CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-565

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	21-565
Drug Name:	Relestat™ (Epinastine HCL Ophthalmic Solution 0.05%)
Indication(s):	Signs and Symptoms of Allergic Conjunctivitis
Applicant:	Allergan, Inc.
	2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534
Date (s):	Submitted: December 19, 2002
	Received: December 27, 2002
	Reviewed: March 31, 2003
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	M. Atiar Rahman, Ph.D. (HFD-725)
Concurring Reviewer:	Stan Lin, Ph.D. (HFD-725)
Medical Division:	Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products (HFD-550)
Clinical Team:	Wiley Chambers M.D. (HFD-550)
Project Manager:	Raphael Rodriguez (HFD-550)
Keywords:	NDA review, Clinical studies, Wilcoxon signed rank tests, Wilcoxon rank sum tests

Table of Contents

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

From the results of the two submitted studies, this reviewer concluded that Epinastine HCL 0.05% showed a marginally statistically significant effect in ocular itching but no significant effect in ocular hyperemia.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this submission the sponsor included reports of two Phase 3 studies, namely Study # 198027-001 (referenced hereafter as Study # 001) and, Study # 198027-002 (referenced hereafter as Study # 003). Study #001 had two arms, namely Epinastine HCL 0.05% and its vehicle. Study #003 had three arms, namely Epinastine HCL 0.05%, its vehicle, and an active comparetor (Levocabastine 0.05%). In Study #001 the primary objective was to establish the significant difference between the study drug (Epinastine) and its vehicle for both ocular itching and [redacted]. In Study #003 the primary objective was to establish the significant difference between the study drug (Epinastine) and its vehicle for ocular itching only. Two of the secondary objectives in Study #003 were to establish the significant difference between the study drug and its vehicle for [redacted], and to establish the non-inferiority of the study drug compared to the comparetor for ocular itching and [redacted]

1.3 STATISTICAL ISSUES AND FINDINGS

There were some differences in the design and conduct of the two submitted studies. In Study #001 the primary efficacy time point was Day 21 and that in Study #003 was Day 14. Also the Study #001 was conducted as conjunctival antigent challenge (CAC) model, while the Study #003 was an environmental study.

Study #001 showed statistically significant effect of the study drug over its vehicle in both ocular itching and [redacted]. Results of Wilcoxon rank-sum rank test on data of Study #003 showed statistically significant reduction of ocular itching compared to that of the vehicle, however the ANOVA analysis did not show such statistical significance.

2 INTRODUCTION

2.1 OVERVIEW

In this NDA the sponsor submitted data to support their claim that the use of Epinastine HCL ophthalmic solution 0.05% (RELESTAT™) is safe and efficacious for the prevention [redacted] allergic conjunctivitis.

2.2 DATA SOURCES

The submission was in hard copy and partially electronic. Submitted data was stored in folder \\Cdsesub1\n21565\N_000\2002-12-19\crt\datasets in FDA's Electronic Document Room (EDR). The data quality of the submission was within acceptable limit.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY # 001

Title: "A single-Center, Double-Masked, Randomized, Vehicle-Controlled Study of the Efficacy and Safety of Epinastine Hydrochloride 0.05% Ophthalmic Solution Used as a Single Dose in Two Occasions in the Conjunctival Antigen Challenge Model in Patients with History of Allergic Conjunctivitis."

3.1.1.1 Design and Objectives

This was a randomized, double-masked, vehicle-controlled, single-centered study designed to compare the safety and efficacy of Epinastine HCL ophthalmic solution 0.05% for the prevention of [redacted] allergic conjunctivitis to those of its vehicle.

The study treatments were randomly assigned by eye. The patients were at least 10 years of age with a known history of allergic conjunctivitis and manifested a positive CAC reaction. Patients' individual eyes were randomly assigned to receive either Epinastine or its vehicle in a 1:1 ratio. There were 3 treatment combinations: Epinastine in both eyes, Epinastine in one eye and vehicle in the other eye, and vehicle in both eyes.

Patients had a screening at Visit 1 (Day 0) and a confirmatory antigen challenge with the antigen at Visit 2 (Day 7). At visit 3 (Day 21), patients received 1 drop of study medication in each eye 15 minutes prior to antigen challenge to determine onset of action. At visit 4 (Day 35), patients received 1 drop of study medication in each eye 8 hours prior to antigen challenge to determine duration of action.

3.1.1.2 Primary Efficacy Endpoint

The primary efficacy measures were ocular itching and [redacted]. Assessments of itching were made 3, 5, and 10 minutes after antigen challenge according to a standardized grading system. Assessments of [redacted] chemosis, tearing, lid swelling, and mucous discharge were made 5, 10, and 20 minutes after antigen challenge according to standardized grading systems. The efficacy timepoint for onset of action was Day 21 (15 minutes challenge) and Day 35 for duration of action (8 hours challenge).

Itching was evaluated by the patient on a scale from 0 to 4 as follows:

0 None
1 An intermittent tickle sensation involving more than just the corner of the eye
2 A mild continuous itch (can be localized) without desire to rub
3 A severe itch with desire to rub
4 An incapacitating itch with an irresistible urge to rub.

[redacted] was evaluated by the examiner [redacted] as follows:

[redacted]

3.1.1.3 Secondary Efficacy endpoint

Secondary efficacy measures were [redacted], chemosis, tearing, lid swelling, and mucous discharge. Chemosis was evaluated by the examiner on a scale from 0 to 4, while Lid swelling was evaluated by the patient on a scale from 0 to 3. Mucous discharge was measured as present or absent.

3.1.1.4 Patient Analyzed

Intent-to-Treat Population: The intent-to-treat (ITT) population included all randomized patients. All patients were analyzed "as randomized" for efficacy variables.

Safety Population: All patients who received at least 1 administration of study medication comprised the safety population, and were to be analyzed "as treated" for the safety variables.

3.1.1.5 Disposition of Patients, Demography

Disposition and demographic characteristics of ITT patients is given in Table 1 and 2, respectively in the appendix. A total of 126 patients were enrolled in the study: 30 patients randomly assigned to receive Epinastine in both eyes (epi/epi), 67 patients randomly assigned to receive Epinastine in one eye and vehicle in the contralateral eye (epi/veh), and 29 patients randomly assigned to receive vehicle in both eyes. All patients completed the study with the exception of patient #3153-1021, who received epi/veh on Day 21 and was lost to follow-up before Day 35.

There were no significant differences among the treatment groups in demographic or baseline characteristics. The mean age was 38.4 years. The majority of patients (88.9%, 112/126) were between 18 and 64 years; 10 patients were 17 years or younger. There was a higher proportion of females (56.3%, 71/126) than males (43.7%, 55/126), however the difference was not statistically significant (p=0.059). The population was primarily Caucasian (95.2%, 120/126). The most common iris colors were brown (46.0%, 58/126) and blue (27.8%, 35/126).

3.1.1.6 Sponsor's Analysis of Primary Efficacy Data

The primary analysis was the paired comparison of Epinastine versus vehicle among patients who received different treatments in contralateral eyes (paired-eyes population). Secondary analyses were the parallel comparison of Epinastine versus vehicle among patients who received the same treatment in both eyes (parallel-patients population), and the parallel comparison considering eyes instead of patients as the independent unit of study (parallel-eyes population). The analyses of efficacy variables were based on raw values.

For the paired-eyes population, bilateral efficacy variables were reduced to the difference between eyes of Epinastine minus vehicle scores at each measurement time. For the parallel-patients population, bilateral efficacy variables were reduced to the mean score over both eyes at each measurement time. For the parallel-eyes population, eyes were treated independently for the efficacy analyses. Comparisons of paired treatments were done with Wilcoxon signed rank tests, and comparisons of parallel treatments (parallel-patients and parallel-eyes populations) were done with Wilcoxon rank sum tests.

Since both ocular itching and [redacted] at all time points was used to determine success or failure, no adjustments for multiplicity was done.

If a pre-challenge value was missing for an efficacy variable, a value of "0" was imputed. For the primary efficacy variables of ocular itching and [redacted] missing data were imputed by the last observation carried forward (LOCF) within the same study visit for Day 21 and Day 35 only. Data were not carried forward from the previous visit. If there were no post-challenge data, data from the pre-challenge time period were carried forward. LOCF was employed for the secondary efficacy variables and analyzes in the same manner as for the primary efficacy variables.

3.1.1.7 Sponsor's Results and Conclusions

Ocular Itching

The primary analysis was comparison of the paired treatments (paired-eyes population) at the onset challenge (Day 21) and the duration challenge (Day 35). Sponsor's results for ocular itching are given in Text Table 1. The ocular itching scores were significantly lower with Epinastine treatment than with vehicle treatment at all measured time points (3, 5, and 10 minutes) post-challenge on both Days 21 and 35 ($p < 0.001$). The mean score pre-challenge was 0 on Days 21 and 35 for both Epinastine-treated and vehicle-treated eyes. The mean scores post-challenge on Day 21 were ≤ 0.49 for Epinastine-treated eyes compared with ≥ 1.93 for vehicle-treated eyes. The mean scores post-challenge on Day 35 were ≤ 0.95 for Epinastine treated eyes compared with ≥ 1.86 for vehicle-treated eyes. Based on the protocol definition of clinical superiority as a 1-grade or greater difference between Epinastine and vehicle, the sponsor considered Epinastine as clinically superior to vehicle for both the onset challenge and the duration challenge.

Reviewer's comment: This reviewer did not find this definition of "clinical superiority" in the submitted protocol. The appropriate statistical method of establishing the superiority is to construct the 95% CI on the centrality parameter and compare the upper confidence limit of calculated confidence interval with a pre-specified superiority margin.

Text Table 1 **Mean Ocular Itching Scores on Day 21 (Onset Challenge) and Day 35 (Duration Challenge) for Paired-Eyes Comparison**

		Epinastine Mean (SD) (N = 67)	Vehicle Mean (SD) (N = 67)	Difference[a] Mean (SD) (N = 67)	P-Value[b]
Day 21					
	Pre-challenge	0.00	0.00	0.00	> 0.999
	3 minutes	0.45 (0.77)	1.99 (1.01)	-1.54 (1.10)	< 0.001
	5 minutes	0.49 (0.89)	2.22 (0.90)	-1.72 (1.10)	< 0.001
	10 minutes	0.41 (0.80)	1.93 (0.94)	-1.51 (1.16)	< 0.001
Day 35					
	Pre-challenge	0.00	0.00	0.00	> 0.999
	3 minutes	0.92 (0.93)	1.86 (0.93)	-0.95 (1.00)	< 0.001
	5 minutes	0.95 (0.94)	2.04 (0.83)	-1.08 (1.00)	< 0.001
	10 minutes	0.80 (0.79)	1.86 (0.90)	-1.06 (1.09)	< 0.001

a Difference = Epinastine minus vehicle; a negative difference favors Epinastine.
b P-value based on Wilcoxon signed rank test on the difference.
Source: Table 11.4.1.1-1 of sponsor's analysis. Standard deviations were calculated by this reviewer.

[redacted]

Results of sponsor's analysis of secondary efficacy endpoints in paired eye population

The [redacted] scores, the chemosis, and lid swelling scores were significantly lower with Epinastine treatment than with vehicle treatment at all measured time points (5, 10, and 20 minutes) post-challenge on both Days 21 and 35 ($p<0.009$). Mucous discharge was rarely reported. There was

no statistically significant difference between Epinastine and vehicle treatment in the frequency of mucous discharge.

Parallel-Eyes Population

Analysis of the parallel-eyes population compared the response to Epinastine and that to vehicle in all patients, and included 127 Epinastine-treated eyes (patients randomized to epi/epi and epi/veh) and 125 vehicle-treated eyes (patients randomized to veh/veh and epi/veh).

Sponsor's results for ocular itching and [redacted] are given in Tables 3 and 4, respectively in the appendix. The ocular itching and the [redacted] scores were significantly lower with Epinastine treatment than with vehicle treatment at all measured time points (3, 5, and 10 minutes) post-challenge on both Days 21 and 35 ($p < 0.001$). At time points 20 minutes these p-values were 0.002 and [redacted] for ocular itching and [redacted], respectively.

Parallel-Patients Population

Analysis of the parallel-patients population compared the response to Epinastine and that to vehicle in patients who received the same treatment in both eyes, 30 patients treated with Epinastine (epi/epi) and 29 patients treated with vehicle (veh/veh). For this analysis, bilateral efficacy variables were reduced to the mean score over both eyes at each measurement time.

Sponsor's results for ocular itching and [redacted] are given in Tables 5 and 6, respectively in the appendix. The ocular itching scores were significantly lower with Epinastine treatment than with vehicle treatment at all measured time points (3, 5, and 10 minutes) post-challenge on both Days 21 and 35. The [redacted] scores were [redacted]

3.1.1.8 Reviewer's Findings and Conclusions

This reviewer verified some of the sponsor's analysis. This reviewer's results agreed with those of the sponsor. Therefore, this reviewer concurred with the sponsor's conclusion.

3.1.2 STUDY # 003

Title: "A Multi-Center, Randomized, Double-Masked, Parallel Group Study Evaluating the Efficacy and Safety of Epinastine Hydrochloride 0.05% Ophthalmic Solution Compared to Vehicle of Epinastine or to Levocabastine 0.05% Ophthalmic Suspension Used Twice Daily for 8 Weeks in an Environmental Study in Adult and Pediatric Patients with Seasonal Allergic Conjunctivitis."

3.1.2.1 Objectives and Design

The objective of this study was to demonstrate the efficacy and safety of Epinastine HCl 0.05% ophthalmic solution in adult and pediatric patients with seasonal allergic conjunctivitis.

This was a multicenter, randomized, double-masked, vehicle- and active-controlled, parallel group, refined (CAC screen) environmental study in adult and pediatric patients with seasonal allergic

conjunctivitis. Patients at least 9 years old with a known history of seasonal allergic conjunctivitis who manifested a positive CAC response at screening were enrolled. Patients were randomly assigned to receive Epinastine HCl 0.05% ophthalmic solution (Epinastine), Levocabastine 0.05% ophthalmic suspension (Levocabastine), or the vehicle of Epinastine (vehicle) in a 2:2:1 ratio. Randomization was stratified by age (9 to 17 years inclusive, ≥ 18 years) to ensure that approximately 25 children completed each active treatment and 13 children completed treatment with vehicle.

Treatment was administered as 1 drop into each eye BID for 56 days (8 weeks). There were 6 scheduled visits during the study: days -42 to -7 (screening), 0 (randomization), 14, 28, 42, and 56 (or study exit).

3.1.2.2 Primary Efficacy Endpoint

The primary efficacy endpoint was the worst daily ocular itching as graded by the patient (diary data). The primary comparison was between Epinastine and vehicle in intent-to-treat population. Patients were analyzed with the treatment to which they were randomly assigned.

Patient self-assessments of ocular itching and [redacted] were collected 3 times daily in a take-home diary. Patients were asked to evaluate their symptoms in the morning prior to instillation of the eye drops, in the afternoon before the second instillation, and at bedtime at least 2 hours after the second instillation.

For each patient, the worst daily ocular itching and [redacted] scores for analysis were taken from the highest of 6 scores (3 evaluations for each eye) recorded by the patient each day. The worst evening ocular itching and [redacted] scores for analysis were taken from the highest of 2 scores (one for each eye) recorded by the patient each evening. These scores were averaged over the 2-week period of peak pollen count for each patient for most analyses, and over the 2-week period of peak ocular itching for a supplemental analysis.

Patient's ocular itching was evaluated using the same grading scale as were used for Study #001, i.e. five grades namely, 0, 1, 2, 3, and 4.

3.1.2.3 Secondary Efficacy endpoint

Secondary efficacy measures were [redacted] Evening ocular itching, Ocular itching (graded by patient, official evaluation), Lid swelling, Tearing, [redacted] Chemosis, and Ocular mucous discharge. Secondary efficacy endpoints were also evaluated using similar grading scale as were used for Study #001.

3.1.2.4 Patient Analyzed

Intent-to-Treat Population: The intent-to-treat (ITT) population included all randomized patients. All patients were analyzed "as randomized" for efficacy variables.

Safety Population: All patients who received at least 1 administration of study medication comprised the safety population, and were to be analyzed "as treated" for the safety variables.

3.1.2.5 Disposition of Patients, Demography, and Baseline Disease Conditions

Patients disposition is given Table 7 in the appendix. A total of 298 patients were enrolled in the study: 118 received Epinastine, 118 received Levocabastine, and 62 received vehicle. All except 4 patients (98.7%, 294/298) completed the study. Two Epinastine-treated patients discontinued from the study due to adverse events, 1 vehicle-treated patient discontinued due to an adverse event, and 1 vehicle-treated patient discontinued due to use of a prohibited concomitant medication. Three patients discontinued by Day 14 and the fourth discontinued by Day 56.

There were no significant differences among the 3 treatment groups in any baseline characteristic. Overall, the mean age in the intent-to-treat population was 32.7 years. The demographic characteristics are given in Table 8 in the appendix. There were 54 children, including 21 treated with Epinastine, 20 treated with Levocabastine, and 13 treated with vehicle. Males comprised 46.6% (139/298) of the patients and females 53.4% (159/298). Racial distribution was 46.3% (138/298) Asian, 44.0% (131/298) Caucasian, 3.7% (11/298) black, 3.7% (11/298) Hispanic, and 2.3% (7/298) other. The most common iris colors were brown (65.1%, 194/298) and blue (18.5%, 55/298).

3.1.2.6 Sponsor's Analysis of Primary Efficacy Data

In the primary analyses, Epinastine was tested for superiority over vehicle for the primary efficacy variable (average worst daily ocular itching) in the intent-to-treat population. Following the protocol, the Wilcoxon rank-sum test was performed for the comparison of diary data between the treatment groups rather than the ANOVA test because of the skewed distribution. The 95% confidence intervals (CI) of the difference between any two treatment groups were calculated using the method by Moses (Hollander and Wolfe, 1973). The large sample approximation was used. The comparison of Epinastine with vehicle was also performed by 2-way ANOVA with factors for treatment, investigator, and treatment-by-investigator interaction, as stated in the protocol and analysis plan. Type III sums of squares was used. In addition, the 2-sided 95% CI for the difference between 2 groups was calculated. The dependent variable was based on the average worst ocular itching score over the 2-week period of peak pollen count. The least squares mean estimates and standard error estimates were based on the 2-way ANOVA.

The secondary analyses of average worst daily ocular itching (the primary efficacy variable) included the superiority comparison of Epinastine over vehicle in the per-protocol population, the comparisons between Epinastine and Levocabastine for non-inferiority in the intent-to-treat and per-protocol populations, and the superiority comparison of Levocabastine over vehicle in the intent-to-treat and per-protocol populations. The same analyses were performed for [redacted]

Establishment of non-inferiority was based on 2-sided 95% CIs for the median difference of the Epinastine average worst daily ocular itching scores minus the Levocabastine scores. Epinastine was to be deemed non-inferior to Levocabastine if the upper end of the 95% CI was < 0.4. In addition, the p-values for the null hypothesis of no difference between the 2 group means were also calculated. The CIs and p-values for the Epinastine and Levocabastine comparison were constructed similarly as those between Epinastine and vehicle.

Reviewer's comment: In the original protocol the null hypothesis was equality of effectiveness of Epinastine and vehicle in treating ocular allergy as measured by worst daily ocular itching. A secondary hypothesis was non-inferiority of Epinastine compared to Levocabastine in per-protocol population. Epinastine was to be deemed non-inferior to Levocabastine if the upper end of the 95% CI was < 0.4.

3.1.2.7 Sponsor's Results and Conclusions

Four variables were analyzed for the 2-week period of pollen count based on the diary data: 1) average worst daily ocular itching, 2) average worst evening ocular itching, [redacted]. Examination of normality by the Shapiro-Wilks test and plots of the data showed that the distributions were non-normal. Therefore, Wilcoxon rank-sum test was applied for the primary analysis. Analysis of variance (ANOVA) was also performed. The primary analysis was the superiority comparison of Epinastine over vehicle in the intent-to-treat population.

Primary Efficacy Variable: Average Worst Daily Ocular Itching

Sponsor's results of average worst daily ocular itching are given in Text Table 3. The median average worst daily ocular itching scores based on the 2-week peak pollen count were 0.45, 0.60, and 0.85 for the Epinastine, Levocabastine, and vehicle groups, respectively The ocular itching scores were significantly better for the Epinastine group than the vehicle group (p = 0.045). The median score was numerically better for the Levocabastine group than the vehicle group; however, the difference was not statistically significant.

Text Table 3 **Median Values for Diary Data Based on 2-Week Peak Pollen Count (Intent-to-Treat Population)**

	Epi (N =118)	Levo (N =118)	Veh (N =62)	P-Values[a] Epi vs Veh	Levo vs Veh	Epi vs Levo
Variable						
Average worst daily ocular itching itching	0.45	0.60	0.85	0.045	0.270	0.364
Average worst evening ocular itching	0.20	0.20	0.40	0.065	0.198	0.609
[redacted]						

a From Wilcoxon rank-sum test.
Source: 11.4.1.1 of Sponsor's analysis

The mean worst daily ocular itching scores were 0.77, 0.86, and 0.93 for the Epinastine, Levocabastine, and vehicle groups, respectively. The mean scores were numerically better for the Epinastine and Levocabastine groups than the vehicle group but the differences were not statistically significant. Results of sponsor's analysis are given in Table 9, in the appendix.

Using the non-parametric approach, the upper limit of the 2-sided 95% CI for the difference between Epinastine and Levocabastine in average worst daily ocular itching based on the 2-week peak pollen period was 0.100, which met the criterion for non-inferiority (< 0.4).

Reviewer's comment: Sponsor's analysis involved three pairwise comparisons for each of the four efficacy endpoints. Therefore, the p-values needed to be adjusted for multiple testing. Also the choice of Wilcoxon rank-sum test as the primary efficacy analysis was conditional on a preliminary test. Therefore, the p-values need to be interpreted cautiously.

Average Worst Evening Ocular Itching

The median average worst evening ocular itching scores were 0.20, 0.20, and 0.40 for the Epinastine, Levocabastine, and vehicle groups, respectively. The median scores were numerically better for the Epinastine and Levocabastine groups than the vehicle group but the differences were

not statistically significant ($p \geq 0.065$). The mean average worst evening ocular itching scores were 0.46 for Epinastine treated patients, 0.53 for Levocabastine-treated patients, and 0.57 for vehicle-treated patients.

[redacted]

Results of sponsor's analysis of secondary efficacy endpoints in paired eye population

The sponsor's analysis showed statistically significant difference between Epinastine and vehicle in ocular mean itching change from baseline on Day 42 ($p=0.031$). The Levocabastine group had a higher mean score of ocular itching than the vehicle group at baseline (0.453 vs. 0.238, $p = 0.053$). After adjustment for this difference at baseline, differences in mean change from baseline in ocular itching were statistically significant at Day 14 (-0.233 vs +0.160, $p = 0.002$) and Day 42 (–0.263 vs. +0.079, $p = 0.006$). [redacted] Lid swellings showed statistically significant difference between the Levocabastine and vehicle groups on Day 14 ($p = 0.038$).

There were no significant differences between either of the active treatment groups and the vehicle group in [redacted] Chemosis, Mucous Discharge, and Tearing.

3.1.2.8 Reviewer's Findings and Conclusions

The sponsor's findings (Text Table 3) showed marginal significance in worst ocular itching. This p-value was calculated based on Wilcoxon rank-sum test. Results of sponsor's ANOVA analysis are given in Tables 9 and 10 in the appendix. Table 9 shows the results of an ANOVA analysis using treatment, investigator, and treatment-by-investigator interaction. Table 10 shows similar results using model with baseline as a covariate. Results from Table 9 show a p-value of 0.284 for the comparison on Epinastine with Vehicle. Results in Table 10 show a p-value of 0.118 for similar comparison. Therefore, results of ANOVA analysis did not show any significant difference between Epinastine and vehicle for worst ocular itching.

Comparing results from Text Table 3, Tables 9 and 10 this reviewer concluded that there was at best a marginally statistically significant difference between Epinastine and vehicle for worst ocular itching. No statistically significant difference was found in [redacted]

3.2 EVALUATION OF SAFETY

3.2.1 SPONSOR'S ANALYSIS OF SAFETY DATA

The sponsor summarized the incidences of adverse events classified by their severity, seriousness, and relation to the study drug. A listing of all adverse events was included.

The incidences of adverse events showed no significant differences among the treatment groups overall or for any individual adverse event. There were no ocular adverse events and no adverse event was considered related to study medication. The only adverse event reported for more than one patient was infection, specifically cold symptoms, which was reported for 3.3% (1/30) of patients in epi/epi group, 7.5% (5/67) of patients in the epi/veh group, and 6.9% (2/29) of patients in the veh/veh group. The incidence of cold symptom was considered as moderate in severity.

There were no death or serious adverse events. From Study #003 two epinastine-treated patients and one vehicle-treated patient discontinued due to an adverse event. No patient discontinued the study due to adverse events from Study #001.

3.2.2 REVIEWER'S ANALYSIS OF SAFETY DATA

This reviewer did not perform any analysis on the safety data. This reviewer refers to the clinical review for safety analysis.

4 FINDINGS IN SPACIAL/SUBGROUP POPULATIONS

The sponsor did not perform any subgroup analysis in either study. Study #003 was designed to recruit both pediatric (<= 17 Years) and adult (>=18 Years) patients. There were about 20% pediatric patients in this study. In the sponsor's efficacy analysis both pediatric and adult patients were lumped together. The effects of Epinastine separately for pediatric and adult patients might be worth looking. Therefore, this reviewer performed an analysis of worst daily ocular itching, sub-grouping the patients by age. This reviewer also performed an analysis of the same variable, sub-grouping the patients by gender. No other sub-group analysis was performed.

4.1 SUB-GROUP ANALYSIS BY AGE

Text Table 4 shows this reviewer's analysis of worst daily ocular itching sub-grouping the patients by age.

Text Table 4 **Median of Average worst daily ocular itching Values Based on 2-Week Peak Pollen Count- Sub-Grouping by Age (Reviewer's table)**

				P-Values[a]		
Population	Epi	Levo	Veh	Epi vs. Veh	Levo vs. Veh	Epi vs. Levo
≤ 17 Years	N=21	N=20	N=13			
	Mdian=0.92	Mdian=0.25	Mdian=0.93	1.00	0.079	0.145
≥ 18 Years	N=97	N=98	N=49			
	Mdian=0.43	Mdian=0.64	Mdian=0.71	0.041	0.638	0.097
All patients	N=118	N=118	N=62			
	Mdian=0.44	Mdian=0.64	Mdian=0.82	0.047	0.254	0.392

a From Wilcoxon rank-sum test.

Results of this sub-group analysis show that Epinastine did not have similar effect on pediatric population as it had on adult population. For pediatric population, the point estimate for Epinastine group was almost the same as that of the vehicle group. However, it should be noted that the study was not designed to study any special sub-groups. For "All patients" there were some differences between the results of sponsor and those of this reviewer. However, the differences were ignorable. This reviewer did not try to resolve these differences.

4.2 SUB-GROUP ANALYSIS BY GENDER

Text Table 5 shows this reviewer's analysis of worst daily ocular itching sub-grouping gender.

Text Table 5 **Median of Average worst daily ocular itching Values Based on 2-Week Peak Pollen Count- Sub-Grouping by Gender (Reviewer's table)**

Population	Epi	Levo	Veh	P-Values[a] Epi vs. Veh	Levo vs. Veh	Epi vs. Levo
Male	N=57	N=56	N=26			
	Mdian=0.21	Mdian=0.53	Mdian=0.85	0.022	0.108	0.309
Female	N=61	N=62	N=36			
	Mdian=0.64	Mdian=0.67	Mdian=0.75	0.657	0.947	0.851
All patients	N=118	N=118	N=62			
	Mdian=0.44	Mdian=0.64	Mdian=0.82	0.047	0.254	0.392

a From Wilcoxon rank-sum test.

Results of this sub-group analysis show that Epinastine did not have similar effect on both sexes. Epinastine showed much less effect on females than on males. It should again be noted that the study was not designed to study any special sub-groups. Note that Levocabastine had similar effect on both sexes.

4.3 SUB-GROUP ANALYSIS BY RACE

No sub-group analysis by race was performed.

4.4 ANALYSIS BY OTHER SPECIAL/SUBGROUP POPULATIONS

No analysis was performed for any other special sub-group.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

In this submission the sponsor included reports of two Phase 3 studies, namely Study #001 and Study #003. In Study #001 the primary objective was to establish the significant difference between the study drug (Epinastine) and its vehicle for both ocular itching and [redacted] in Study #003 the primary objective was to establish the significant difference between the study drug (Epinastine) and its vehicle for ocular itching only. Two of the secondary objective ware to establish the significant difference between the study drug (Epinastine) and its vehicle for [redacted] and to establish the non-inferiority of the study drug and the comparetor.

There were some differences in the design and conduct of the two submitted studies. In Study #001 the primary efficacy time point was Day 21 and that in Study #003 was Day 14. Also the Study #001

was conducted as conjunctival antigent challenge model, while the Study #003 was an environmental study. Therefore, the collective evidences should be interpreted carefully with clinical justifications.

This reviewer based his overall evaluation of effectiveness of the drug on both ocular itching and [redacted] Based on the protocol, the sponsor considered only the outcome of their non-parametric tests (Wilcoxon signed rank test for Study #001 and Wilcoxon rank-sum test for Study #003) for overall conclusion. In this reviewer's conclusion outcome of the ANOVA analysis were also taken into account to see the robustness of the results.

5.2 CONCLUSIONS AND RECOMMENDATIONS

From the results of the two submitted studies, this reviewer concluded that Epinastine HCL 0.05% showed a marginally statistically significant effect in ocular itching [redacted]. Sub-group analyses showed difference in the reduction of ocular itching between pediatric and adult patients. Similar difference in reduction of ocular itching was also found between male and female patients.

M. Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Stan Lin, Ph.D.
Team Leader

cc:
Archival NDA 21-565
HFD-550/Division File
HFD-550/Dr. Chambers
HFD-550/Mr. Rodrigues

HFD-725/ Chron
HFD-725/ Dr. Huque
HFD-725/ Dr. Lin
HFD-725/ Dr. Rahman
HFD-700/Dr. Anello

6 APPENDIX

Table 1
Patient Disposition
(Sutdy #001, Intent-to-Treat Population)

	Epi/Epi [a] (N=30)		Epi/Veh [b] (N=67)		Veh/Veh [c] (N=29)		Total (N=126)	
Disposition:								
Enrolled	30		67		29		126	
Completed	30 (100.0%)		66 (98.5%)		29 (100.0%)		125 (99.2%)	
PATIENT DISCONTINUED DUE TO:								
Lack of Efficacy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Adverse Events	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Pregnancy	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Administrative Reasons:								
Lost to Follow-up	0	(0.0%)	1	1.5%)	0	(0.0%)	1	(0.8%)
Relocated	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Personal reasons	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Protocol Violations:								
Improper Entry	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-Compliance	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Other	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
TOTAL DISCONTINUED	0		1		0		1	

[a] Epinastine applied to both eyes.
[b] Epinastine applied to one eye and vehicle applied to the contralateral eye.
[c] Vehicle applied to both eyes.
Source: Table 1, Section 14.1 of Sponsor's Analysis

Table 2
Demographics
(Study #001, Intent-to-Treat Population)

	Epi/Epi [a] (N=30)	Epi/Veh [b] (N=67)	Veh/Veh [c] (N=29)	Total (N=126)	P-value [d]
Age (years)					
N	30	67	29	126	0.324 [e]
Mean	36.8	38.4	40.0	38.4	
SD	13.38	14.16	10.91	13.24	
Median	40.0	37.0	42.0	39.5	
Min	11	12	11	11	
Max	60	67	54	67	
<= 17 years	4 (13.3%)	5 (7.5%)	1 (3.4%)	10 (7.9%)	
18 - 64 years	26 (86.7%)	58 (86.6%)	28 (96.6%)	112 (88.9%)	
>= 65 years	0 (0.0%)	4 (6.0%)	0 (0.0%)	4 (3.2%)	
Sex					
N	30	67	29	126	0.497 [f]
Male	14 (46.7%)	30 (44.8%)	11 (37.9%)	55 (43.7%)	
Female	16 (53.3%)	37 (55.2%)	18 (62.1%)	71 (56.3%)	
Race					
N	30	67	29	126	
Caucasian	28 (93.3%)	64 (95.5%)	28 (96.6%)	120 (95.2%)	
Black	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Asian	1 (3.3%)	1 (1.5%)	0 (0.0%)	2 (1.6%)	
Hispanic	1 (3.3%)	2 (3.0%)	0 (0.0%)	3 (2.4%)	
Other [h]	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (0.8%)	
White	28 (93.3%)	64 (95.5%)	28 (96.6%)	120 (95.2%)	>0.999 [g]
Non-White	2 (6.7%)	3 (4.5%)	1 (3.4%)	6 (4.8%)	

[a] Epinastine applied to both eyes.
[b] Epinastine applied to one eye and vehicle applied to the contralateral eye.
[c] Vehicle applied to both eyes.
[d] P-values are for Epi/Epi vs. Veh/Veh comparison (parallel patient comparison).
[e] P-value based on a two-sample t-test.
[f] P-value based on the Pearson chi-square test for two-by-two tables.
[g] P-value based on the Fisher's exact test for two-by-two tables.
[h] The race "other" includes Indian.
Source: **Table 2, Section 14.1 of Sponsor's Analysis**

Table 2 (Continue)
Demographics
(Study #001, Intent-to-Treat Population)

	Epi/Epi [a] (N=30)	Epi/Veh [b] (N=67)	Veh/Veh [c] (N=29)	Total (N=126)	P-value [d]
Iris Color					
N	30	67	29	126	
Blue	7 (23.3%)	19 (28.4%)	9 (31.0%)	35 (27.8%)	
Brown	15 (50.0%)	28 (41.8%)	15 (51.7%)	58 (46.0%)	
Green	3 (10.0%)	6 (9.0%)	2 (6.9%)	11 (8.7%)	
Hazel	5 (16.7%)	14 (20.9%)	3 (10.3%)	22 (17.5%)	
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Dark [e]	15 (50.0%)	28 (41.8%)	15 (51.7%)	58 (46.0%)	0.895 [g]
Light [f]	15 (50.0%)	39 (58.2%)	14 (48.3%)	68 (54.0%)	
Weight (kg)					
N	30	67	29	126	0.384 [h]
Mean	77.74	77.81	82.72	78.92	
SD	21.565	18.358	22.041	19.975	
Median	74.75	75.50	79.50	75.70	
Min	31.8	50.0	50.0	31.8	
Max	127.3	126.4	138.6	138.6	
Height (cm)					
N	30	67	29	126	0.733 [h]
Mean	168.31	168.82	169.22	168.79	
SD	10.569	9.819	9.664	9.891	
Median	167.60	167.60	170.20	167.60	
Min	151.1	152.4	149.9	149.9	
Max	193.0	193.0	188.0	193.0	

[a] Epinastine applied to both eyes.
[b] Epinastine applied to one eye and vehicle applied to the contralateral eye.
[c] Vehicle applied to both eyes.
[d] P-values are for Epi/Epi vs. Veh/Veh comparison (parallel patient comparison).
[e] Dark irises: brown.
[f] Light irises: blue, green, hazel, and others.
[g] P-value based on the Pearson chi-square test for two-by-two tables.
[h] P-value based on a two-sample t-test.
Source: Table 2, Section 14.1 of Sponsor's Analysis

Table 3

Mean Ocular Itching Scores on Day 21 (Onset Challenge) and Day 35 (Duration Challenge) for Parallel-Eyes Comparison (Study #001, Intent-to-Treat Population)

		Epinastine (N = 127)	Vehicle (N = 125)	Difference[a]	P-Value[b]
Day 21					
	Pre-challenge	0.00	0.00	0.00	> 0.999
	3 minutes	0.59	1.97	-1.39	< 0.001
	5 minutes	0.70	2.06	-1.36	< 0.001
	10 minutes	0.63	1.76	-1.13	< 0.001
Day 35					
	Pre-challenge	0.00	0.00	0.00	> 0.999
	3 minutes	1.02	1.74	-0.72	< 0.001
	5 minutes	1.05	1.92	-0.87	< 0.001
	10 minutes	0.88	1.69	-0.80	< 0.001

a Difference = Epinastine minus vehicle; a negative difference favors Epinastine.
b P-value based on Wilcoxon rank sum test on the mean values.
Source: Table 11.4.2.8-1 of Sponsor's Analysis

Table 4

Mean Scores on Day 21 (Onset Challenge) and Day 35 (Duration Challenge) for Parallel-Eyes Comparison (Study #001, Intent-to-Treat Population)

Table 5
Mean Ocular Itching Scores on Day 21 (Onset Challenge) and Day 35 (Duration Challenge) for Parallel-Patients Comparison (Study #001, Intent-to-Treat Population)

		Epinastine (N = 30)	Vehicle (N = 29)	Difference[a]	P-Value[b]
Day 21					
	Pre-challenge	0.00	0.00	0.00	> 0.999
	3 minutes	0.74	1.95	-1.21	< 0.001
	5 minutes	0.93	1.88	-0.95	< 0.001
	10 minutes	0.88	1.57	-0.69	0.001
Day 35					
	Pre-challenge	0.00	0.00	0.00	> 0.999
	3 minutes	1.13	1.60	-0.47	0.034
	5 minutes	1.15	1.78	-0.63	0.008
	10 minutes	0.98	1.49	-0.51	0.015

a Difference = Epinastine minus vehicle; a negative difference favors Epinastine.
b P-value based on Wilcoxon rank sum test on the mean values.
Source: Table 11.4.2.8-3 of Sponsor's Analysis

Table 6
Mean [redacted] Scores on Day 21 (Onset Challenge) and Day 35 (Duration Challenge) for Parallel-Patients Comparison (Study #001, Intent-to-Treat Population)

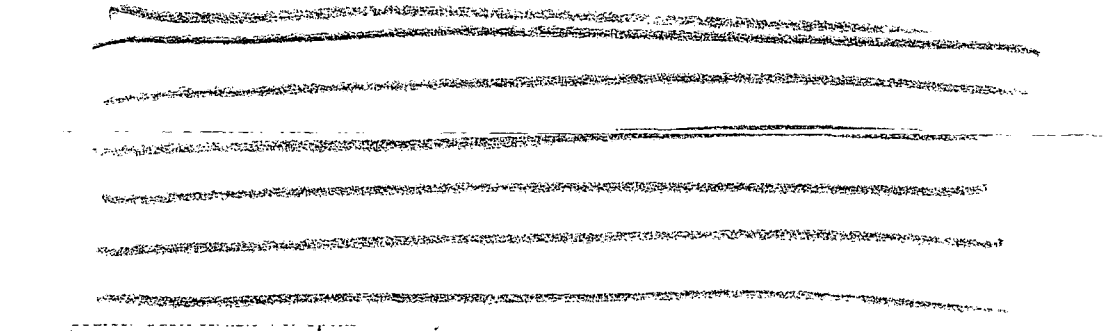

Table 7
Patient Disposition
(Study #003, Intent-to-Treat Population)

	Epinastine (N=118)	Levocabastine (N=118)	Vehicle (N=62)	Total (N=298)
Disposition:				
Enrolled	118	118	62	298
Completed	116 (98.3%)	118 (100.0%)	60 (96.8%)	294 (98.7%)
PATIENT DISCONTINUED DUE TO:				
Lack of Efficacy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Adverse Events	2 (1.7%)	0 (0.0%)	1 (1.6%)	3 (1.0%)
Administrative Reasons:				
Lost to Follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Inability to Continue	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patient/Parent/LAR Choice	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol Violations:				
Improper Entry	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-Compliance	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Concomitant Therapy	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.3%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TOTAL DISCONTINUED	2	0	2	4

Note: LAR = legally authorized representative.
Source: Table 1, Section 14.1 of Sponsor's Analysis

Table 8
Demographics
(Study #003, Intent-to-Treat Population)

	Epinastine (N=118)	Levocabastine (N=118)	Vehicle (N=62)	Total (N=298)	P-value [a]
Age (years)					
N	118	118	62	298	0.622
Mean	33.6	32.5	31.5	32.7	
SD	15.29	13.55	15.18	14.58	
Median	33.5	33.0	30.0	33.0	
Min	9	9	11	9	
Max	71	66	71	71	
<= 17 years	21 (17.8%)	20 (16.9%)	13 (21.0%)	54 (18.1%)	
18-64 years	92 (78.0%)	97 (82.2%)	47 (75.8%)	236 (79.2%)	
>= 65 years	5 (4.2%)	1 (0.8%)	2 (3.2%)	8 (2.7%)	
Sex					
N	118	118	62	298	0.700
Male	57 (48.3%)	56 (47.5%)	26 (41.9%)	139 (46.6%)	
Female	61 (51.7%)	62 (52.5%)	36 (58.1%)	159 (53.4%)	
Race					
N	118	118	62	298	
Caucasian	51 (43.2%)	52 (44.1%)	28 (45.2%)	131 (44.0%)	
Black	4 (3.4%)	6 (5.1%)	1 (1.6%)	11 (3.7%)	
Asian	57 (48.3%)	53 (44.9%)	28 (45.2%)	138 (46.3%)	
Hispanic	2 (1.7%)	4 (3.4%)	5 (8.1%)	11 (3.7%)	
Other [b]	4 (3.4%)	3 (2.5%)	0 (0.0%)	7 (2.3%)	
White	51 (43.2%)	52 (44.1%)	28 (45.2%)	131 (44.0%)	0.969
Non-White	67 (56.8%)	66 (55.9%)	34 (54.8%)	167 (56.0%)	

[a] The P-value for age is based on one-way ANOVA.
The P-value for sex is based on the Pearson chi-square test for three-by-two tables.
The P-value for race is based on the Pearson chi-square test for three-by-two tables.
[b] Other: Filipino, Caucasian/Asian, Afro-American/Asian, and Hispanic/Asian.
Source: Table 3, Section 14.1 of Sponsor's Analysis

Table 8 Continued)
Demographics
(Study #003, Intent-to-Treat Population)

	Epinastine (N=118)	Levocabastine (N=118)	Vehicle (N=62)	Tota l (N=298)	P-value [a]
Iris Color					
N	118	118	62	298	
Blue	18 (15.3%)	21 (17.8%)	16 (25.8%)	55 (18.5%)	
Brown	75 (63.6%)	81 (68.6%)	38 (61.3%)	194 (65.1%)	
Green	10 (8.5%)	4 (3.4%)	1 (1.6%)	15 (5.0%)	
Hazel	13 (11.0%)	11 (9.3%)	7 (11.3%)	31 (10.4%)	
Other	2 (1.7%)	1 (0.8%)	0 (0.0%)	3 (1.0%)	
Dark [b]	75 (63.6%)	81 (68.6%)	38 (61.3%)	194 (65.1%)	0.557
Light [c]	43 (36.4%)	37 (31.4%)	24 (38.7%)	104 (34.9%)	
Weight (kg)					
N	118	118	62	298	0.346
Mean	66.58	70.37	67.79	68.3 3	
SD	19.029	21.930	18.942	20.217	
Median	65.90	68.20	64.75	65.9 0	
Min	27.3	27.3	25.0	25.0	
Max	132.7	159.1	115.9	159. 1	
Height (cm)					
N	118	118	62	298	0.513
Mean	165.21	166.78	167.15	166. 24	
SD	13.509	12.653	10.384	12.563	
Median	165.10	166.35	166.35	165. 10	
Min	121.9	121.9	134.6	121. 9	
Max	200.7	198.1	188.0	200. 7	

[a] The P-value for the iris grouping is based on the Pearson chi-square test for three-by-two tables. The P-values for weight and height are based on one-way ANOVA.
[b] Dark irises: brown.
[c] Light irises: blue, green, hazel, and others.
Source: Table 3, Section 14.1 of Sponsor's Analysis

Table 9
Summary Statistics of Average Worst Daily Ocular Itching Score Based on 2-Week Peak Pollen Count
(Study #003, Intent-to-Treat Population)

	Epinastine (N=118)	Levocabastine (N=118)	Vehicle (N=62)	Interaction P-value	Epinastine vs. Vehicle P-value, Difference, (CI) [a,b]	Levocabastine vs. Vehicle P-value, Difference, (CI) [a,b]	Epinastine vs. Levocabastine P-value, Difference, (CI) [a,b]
N	118	118	62	0.436	0.284	0.559	0.556
Mean	0.77	0.86	0.93		-0.14	-0.08	-0.06
SD	0.856	0.860	0.760		(-0.394, 0.116)	(-0.330, 0.179)	(-0.275, 0.148)
Median	0.45	0.60	0.85				
Min	[redacted]						
Max							

Note: The difference of treatment A versus treatment B i s calculated as treatment A minus treatment B. Thus, a positive difference between the groups indicates a higher severity for treatment A.
Itching scored using the following scale: 0 = absent/ 1= mild / 2 = moderate / 3 = severe / 4 = extremely severe. Half-grade increments were allowed.
[a] P-values are from pairwise contrasts from the two-way ANOVA model including the factors of treatment, investigator, treatment- by-investigator interaction. Type III sum of squares is used.
[b] The 95% confidence intervals are based on the difference between the least squares mean estimates from the two-way ANOVA model.
Source: Table 1.1, Section 14.5 of Sponsor's Analysis

Table 10
Ocular Itching by Visit
Analysis of Covariance of Change from Baseline With Baseline as Covariate
(Study #003, Intent-to-Treat Population)

Visit Day=14
General Linear Models Procedure
Least Squares Means

TRTCD	CHGBL LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN(i)=LSMEAN(j) i/j	1	2	3
Epinastine	-0.03405406	0.05401062	0.5289	1	.	0.0549	0.1177
Levocab	-0.18180768	0.05438629	0.0009	2	0.0549	.	0.0019
Vehicle	0.11362874	0.07708299	0.1415	3	0.1177	0.0019	.

NOTE: To ensure overall protection level, only probabilities associated with pre-planned comparisons should be used.
Source: Table 11, Section 14.5 of Sponsor's Analysis

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Atiar Rahman
4/1/03 04:07:02 PM
BIOMETRICS

Stan Lin
4/1/03 04:26:03 PM
UNKNOWN