches are pooled	POOLED		
Clemastine Fumarate Content		The regression lines have separate slopes & Intercepts	210450A 210450B 210450C		
Degradation of Clemastine Fumarate		All batches are pooled	POOLED		
Hardness Average of Five Tables		The regression lines are Parallel	210450A 210450B 210450C		
Hardness Maximum of Five Tables		The regression lines are Parallel	210450A 210450B 210450C		
Hardness Minimum of Five Tables		The regression lines are Parallel	210450A 210450B 210450C		
Loss on Drying		All batches are pooled	POOLED		
Degradation of Clemastine Fumarate		All batches are pooled	POOLED		
Degradation of Clemastine Fumarate		All batches are pooled	POOLED		
Pseudoephedrine Hydrochloride Content		The regression lines have separate slopes & Intercepts	210450A 210450B 210450C		
Acetaminophen Dissolution rate at 30 minutes	Q =	The regression lines have separate slopes & Intercepts	210450A 210450B 210450C		
Clemastine Dissolution rate at 30 minutes	Q =	The regression lines have separate slopes & Intercepts	210450A 210450B 210450C		
Pseudoephedrine(Min) Dissolution rate at 30 minutes	Q =	All batches are pooled	POOLED		

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Figure A

Expiry Date Analysis for Tavist® Allergy/Sinus/Headache

Stored with — Packaging at 25°C/60%RH Condition

For Loss on Drying Parameter

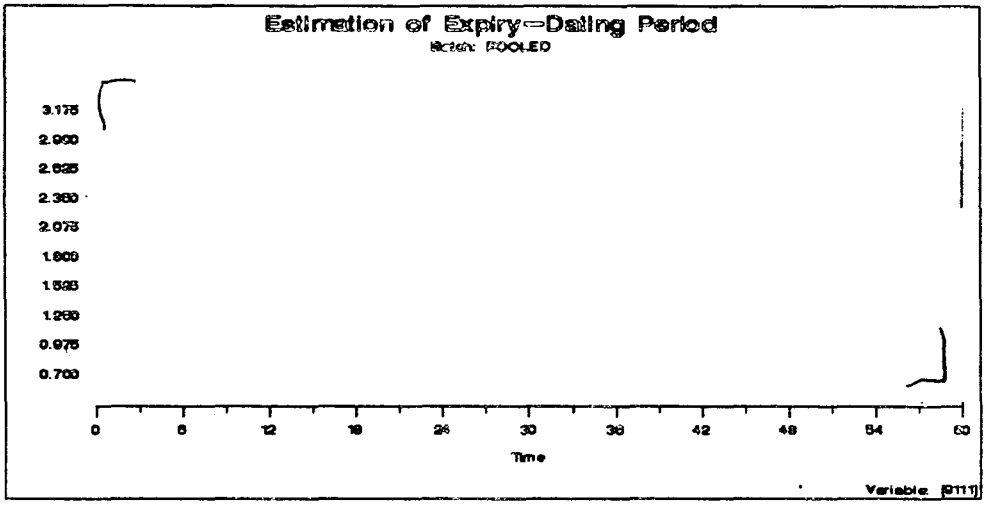
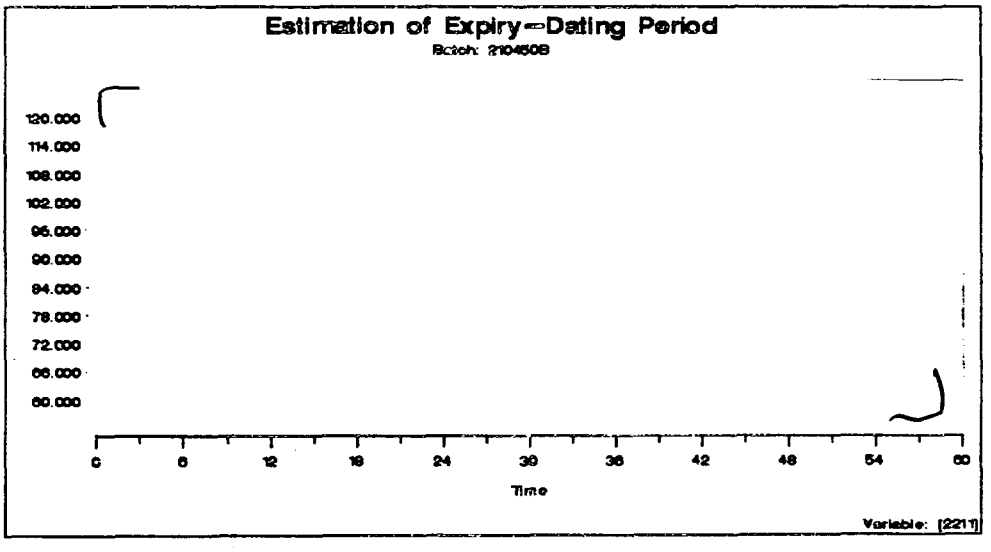


Figure B

Expiry Date Analysis for Tavist® Allergy/Sinus/Headache

Stored with — Packaging at 25°C/60%RH Condition

For Clemastine Dissolution Rate at 30 Minutes



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File name: STAB21_082.doc

/s/

Feng Zhou
2/28/01 11:27:51 AM
BIOMETRICS

Karl Lin
2/28/01 11:31:43 AM
BIOMETRICS
Concur with review

APPEARS THIS WAY
ON ORIGINAL