CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20706

STATISTICAL REVIEW(S)

J. Holmes

AUG 14

Statistical Review and Evaluation

Preclinical Animal Carcinogenicity Review

NDA:	20-706 [Related IND]
Drug Class:	Topical Ophthalmic Solution
Name of Drug:	EMADINE ™ 0.05% [Emedastine Difumarate] KG-2413 [ALO3432A]
Applicant:	Alcon Laboratories, Inc. 6201 S. Freeway, Fort Worth, Texas 76134 (817) 293-0450
Submission Date:	March 26, 1996
Indications:	Relief within Minutes of Signs and Symptoms of Allergic Conjunctivitis
Preclinical Studies:	S366_102 and S366_103
Documents Reviewed:	NDA Archival Volumes 9 through 12 & Unbound Pages 8-2097 through 2591
Statistical Reviewer:	Lillian Patrician, MS, MBA
Pharmacologist:	Josie Yang, PhD
Applicant Contact Person:	Susan Caballa (817) 568-6296 / Robert Roehrs (817) 551-8764
45 Day Meeting Date:	May 06, 1996

I. Background

EMADINE ™ 0.05% has an active ingredient (Emedastine), which is a topically effective histamine H1 antagonist with a rapid onset of action. It is being submitted for the treatment of symptomatic relief (within minutes and for at least four hours) of allergic conjunctivitis.

The sponsor reports having conducted two rodent carcinogenicity studies, S366_102 and S366_103, to determine any oncogenic potential when administering graduated dosage levels of the drug to the animals' daily diet. Both male and female animals received KG-2413 (ALO3432A) [1-(2-Ethoxyethyl)-2-(4-Methyl homopiperazinyl) Benzimidazole Difumarate]. Study S366_103 included Fischer CDF (F-344) strain rats randomly assigned to dose groups of Control, 0.01%, 0.03%, and 0.10% per day for up to 104 weeks. Study S366_102 included B6C3F1 strain mice randomly assigned to dose groups of Control, 0.01%, 0.03%, and 0.10% per day for 104 weeks. The sponsor concludes that KG-2413 showed no oncogenic potential, and reports no effect on survival nor any treatment related clinical signs.

II. Rat Study S366_103

Study S366_103 included male and female Fischer CDF (F-344) strain rats randomly assigned to dose groups of Control, 0.01%, 0.03%, and 0.10% per day (50 per sex and dose group) for up to 104 weeks. Dose group animals received oral doses of KG-2413 in daily animal feed. These dose levels were equivalent to 5.36, 16.14, and 53.55 mg/kg/day given to the male rats, and 6.5, 19.55, and 67.31 mg/kg/day to the females. The study began with a total of 251 male and 252 female rats of seven weeks in age and 88.3 to 139.8 g in weight. Two hundred animals per sex were examined by a veterinarian for general physical condition and were then randomized to the four treatment groups according to a weight randomization scheme designed to ensure homogeneity of body weights across these groups.

Animals were examined twice daily for evidence of reaction to treatment and for ill health. More detailed exams were performed weekly. Interim sacrifices were performed on humane grounds to prevent unnecessary or prolonged suffering and on debilitated animals judged to be *in extremis*. These sacrifices included complete necropsy, which involved examination of external surfaces; all orifices; cranial cavity; carcass; cervical tissues and organs; thoracic, abdominal, and pelvic cavities; external surface of the brain; nasal cavity; and paranasal sinuses. There was histopathological examination of 37 separate tissue samples.

All animals remaining live at end of the 104 weeks of study were sacrificed and microscopically examined. Microscopic examinations of tissue were also performed for animals that died or were killed *in extremis* during the study.

Sponsor's Analysis: The sponsor's report refers to, but gives no explanation to having used, Bartlett's Test, Dunnett's t-test for Control versus treatment comparisons, Levene's Test for homogeneity of variances, the Modified Tukey-Kramer Test for all paired comparisons, the Terpstra-Jonckheere Test, linear regression, and Rao's Growth Analysis. Data were transformed and tested for variance homogeneity prior to unspecified analyses.

The sponsor reports no statistically significant differences in pathological findings (neither non-neoplastic nor neoplastic) considered to be related to treatment. The sponsor's evaluation of clinical pathology data revealed a spontaneous occurrence of lymphocytic leukemia in the high dose group male rats and 0.01% and 0.03% group females. This was deemed to be unrelated to treatment.

Reviewer's Analysis: The survival data analysis used the methods described in the papers of Cox (Regression Models and Life Tables, Journal of the Royal Statistical Society, B, 34, 187-220, 1972), and of Gehan (A Generalized Wilcoxon Test for Comparing Arbitrarily Singly Censored Samples, Biometrika, 52, 203-223, 1965). The reviewer's analysis also applied the death rate method described in the paper of Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments" in Long Term and Short Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980). Tumor data anaysis used the Peto methods and the method of exact permutation trend test.

Reviewer's Summary of Data from Study S366_103 with 104 Weeks on Treatment

S366_103 [Rat]	Males				Females			
	Control	0.01%	0.03%	0.10%	Control	0.01%	0.03%	0.10%
# Animals in Study	50	50	50	50	50	50	50	50
Survival Rates at Week 52	1.00	0.98	1.00	0.98	1.00	1.00	1.00	0.98
Survival Rates at Week 104	0.70	0.70	0.72	0.78	0.68	0.72	0.68	0.76
Mortality Rate at Week 104	0.30	0.30	0.28	0.22	0.32	0.28	0.32	0.24
Mortality During Treatment Period	15	15	14	11	16	14	16	12
Mortality Following Treatment Period	35	35	36	39	34	36	34	38

1. Survival Analysis:

Intercurrent mortality rates for both male and female rats *(See Tables 1M and 1F on pages 10-11)* were tested for linear trend according to the Peto death rate method using time intervals 0-52; 53-78; and 79-104. The results of the age-adjusted Peto test for male and female rats showed no evidence of a significant linear trend in intercurrent mortality.

The Cox and generalized Wilcoxon tests were used to test for homogeneity of survival distributions of all dose groups, including Control (separately for males and females). Cox test p-values were 0.7403 for males and 0.8940 for females. Thus, there was no evidence of statistically significant differences in survival distribution at the 0.05 level.

The generalized Wilcoxon test gives more weight to early differences in death rates between groups than the Cox analysis. These also resulted in no statistically significant differences in survival distributions for either male or female rats, with p-values of 0.6973 and 0.8999 for males and females, respectively.

Plots of Kaplan-Meier estimates illustrate survival distributions of the Control and treated groups for male and female rats *(Figures 1M and 1F on pages 34 - 35).*

2. Tumor Data Analysis:

To test the positive linear trend in tumor rates, the reviewer's analysis used an extension of the Fisher exact test referred to as the method of exact permutation trend test. The sponsor reported three definitions for a tumor's relation to cause of death. Using Peto et al. (1980), the sponsor's 'tumor-caused death' followed Peto's 'death rate method', whereas the second and third definitions of 'non-tumor-caused death' and 'unknown' followed the 'prevalence method'. The reviewer's analysis used time intervals of 0-52; 53-78; 79-104 weeks; and terminal sacrifice.

The reviewer's tumor data analysis followed three approaches: (1) an age-adjusted or time-adjusted exact permutation trend test; (2) a pairwise comparison between Control and high dose group per sex; and (3) an age-unadjusted trend test.

To adjust for multiplicity, the reviewer followed a standard decision rule in regard to the effect of multiple testings on inflating the overall false positive rate. A positive linear trend is considered not to occur by chance of variation alone if the p-value is less than 0.005 for common tumors, and less than 0.025 for rare tumors. Using this adjustment, the reviewer's analysis determined exact p-values for tumors either fatal or non-fatal to all animals, and the asymptotic p-values for tumors considered fatal to some but not all animals. There were no statistically significant linear trends for any tumor types in male and female rats (***Tables 2M and 2F on pages 12 - 17***).

The incidence rates of tumors were then compared between the Control and the 0.10% high dose group using a pairwise comparison ***(Tables 3M and 3F on pages 18 - 21)***. No significant differences were found.

3. Validity of Experiment

The validity of the experiment depends on sufficient numbers of animals being exposed to drug/chemical over an adequate time period so as to be at risk of forming late-developing tumors. Some experts in the field have suggested that between weeks 80-90, a 50 percent survival rate of the 50 initial animals in the high dose group will be considered as a sufficient number at adequate exposure [Haseman through personal communication with Dr. Karl Lin]. If the number of animals in each treatment group and sex group is less than or greater than 50, the percentage can vary. However, there should be 20 to 30 animals remaining live during these weeks. Additionally, Chu, Ceuto, and Ward ["Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays", Journal of Toxicology and Environmental Health, 8, 1981, pp. 251-280] propose that for studies in which there is no evidence of carcinogenic effect of the chemical/drug, animals in the high dose group should have greater than 50 percent survival at one year (52 weeks) into study.

At week 52, the survival rates of rats in the high dose group of this study were 98% for both males and females. This represents greater than 50 percent survival at one year into study. At the end of treatment or week 104, the survival rates decreased to 74% for males and 82% for females, which is still above the 50 percent survival rate. Therefore, the study meets both criteria for sufficient numbers of animals exposed over an adequate time period.

The validity of the experiment also depends on the administration of a large enough drug dose so as to present a tumor challenge to the animals. The same paper by Chu, Ceuto, and Ward identifies dose adequacy according to:

(1) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls";
(2) "The administered dose is also considered a Maximum Tolerated Dose (MTD) if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical";

(3) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls".

Mortality rates for male rats during the 104 weeks of treatment were 30% for Controls and 30%, 28%, and 22% for the low, medium and high dose groups, respectively. The rates for females were 32% (Controls) and 28%, 32%, and 24% (low, medium, and high dose groups). There was no evidence of increased mortality in the dose group animals.

The sponsor reports, "Overall bodyweight gains and food intake of males and females receiving high dose of 0.10% were lower than those of their Controls", possibly due to reduced food intake for the high dose animals during later weeks of the experiment. Therefore, this criteria meets requirements for dose adequacy. Any clinical signs or severe histopathologic toxic effects attributed to the chemical should also be considered when determining dose adequacy and experimental validity.

This reviewer's examination of tumor data was consistent with the sponsor's results and found no evidence of a significant linear trend in tumor incidence across dose groups nor a statistically significant difference in tumor incidence between Control and high dose group.

III. Mouse Study S366_102

Study S366_102 included male and female B6C3F1 mice randomly assigned to dose groups of Control, 0.01%, 0.03%, and 0.10% per day (50 per sex and dose group) for at least 104 weeks. Dose group animals received oral doses of KG-2413 in daily animal feed. These doses were equivalent to 15.23, 44.42, and 170.47 mg/kg/day of drug compound given to the male mice, and 16.85, 56.91, and 218.01 mg/kg/day to the females. The study began with a total of 247 male and 251 female mice (approximately seven weeks old) of 13.4 to 25.4 g in weight. Two hundred animals per sex were examined by a veterinarian for general physical condition and were then randomized to the four treatment groups according to a weight randomization scheme designed to ensure homogeneity of body weights across these groups.

Animals were examined twice daily for evidence of reaction to treatment and for ill health. More detailed exams were performed weekly. Interim sacrifices were performed on humane grounds to prevent unnecessary or prolonged suffering and on debilitated animals judged to be *in extremis*. These sacrifices included complete necropsy, which involved examination of external surfaces; all orifices; cranial cavity; carcass; cervical tissues and organs; thoracic, abdominal, and pelvic cavities; external surface of the brain; nasal cavity; and paranasal sinuses. There was histopathological examination of 37 separate tissue samples.

Microscopic examinations of tissue were performed for all animals following the scheduled treatment period of 104 weeks, and for animals that died or were killed *in extremis* during the study.

Sponsor's Analysis: The sponsor's report refers to, but gives no explanation to having used, Bartlett's Test, Dunnett's t-test for Control versus treatment comparisons, and Levene's Test for homogeneity of variances. Data were transformed and tested for variance homogeneity prior to unspecified analyses. The sponsor reports no statistically significant differences in pathological findings (neither non-neoplastic nor neoplastic) considered to be related to treatment.

Reviewer's Analysis:

Reviewer's Summary of Data from Study S366_102 with 104 Weeks on Treatment

S366_102 [Mouse]	Males				Females			
	Control	0.01%	0.03%	0.10%	Control	0.01%	0.03%	0.10%
# Animals in Study	50	50	50	50	50	50	50	50
Survival Rates at Week 52	0.98	0.94	0.96	0.98	0.96	0.83	0.98	0.88
Survival Rates at Week 104	0.86	0.78	0.82	0.86	0.78	0.78	0.68	0.86
Mortality Rate at Week 104	0.14	0.22	0.18	0.14	0.22	0.22	0.32	0.14
Mortality During Treatment Period	7	11	9	7	11	11	16	7
Mortality Following Treatment Period	43	39	41	43	39	39	34	43

1. Survival Analysis:

Intercurrent mortality rates for both male and female mice ***(Tables 4M and 4F on pages 22 - 23)*** were tested for linear trend according to the Peto death rate method using time intervals 0-52; 53-78; and 79-104. The results of the age-adjusted Peto test for both sexes show no evidence of a significant linear trend in intercurrent mortality.

The Cox and generalized Wilcoxon tests were used to test for homogeneity of survival distributions of all dose groups, including Control (separately for males and females). Cox test p-values were 0.6956 for males and 0.1878 for females. There was no statistically significant difference in survival distribution at the 0.05 level for either male or female mice.

The generalized Wilcoxon test gives more weight to early differences in death rates between groups than the Cox analysis. These resulted in a p-value of 0.7137 for male mice, and a p-value of 0.1795 for female mice. Thus, there was no evidence of a statistically significant difference in homogeneity of survival distributions.

Plots of Kaplan-Meier estimates illustrate survival distributions of the Control and treated groups for male and female mice ***(Figures 2M and 2F on pages 35 - 36).***

2. Tumor Data Analysis:

To test the positive linear trend in tumor rates, the reviewer's analysis used an extension of the Fisher exact test referred to as the method of exact permutation trend test. The sponsor reported three definitions for a tumor's relation to cause of death. Using Peto et al. (1980), the sponsor's 'tumor-caused death' followed Peto's 'death rate method', whereas the second and third definitions of 'non-tumor-caused death' and 'unknown' followed the 'prevalence method'. The reviewer analysis used time intervals of 0-52; 53-78; 79-104 weeks; and terminal sacrifice.

The reviewer's tumor data analysis followed three approaches: (1) an age-adjusted or time-adjusted exact permutation trend test; (2) a pairwise comparison between Control and high dose group per sex; and (3) an age-unadjusted trend test.

To adjust for multiplicity, the reviewer followed a standard decision rule in regard to the effect of multiple testings on inflating the overall false positive rate. A positive linear trend is considered not to occur by chance of variation alone if the p-value is less than 0.005 for common tumors, and less than 0.025 for rare tumors. Using this adjustment, the reviewer's analysis determined exact p-values for tumors either fatal or non-fatal to all animals, and asymptotic p-values for tumors considered fatal to some but not all animals. There were no statistically significant linear trends for any tumor types in male and female mice *(Tables 5M and 5F on pages 24 - 28)*.

The incidence rates of tumors were then compared between the Control and the 0.10% high dose group using pairwise comparisons *(Tables 6M and 6F on pages 29 - 32)*. In examining the incidence of malignant hepatocellular carcinoma of the liver in male mice, the comparison between Control and high dose group determined an exact p-value of 0.0548. One such tumor was reported in the Control group. This represented a 2% (1/50) incidence, which classified this as a common tumor. Because this tumor was typed as fatal to some but not all animals, the asymptotic p-value of 0.9750 was used to conclude that there was no evidence of a statistically significant difference at the 0.005 level. The comparisons of all other incidence rates of tumors also found no statistically significant differences between Control and high dose group animals.

3. Validity of Experiment

As explained in the Reviewer's Analysis for Rat Study S366_103 on page 4 of this report, the validity of the experiment depends on sufficient numbers of animals being exposed to drug/chemical over an adequate time period so as to be at risk of forming late-developing tumors.

At week 52, the survival rates of mice in the high dose group of this study were 98% for males and 88% for females, which represents greater than 50 percent survival at one year into study. At end of the treatment period of week 104, the survival rates decreased to 86% and 86% for high dose group male and female mice, respectively, which again was

greater than the suggested 50 percent survival rate. Therefore, the study meets both criteria for sufficient numbers of animals exposed over an adequate time period.

The validity of the experiment also depends on the administration of a large enough drug dose so as to present a tumor challenge to the animals.

Mortality rates for male mice during the 104 weeks of treatment were 14% for Controls and 22%, 18%, and 14% for the low, medium and high dose groups, respectively. The rates for females were 22% (Controls) and 22%, 32%, and 14% (low, medium, and high dose groups). There was no evidence of increased mortality in the dose group animals.

The mean body weights for the high dose group animals (both sexes) remained lower than the Control group throughout the study. For each sex, the sponsor reports statistically significant lower mean body weight values for the dosed group animals over the Control groups at varying time periods. Therefore, this criteria meets requirements for dose adequacy. Any clinical signs or severe histopathologic toxic effects attributed to the chemical should also be considered when determining dose adequacy and experimental validity.

This reviewer's examination of tumor data was consistent with the sponsor's results and found no evidence of a significant linear trend in tumor incidence across dose groups nor a statistically significant difference in tumor incidence between Control and high dose group.

IV. Reviewer's Conclusions, which may be Conveyed to the Sponsor

1. The sponsor reports that KG-2413 was administered via the rodent animal feed in accordance to how the chemical would be used under clinical treatment. Instead, this new chemical entity is intended as a topical ophthalmic solution for the treatment of symptomatic relief of allergic conjunctivitis. It is not intended for human consumption via ingestion.

2. As reported in the Reviewer's Analysis on pages 5 and 8 of this report, the dose adequacy and validity of these two studies should be confirmed within the context of any clinical signs or severe histopathologic toxic effects exhibited by animals that were treated with the chemical. Nevertheless, this reviewer's examination of tumor data was consistent with the sponsor's results and found no tumors indicating a significant linear dose-tumor trend or a statistically significant difference in tumor incidence between Control and high dose groups.

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This report has a total of thirty-six [36] pages, including 6 Tables, and 2 Figures.

Table 1M

MALE RAT STUDY S366_103

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Intercurrent Mortality Rates

Animal Type: RAT

Sex: MALE

	Dose											
	Ctrl			Low			Med			High		
Time(wks)	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
0-52	.	.	.	1	50	2.0	.	.	.	1	50	2.0
53-78	1	50	2.0	2	49	6.0	.	.	.	.	.	.
79-104	14	49	30.0	12	47	30.0	14	50	28.0	10	49	22.0
FNL KILL	35	50	70.0	35	50	70.0	36	50	72.0	39	50	78.0

Table 1F

FEMALE RAT STUDY S366_103

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Intercurrent Mortality Rates

Animal Type: RAT

Sex: FEMALE

	Dose											
	Ctrl			Low			Med			High		
Time(wks)	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
0-52	.	.	.	.	.	.	.	.	.	1	50	2.0
53-78	2	50	4.0	2	50	4.0	4	50	8.0	3	49	8.0
79-104	14	48	32.0	12	48	28.0	12	46	32.0	8	46	24.0
FNL KILL	34	50	68.0	36	50	72.0	34	50	68.0	38	50	76.0

Table 2M

MALE RAT STUDY S366_103

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

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Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: MALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 0.01	Dose 0.03	Dose 0.10
ADRENAL, CORTEX	B-ADENOMA	S-	0.2000	(1.0000)	0/50	0	1	0
ADRENAL, MEDULLA	B-BENIGN PHEOCHROMOCYTOMA	S-	0.5078	(0.9699)	2/50	2	6	1
ADRENAL, MEDULLA	M-GANGLIONEUROMA	S-	0.0859	(1.0000)	1/50	0	0	1
ADRENAL, MEDULLA	M-MALIGNANT PHEOCHROMOCYT	M-	(0.5173)	1.0000	0/50	2	1	2
BRAIN W/STEM	M-MENINGIOMA	S-	0.7854	(1.0000)	0/50	0	0	1
DUODENUM	B-LEIOMYOMA	S-	0.4152	(1.0000)	0/50	0	0	1
HEMATO NEOPLASIA	M-HISTIOCYTIC SARCOMA	M-	(0.9988)	1.0000	0/50	1	1	0
HEMATO NEOPLASIA	M-MONONUCLEAR CELL LEUKEM	M-	(0.2362)	1.0000	23/50	18	20	30
JEJUNUM	M-CARCINOMA	S-	0.0925	(0.8078)	0/50	1	0	0
JEJUNUM	M-LEIOMYOSARCOMA	S-	0.2690	(1.0000)	0/50	0	0	1
KIDNEY	M-TRANSITIONAL CELL CARCI	S-	0.8934	(1.0000)	0/50	0	1	0
LIVER	B-HEPATOCELLULAR ADENOMA	S-	0.2000	(1.0000)	2/50	0	0	2
LIVER	M-HEPATOCELLULAR CARCINOM	S-	0.2690	(1.0000)	1/50	0	4	0
LUNG	B-ALVEO/BRONCH ADENOMA	S-	0.7621	(1.0000)	0/50	0	0	1
MAMMARY GLAND	B-FIBROADENOMA	M-	(1.0000)	1.0000	5/50	1	4	4
MAMMARY GLAND	M-CARCINOMA	S-	0.2634	(1.0000)	0/50	1	1	1
BONE, OTHER	M-OSTEOSARCOMA	S-	0.5173	(1.0000)	0/50	1	2	0

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

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Table 2M

MALE RAT STUDY S366_103

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: MALE

CAVITY, ORAL	B-SQUAMOUS CELL PAPILLOMA	S-	0.2690	(1.0000)	0/50	1	0	0
CAVITY, ORAL	M-SQUAMOUS CELL CARCINOMA	S-	0.2000	(1.0000)	0/50	0	1	0
PANCREAS	B-ACINAR CELL ADENOMA	S-	0.7586	(1.0000)	2/50	1	5	0
PANCREAS	B-ISLET CELL ADENOMA	S-	0.8944	(1.0000)	5/50	7	1	2
PANCREAS	B-MIXED ACINAR-ISLET CELL	S-	0.0116	(0.9852)	1/50	1	2	0
PANCREAS	M-ACINAR CELL CARCINOMA	S-	0.9549	(1.0000)	0/50	0	1	0
PANCREAS	M-ISLET CELL CARCINOMA	S-	0.2690	(1.0000)	1/50	1	1	5
CAVITY, ABDOM	M-CHORDOMA	S-	0.5082	(1.0000)	0/50	1	0	1
CAVITY, ABDOM	M-MALIGNANT MESOTHELIOMA	M-	(0.8153)	1.0000	2/50	2	3	1
PREPUTIAL GLAND	B-ADENOMA	S-	0.2690	(1.0000)	2/50	1	1	0
PREPUTIAL GLAND	M-CARCINOMA	S-	0.1484	(0.9842)	1/50	0	1	0
PITUITARY	B-ADENOMA	M-	(1.0000)	1.0000	15/50	25	15	18
PITUITARY	M-CARCINOMA	S-	0.6388	(1.0000)	0/50	0	2	2
PROSTATE	B-ADENOMA	S-	1.0000	(1.0000)	0/50	0	0	1
PARATHYROID	B-ADENOMA	S-	0.4298	(0.9995)	0/50	0	0	1
MAND SALIVARY GL	M-CARCINOMA	S-	0.2929	(1.0000)	1/50	0	0	0
SPLEEN	M-HEMANGIOSARCOMA	S-	0.0759	(0.5629)	1/50	0	0	0
SUBCUTANEOUS TIS	B-FIBROMA	M-	(0.6439)	1.0000	1/50	5	2	1
SUBCUTANEOUS TIS	B-LIPOMA	S-	0.7586	(1.0000)	0/50	1	1	0
SUBCUTANEOUS TIS	B-NEUROFIBROMA	S-	0.5547	(1.0000)	0/50	1	0	0

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

MALE RAT STUDY S366_103

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: MALE

SUBCUTANEOUS TIS	M-FIBROSARCOMA	S-	0.9840	(1.0000)	0/50	0	0	1
SUBCUTANEOUS TIS	M-MYXOSARCOMA	M-	(0.7836)	1.0000	1/50	1	0	0
SUBCUTANEOUS TIS	M-NEUROFIBROSARCOMA	S-	0.7586	(1.0000)	0/50	0	1	0
SKIN, OTHER	B-KERATOACANTHOMA	S-	0.2916	(1.0000)	2/50	1	0	0
SKIN, OTHER	B-SEBACEOUS ADENOMA	S-	0.6388	(1.0000)	0/50	1	0	0
SKIN, OTHER	B-SQUAMOUS CELL PAPILLOMA	S-	1.0000	(1.0000)	2/50	0	1	1
SKIN, OTHER	M-ADNEXAL GLAND ADENOCARC	S-	0.7687	(1.0000)	0/50	1	0	0
SKIN, OTHER	M-BASAL CELL CARCINOMA	S-	0.7430	(1.0000)	2/50	2	0	1
STOMACH, NONGL	M-SQUAMOUS CELL CARCINOMA	S-	0.9302	(1.0000)	0/50	0	0	1
CAVITY, THORACIC	M-OSTEOSARCOMA	S-	0.8084	(1.0000)	1/50	0	0	0
TESTIS	B-BENIGN INTERSTIT CELL	S-	0.9431	(1.0000)	46/50	41	44	47
THYMUS	M-CARCINOMA	S-	0.2500	(1.0000)	1/50	0	0	0
THYROID	B-"C" CELL ADENOMA	S-	0.7586	(1.0000)	13/50	7	8	16
THYROID	B-FOLLICULAR CELL ADENOMA	S-	0.4800	(1.0000)	2/50	0	1	0
THYROID	M-"C" CELL CARCINOMA	M-	(0.6480)	1.0000	4/50	3	0	0

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Table 2M

MALE RAT STUDY S366_103

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: MALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 0.01	Dose 0.03	Dose 0.10
THYROID	M-FOLLICULAR CELL CARCINO	S-	0.7586	(1.0000)	0/50	0	0	1
URINARY BLADDER	B-TRANSITIONAL CELL PAPIL	S-	0.5130	(1.0000)	0/50	1	2	0
ZYMBAL'S GLAND	M-SQUAMOUS CELL CARCINOMA	S-	0.7586	(1.0000)	0/50	1	0	0

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

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Table 2F

FEMALE RAT STUDY S366_103

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: FEMALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 0.01	Dose 0.03	Dose 0.10
ADRENAL, CORTEX	B-ADENOMA	S-	0.3857	(0.9355)	2/50	0	1	0
ADRENAL, MEDULLA	B-BENIGN PHEOCHROMOCYTOMA	S-	0.8981	(1.0000)	1/50	2	3	1
CLITORAL GLAND	M-CARCINOMA	S-	0.5967	(1.0000)	0/50	1	0	0
UTERUS, CERVIX	M-NEUROFIBROSARCOMA	S-	0.0812	(0.9989)	2/50	0	0	0
HEMATO NEOPLASIA	M-HISTIOCYTIC SARCOMA	S-	0.8420	(1.0000)	0/50	0	1	1
HEMATO NEOPLASIA	M-LEUKEMIA, GRANULOCYTIC	S-	0.4348	(1.0000)	0/50	1	0	0
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, LYM	S-	0.7213	(1.0000)	0/50	0	1	0
HEMATO NEOPLASIA	M-MONONUCLEAR CELL LEUKEM	M-	(0.7771)	0.9989	20/50	19	26	16
LIVER	B-HEPATOCELLULAR ADENOMA	S-	0.1739	(1.0000)	0/50	0	1	0
MAMMARY GLAND	B-FIBROADENOMA	M-	(0.9440)	1.0000	10/50	10	5	5
MAMMARY GLAND	M-CARCINOMA	S-	0.1739	(1.0000)	1/50	3	0	0
BONE, OTHER	M-OSTEOSARCOMA	S-	1.0000	(1.0000)	0/50	1	0	0
OVARY	B-BENIGN GRAN/THECA CELL	S-	0.3806	(0.9705)	1/50	1	0	0
OVARY	M-MALIGNANT GRANULOSA/THE	S-	0.0477	(0.9999)	1/50	0	0	0
PANCREAS	B-ISLET CELL ADENOMA	S-	0.6101	(1.0000)	0/50	0	0	1
PANCREAS	B-MIXED ACINAR-ISLET CELL	S-	0.6102	(1.0000)	0/50	0	0	1
CAVITY, ABDOM	M-CHORDOMA	S-	1.0000	(1.0000)	0/50	0	0	1

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Table 2F

FEMALE RAT STUDY S366_103

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Test of Trend Based on the Tumor Data

Animal Type: RAT

Sex: FEMALE

PITUITARY	B-ADENOMA	M-	(0.1797)	1.0000	21/50	23	24	24
PARATHYROID	B-ADENOMA	S-	1.0000	(1.0000)	1/50	0	1	0
SUBCUTANEOUS TIS	B-FIBROMA	S-	0.9213	(1.0000)	0/50	2	0	0
SUBCUTANEOUS TIS	B-LIPOMA	S-	0.1893	(1.0000)	0/50	0	1	0
SUBCUTANEOUS TIS	B-NEUROFIBROMA	S-	0.9621	(1.0000)	1/50	0	0	0
SUBCUTANEOUS TIS	M-NEUROFIBROSARCOMA	S-	0.8399	(0.9945)	1/50	0	0	0
SKIN, OTHER	B-SQUAMOUS CELL PAPILLOMA	S-	0.5070	(1.0000)	0/50	1	0	0
SKIN, OTHER	M-SQUAMOUS CELL CARCINOMA	S-	0.8182	(1.0000)	0/50	0	2	0
THYMUS	M-CARCINOMA	S-	0.7605	(1.0000)	1/50	0	0	0
THYROID	B-"C" CELL ADENOMA	S-	0.7605	(1.0000)	8/50	12	12	8
THYROID	B-FOLLICULAR CELL ADENOMA	S-	0.5210	(1.0000)	1/50	1	1	0
THYROID	M-"C" CELL CARCINOMA	S-	0.2500	(1.0000)	1/50	2	1	4
URINARY BLADDER	B-TRANSITIONAL CELL PAPIL	S-	0.8217	(1.0000)	0/50	2	0	2
UTERUS	B-ADENOMA	S-	0.7517	(1.0000)	2/50	0	0	1
UTERUS	B-ENDOMETRIAL STROMAL POL	M-	(1.0000)	1.0000	15/50	8	6	13
UTERUS	M-CARCINOMA	M-	(1.0000)	1.0000	0/50	1	1	3
UTERUS	M-ENDOMETRIAL STROMAL SAR	M-	(0.5070)	1.0000	1/50	2	1	1
ZYMBAL'S GLAND	M-SQUAMOUS CELL CARCINOMA	S-	0.7605	(1.0000)	0/50	1	0	0

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Table 3M

MALE RAT STUDY S366_103

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Pairwise Comparisons

Dosage Pair: 0.00 vs 0.10

ANIMAL: RATS
SEX: MALE

Organ	Tumor	Exact p	Asmp p	Dose: 0.00	Dose: 0.10
BRAIN W/STEM	M-MENINGIOMA	0.4167	(1.0000)	0	1
PITUITARY	B-ADENOMA	0.3336	(0.9211)	15	18
PITUITARY	M-CARCINOMA	0.2743	(1.0000)	0	2
ADRENAL, MEDULLA	B-BENIGN PHEOCHROMOCYTOMA	0.8991	(1.0000)	2	1
ADRENAL, MEDULLA	M-GANGLIONEUROMA	0.7241	(1.0000)	1	1
ADRENAL, MEDULLA	M-MALIGNANT PHEOCHROMOCYTOMA	(0.2743)	1.0000	0	2
THYROID	M-"C" CELL CARCINOMA	(1.0000)	1.0000	4	0
THYROID	B-"C" CELL ADENOMA	0.4396	(0.9736)	13	16
THYROID	M-FOLLICULAR CELL CARCINOMA	0.5270	(1.0000)	0	1
THYROID	B-FOLLICULAR CELL ADENOMA	1.0000	(1.0000)	2	0
PARATHYROID	B-ADENOMA	0.5270	(1.0000)	0	1
LUNG	B-ALVEO/BRONCH ADENOMA	0.4167	(1.0000)	0	1
LIVER	M-HEPATOCELLULAR CARCINOMA	1.0000	(1.0000)	1	0
LIVER	B-HEPATOCELLULAR ADENOMA	0.6902	(1.0000)	2	2
SPLEEN	M-HEMANGIOSARCOMA	(1.0000)	1.0000	1	0
STOMACH, NONGL	M-SQUAMOUS CELL CARCINOMA	0.4167	(1.0000)	0	1
DUODENUM	B-LEIOMYOMA	0.5270	(1.0000)	0	1
JEJUNUM	M-LEIOMYOSARCOMA	0.5270	(1.0000)	0	1
PANCREAS	B-ACINAR CELL ADENOMA	1.0000	(1.0000)	2	0
PANCREAS	M-ISLET CELL CARCINOMA	0.0588	(0.9907)	1	5
PANCREAS	B-ISLET CELL ADENOMA	0.9414	(1.0000)	5	2

Note: An '*' indicates that the dose-tumor association may be significant for the selected dose pair because the p-value <= 0.05.

MALE RAT STUDY S366_103

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Pairwise Comparisons

Dosage Pair: 0.00 vs 0.10

ANIMAL: RATS
SEX: MALE

PANCREAS	B-MIXED ACINAR-ISLET CELL TU	(1.0000)	1.0000	1	0
TESTIS	B-BENIGN INTERSTIT CELL	0.6190	(1.0000)	46	47
PROSTATE	B-ADENOMA	0.5270	(1.0000)	0	1
MAND SALIVARY GL	M-CARCINOMA	(1.0000)	1.0000	1	0
THYMUS	M-CARCINOMA	1.0000	(1.0000)	1	0
MAMMARY GLAND	B-FIBROADENOMA	0.7661	(0.9999)	5	4
MAMMARY GLAND	M-CARCINOMA	0.5270	(1.0000)	0	1
HEMATO NEOPLASIA	M-MONONUCLEAR CELL LEUKEMIA	0.2665	(0.8539)	23	30
SKIN, OTHER	M-BASAL CELL CARCINOMA	(0.8991)	1.0000	2	1
SKIN, OTHER	B-KERATOACANTHOMA	1.0000	(1.0000)	2	0
SKIN, OTHER	B-SQUAMOUS CELL PAPILLOMA	0.8715	(1.0000)	2	1
CAVITY, ABDOM	M-MALIGNANT MESOTHELIOMA	0.8648	(1.0000)	2	1
CAVITY, ABDOM	M-CHORDOMA	0.5270	(1.0000)	0	1
CAVITY, THORACIC	M-OSTEOSARCOMA	1.0000	(1.0000)	1	0
PREPUTIAL GLAND	M-CARCINOMA	1.0000	(1.0000)	1	0
PREPUTIAL GLAND	B-ADENOMA	1.0000	(1.0000)	2	0
SUBCUTANEOUS TIS	B-FIBROMA	0.7159	(1.0000)	1	1
SUBCUTANEOUS TIS	M-MYXOSARCOMA	1.0000	(1.0000)	1	0
SUBCUTANEOUS TIS	M-FIBROSARCOMA	0.5000	(1.0000)	0	1

Note: An '*' indicates that the dose-tumor association may be significant for the selected dose pair because the p-value <= 0.05.

Table 3F

FEMALE RAT STUDY S366_103

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Pairwise Comparisons

Dosage Pair: 0.00 vs 0.10

ANIMAL: RATS
SEX: FEMALE

Organ	Tumor	Exact p	Asmp p	Dose: 0.00	Dose: 0.10
PITUITARY	B-ADENOMA	0.3766	(0.9448)	21	24
ADRENAL, CORTEX	B-ADENOMA	1.0000	(1.0000)	2	0
ADRENAL, MEDULLA	B-BENIGN PHEOCHROMOCYTOMA	0.7805	(1.0000)	1	1
THYROID	M-"C" CELL CARCINOMA	0.1731	(0.9993)	1	4
THYROID	B-"C" CELL ADENOMA	(0.7044)	0.9989	8	8
THYROID	B-FOLLICULAR CELL ADENOMA	1.0000	(1.0000)	1	0
PARATHYROID	B-ADENOMA	1.0000	(1.0000)	1	0
PANCREAS	B-ISLET CELL ADENOMA	0.3636	(1.0000)	0	1
PANCREAS	B-MIXED ACINAR-ISLET CELL TU	0.3636	(1.0000)	0	1
OVARY	B-BENIGN GRAN/THECA CELL	(1.0000)	1.0000	1	0
OVARY	M-MALIGNANT GRANULOSA/THECA	1.0000	(1.0000)	1	0
UTERUS	B-ENDOMETRIAL STROMAL POLYP	0.7641	(0.9962)	15	13
UTERUS	M-CARCINOMA	0.1330	(1.0000)	0	3
UTERUS	M-ENDOMETRIAL STROMAL SARCOM	0.7475	(1.0000)	1	1
UTERUS	B-ADENOMA	0.8996	(1.0000)	2	1
UTERUS, CERVIX	M-NEUROFIBROSARCOMA	1.0000	(1.0000)	2	0
URINARY BLADDER	B-TRANSITIONAL CELL PAPILLOM	(0.1919)	1.0000	0	2
THYMUS	M-CARCINOMA	1.0000	(1.0000)	1	0
MAMMARY GLAND	B-FIBROADENOMA	0.9317	(1.0000)	10	5
MAMMARY GLAND	M-CARCINOMA	1.0000	(1.0000)	1	0
HEMATO NEOPLASIA	M-MONONUCLEAR CELL LEUKEMIA	0.8474	(0.9956)	20	16

Note: An '*' indicates that the dose-tumor association may be significant for the selected dose pair because the p-value <= 0.05.

Table 3F

FEMALE RAT STUDY S366_103

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Pairwise Comparisons

Dosage Pair: 0.00 vs 0.10

ANIMAL: RATS
SEX: FEMALE

HEMATO NEOPLASIA	M-HISTIOCYTIC SARCOMA	0.4947	(1.0000)	0	1
CAVITY, ABDOM	M-CHORDOMA	0.5000	(1.0000)	0	1
SUBCUTANEOUS TIS	B-NEUROFIBROMA	(1.0000)	1.0000	1	0
SUBCUTANEOUS TIS	M-NEUROFIBROSARCOMA	(1.0000)	1.0000	1	0

Note: An '*' indicates that the dose-tumor association may be significant for the selected dose pair because the p-value <= 0.05.

Table 4M

MALE MOUSE STUDY S366_102

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Intercurrent Mortality Rates

Animal Type: MOUSE

Sex: MALE

	Dose											
	Ctrl			Low			Med			High		
	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
Time(wks)												
0-52	1	50	2.0	3	50	6.0	2	50	4.0	1	50	2.0
53-78	1	49	4.0	.	.	.	4	48	12.0	4	49	10.0
79-104	5	48	14.0	8	47	22.0	3	44	18.0	2	45	14.0
FNL KILL	43	50	86.0	39	50	78.0	41	50	82.0	43	50	86.0

Table 4F

FEMALE MOUSE STUDY S366_102

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Intercurrent Mortality Rates

Animal Type: MOUSE

Sex: FEMALE

	Dose											
	Ctrl			Low			Med			High		
Time(wks)	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died	No. Died	No. Risk	Cumu Pct. Died
0-52	1	50	2.0	1	50	2.0	4	50	8.0	.	.	.
53-78	2	49	6.0	3	49	8.0	3	46	14.0	3	50	6.0
79-104	8	47	22.0	7	46	22.0	9	43	32.0	4	47	14.0
FNL KILL	39	50	78.0	39	50	78.0	34	50	68.0	43	50	86.0

Table 5M

MALE MOUSE STUDY S366_102

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: MALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 0.01	Dose 0.03	Dose 0.10
ADRENAL, CORTEX	B-ADENOMA	S-	0.5958	(1.0000)	2/50	0	0	1
ADRENAL, MEDULLA	M-MALIGNANT PHEOCHROMOCYT	S-	0.2540	(1.0000)	0/50	0	0	1
MARROW, FEMUR	M-HEMANGIOSARCOMA	S-	0.2590	(1.0000)	1/50	0	0	0
HARDERIAN GLAND	B-ADENOMA	S-	0.9296	(1.0000)	5/50	3	2	6
HARDERIAN GLAND	M-CARCINOMA	S-	0.4239	(0.9904)	1/50	2	2	1
HEMATO NEOPLASIA	M-HISTIOCYTIC SARCOMA	S-	0.2806	(0.9856)	0/50	1	0	0
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, HIS	S-	0.8408	(1.0000)	2/50	3	0	3
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, LYM	S-	0.8036	(0.9995)	0/50	1	0	1
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, MIX	S-	0.4521	(1.0000)	0/50	1	0	1
JEJUNUM	M-CARCINOMA	S-	0.9290	(1.0000)	1/50	0	0	0
LIVER	B-HEPATOCELLULAR ADENOMA	M-	(1.0000)	1.0000	7/50	10	9	6
LIVER	B-HEPATOCELLULAR ADENOMA,	S-	0.1340	(0.9999)	1/50	2	3	0
LIVER	M-HEMANGIOSARCOMA	M-	(0.2590)	1.0000	1/50	1	2	3
LIVER	M-HEPATOCELLULAR CARCINOM	M-	(0.8377)	1.0000	1/50	8	7	6
LIVER	M-HEPATOCELLULAR CARCINOM	S-	1.0000	(1.0000)	6/50	1	0	1
LUNG	B-ALVEO/BRONCH ADENOMA	M-	(0.7391)	1.0000	5/50	8	10	7
LUNG	M-ALVEO/BRONCH CARCINOMA	M-	(0.7409)	1.0000	6/50	5	7	2

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Table 5M

MALE MOUSE STUDY S366_102

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: MALE

LN, MESENTERIC	M-HEMANGIOSARCOMA	S-	0.5060	(1.0000)	0/50	1	0	0
PANCREAS	B-ISLET CELL ADENOMA	S-	0.7488	(1.0000)	0/50	0	0	1
PANCREAS	M-ISLET CELL CARCINOMA	S-	0.2223	(0.9942)	0/50	1	0	0
CAVITY, ABDOM	B-HEMANGIOMA	S-	0.6162	(1.0000)	0/50	0	1	0
CAVITY, ABDOM	M-HEMANGIOSARCOMA	S-	1.0000	(1.0000)	0/50	0	0	1
PREPUTIAL GLAND	M-HEMANGIOSARCOMA	S-	0.3506	(1.0000)	0/50	0	0	1
SPLEEN	B-HEMANGIOMA	S-	0.3168	(1.0000)	1/50	0	0	1
SPLEEN	M-HEMANGIOSARCOMA	S-	0.3171	(1.0000)	3/50	2	6	1
STOMACH, NONGL	B-SQUAMOUS CELL PAPILLOMA	S-	0.7409	(1.0000)	1/50	0	0	0
TESTIS	B-BENIGN INTERSTIT CELL	S-	0.5060	(1.0000)	0/50	0	1	0
THYMUS	M-THYMOMA	S-	0.2590	(1.0000)	0/50	1	0	0
TRACHEA	B-MYXOMA	S-	0.2590	(1.0000)	0/50	0	0	1

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Table 5F

FEMALE MOUSE STUDY S366_102

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: FEMALE

Organ Name	Tumor Name	Tumor Type	Exact p	Asymp p	#Incid /Ctrls	Dose 0.01	Dose 0.03	Dose 0.10
ADRENAL, CORTEX	B-ADENOMA	S-	0.5776	(0.9990)	1/50	0	0	0
ADRENAL, CORTEX	M-CARCINOMA	S-	0.2774	(1.0000)	0/50	0	1	0
ADRENAL, MEDULLA	B-BENIGN PHEOCHROMOCYTOMA	S-	0.6373	(1.0000)	0/50	0	0	1
BRAIN W/STEM	M-EPENDYMOMA	S-	1.0000	(1.0000)	0/50	0	0	1
COLON	M-HEMANGIOSARCOMA	S-	0.4944	(1.0000)	0/50	0	0	1
UTERUS, CERVIX	M-SQUAMOUS CELL CARCINOMA	S-	0.2774	(1.0000)	1/50	0	0	0
MUSCLE, DIAPHRM	M-FIBROSARCOMA	S-	1.0000	(1.0000)	0/50	1	0	0
HARDERIAN GLAND	B-ADENOMA	S-	0.6373	(1.0000)	4/50	2	1	2
HARDERIAN GLAND	M-CARCINOMA	M-	(0.5900)	1.0000	1/50	0	3	0
HARDERIAN GLAND	M-FIBROSARCOMA	S-	0.4968	(1.0000)	0/50	1	0	0
HEMATO NEOPLASIA	M-HISTIOCYTIC SARCOMA	S-	0.8292	(1.0000)	0/50	0	1	1
HEMATO NEOPLASIA	M-LEUKEMIA, GRANULOCYTIC	S-	0.5732	(1.0000)	0/50	0	1	0
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, HIS	M-	(0.9945)	1.0000	4/50	2	4	5
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, LYM	M-	(0.2039)	0.9976	3/50	4	1	2
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, LYM	M-	(0.0258)	1.0000	1/50	1	1	3
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, MIX	M-	(0.7484)	1.0000	2/50	5	4	1
JEJUNUM	M-CARCINOMA	S-	0.2774	(1.0000)	1/50	1	0	0

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Table 5F

FEMALE MOUSE STUDY S366_102

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: FEMALE

LIVER	B-HEPATOCELLULAR ADENOMA	S-	0.2774	(1.0000)	5/50	0	2	5
LIVER	B-HEPATOCELLULAR ADENOMA,	S-	0.9379	(1.0000)	1/50	1	0	1
LIVER	M-HEMANGIOSARCOMA	M-	(0.4002)	1.0000	1/50	1	1	0
LIVER	M-HEPATOCELLULAR CARCINOM	M-	(0.7484)	1.0000	0/50	1	0	3
LUNG	B-ALVEO/BRONCH ADENOMA	S-	0.7484	(1.0000)	2/50	2	4	2
LUNG	M-ALVEO/BRONCH CARCINOMA	S-	1.0000	(1.0000)	0/50	0	1	0
MAMMARY GLAND	B-FIBROADENOMA	S-	0.8343	(1.0000)	0/50	0	1	0
MAMMARY GLAND	B-INTRADUCTAL PAPILLARY A	S-	1.0000	(1.0000)	0/50	1	0	0
MAMMARY GLAND	M-CARCINOMA	S-	0.4968	(1.0000)	1/50	0	0	1
MUSCLE, OTHER	M-OSTEOSARCOMA	S-	1.0000	(1.0000)	0/50	0	1	0
OVARY	B-BENIGN GRAN/THECA CELL	S-	1.0000	(1.0000)	0/50	0	1	0
OVARY	B-CYSTADENOMA	S-	0.7515	(1.0000)	1/50	0	2	1
OVARY	M-HEMANGIOSARCOMA	S-	0.7484	(1.0000)	1/50	0	0	0
OVARY	M-MALIGNANT GRAN/THECA CE	S-	0.4643	(1.0000)	0/50	1	0	0
PANCREAS	B-ISLET CELL ADENOMA	S-	0.7375	(1.0000)	0/50	1	0	0
PITUITARY	B-ADENOMA	S-	0.7468	(1.0000)	5/50	5	6	5
PITUITARY	M-CARCINOMA	S-	0.7484	(1.0000)	0/50	1	1	0
SPLEEN	B-HEMANGIOMA	S-	0.7484	(1.0000)	0/50	1	0	0
SPLEEN	M-HEMANGIOSARCOMA	M-	(0.4792)	1.0000	3/50	3	0	0
SUBCUTANEOUS TIS	M-BASAL CELL CARCINOMA	S-	0.9043	(1.0000)	0/50	1	0	0

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

Table 5F

FEMALE MOUSE STUDY S366_102

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Test of Trend Based on the Tumor Data

Animal Type: MOUSE

Sex: FEMALE

SUBCUTANEOUS TIS	M-FIBROSARCOMA	M-	(0.4968)	1.0000	1/50	1	1	0
SUBCUTANEOUS TIS	M-LIPOSARCOMA	S-	0.2738	(0.9956)	0/50	1	0	0
SKIN, OTHER	B-FIBROMA	S-	0.7793	(1.0000)	1/50	0	0	0
SKIN, OTHER	B-HEMANGIOMA	S-	0.1982	(1.0000)	1/50	0	0	0
SKIN, OTHER	M-MELANOMA	S-	0.1309	(0.9999)	1/50	0	0	0
SKIN, OTHER	M-NEUROFIBROSARCOMA	S-	0.5031	(1.0000)	0/50	0	0	1
STOMACH, GL	B-ADENOMA	S-	1.0000	(1.0000)	0/50	0	0	1
THYROID	B-FOLLICULAR CELL ADENOMA	S-	1.0000	(1.0000)	0/50	1	1	0
THYROID	M-"C" CELL CARCINOMA	S-	1.0000	(1.0000)	1/50	0	0	0
UTERUS	B-ENDOMETRIAL STROMAL POL	S-	0.2774	(1.0000)	2/50	0	0	0
UTERUS	B-HEMANGIOMA	S-	0.7471	(1.0000)	0/50	0	1	0
UTERUS	B-LEIOMYOMA	S-	0.7484	(1.0000)	1/50	0	0	0
UTERUS	M-CARCINOMA	M-	(0.8248)	1.0000	1/50	1	1	0
UTERUS	M-HEMANGIOSARCOMA	S-	0.4918	(1.0000)	0/50	1	0	0
UTERUS	M-NEUROFIBROSARCOMA	S-	0.7514	(1.0000)	0/50	1	0	0

Note: Tumor Type=M indicates that the tumor is fatal to some but not all animals. Tumor Type=S indicates that the tumor is either fatal or non-fatal to all animals.

An '+' indicates a significant linear dose-tumor trend.
A '-' indicates a non-significant linear dose-tumor trend.

MALE MOUSE

STUDY S366_102 [NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Pairwise Comparisons

Dosage Pair: 0.00 vs 0.10

ANIMAL: MICE
SEX: MALE

Organ	Tumor	Exact p	Asmp p	Dose: 0.00	Dose: 0.10
ADRENAL, CORTEX	B-ADENOMA	0.8794	(1.0000)	2	1
ADRENAL, MEDULLA	M-MALIGNANT PHEOCHROMOCYTOMA	0.4948	(1.0000)	0	1
TRACHEA	B-MYXOMA	0.5000	(1.0000)	0	1
LUNG	M-ALVEO/BRONCH CARCINOMA	0.9686	(1.0000)	6	2
LUNG	B-ALVEO/BRONCH ADENOMA	0.3395	(0.9899)	5	7
SPLEEN	M-HEMANGIOSARCOMA	0.9419	(1.0000)	3	1
SPLEEN	B-HEMANGIOMA	0.7529	(1.0000)	1	1
LIVER	B-HEPATOCELLULAR ADENOMA	0.7257	(0.9995)	7	6
LIVER	M-HEPATOCELLULAR CARCINOMA	0.0548	(0.9750)	1	6
LIVER	M-HEPATOCELLULAR CARCINOMA,M	0.9868	(1.0000)	6	1
LIVER	M-HEMANGIOSARCOMA	0.3161	(1.0000)	1	3
LIVER	B-HEPATOCELLULAR ADENOMA,MUL	(1.0000)	1.0000	1	0
STOMACH, NONGL	B-SQUAMOUS CELL PAPILLOMA	(1.0000)	1.0000	1	0
JEJUNUM	M-CARCINOMA	1.0000	(1.0000)	1	0
PANCREAS	B-ISLET CELL ADENOMA	(0.5000)	1.0000	0	1
HARDERIAN GLAND	B-ADENOMA	0.5000	(0.9981)	5	6
HARDERIAN GLAND	M-CARCINOMA	0.7529	(1.0000)	1	1
MARROW, FEMUR	M-HEMANGIOSARCOMA	1.0000	(1.0000)	1	0
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, HISTIO	0.5000	(1.0000)	2	3
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, MIXED	0.5000	(1.0000)	0	1
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, LYMPHB	0.5056	(1.0000)	0	1

Note: An '*' indicates that the dose-tumor association may be significant for the selected dose pair because the p-value <= 0.05.

Table 6M

MALE MOUSE

STUDY S366_102 [NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Pairwise Comparisons

Dosage Pair: 0.00 vs 0.10

ANIMAL: MICE
SEX: MALE

CAVITY, ABDOM	M-HEMANGIOSARCOMA	0.5000	(1.0000)	0	1
PREPUTIAL GLAND	M-HEMANGIOSARCOMA	0.5000	(1.0000)	0	1

Note: An '*' indicates that the dose-tumor association may be significant for the selected dose pair because the p-value <= 0.05.

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FEMALE MOUSE STUDY S366_102

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Pairwise Comparisons

Dosage Pair: 0.00 vs 0.10

ANIMAL: MICE
SEX: FEMALE

Organ	Tumor	Exact p	Asmp p	Dose: 0.00	Dose: 0.10
BRAIN W/STEM	M-EPENDYMOMA	0.5244	(1.0000)	0	1
PITUITARY	B-ADENOMA	0.6926	(0.9998)	5	5
ADRENAL, CORTEX	B-ADENOMA	1.0000	(1.0000)	1	0
ADRENAL, MEDULLA	B-BENIGN PHEOCHROMOCYTOMA	0.5244	(1.0000)	0	1
THYROID	M-"C" CELL CARCINOMA	1.0000	(1.0000)	1	0
LUNG	B-ALVEO/BRONCH ADENOMA	(0.7283)	1.0000	2	2
SPLEEN	M-HEMANGIOSARCOMA	(1.0000)	1.0000	3	0
LIVER	B-HEPATOCELLULAR ADENOMA	(0.6926)	0.9998	5	5
LIVER	M-HEPATOCELLULAR CARCINOMA	(0.1389)	1.0000	0	3
LIVER	M-HEMANGIOSARCOMA	1.0000	(1.0000)	1	0
LIVER	B-HEPATOCELLULAR ADENOMA,MUL	0.7769	(1.0000)	1	1
STOMACH, GL	B-ADENOMA	0.5244	(1.0000)	0	1
JEJUNUM	M-CARCINOMA	1.0000	(1.0000)	1	0
COLON	M-HEMANGIOSARCOMA	0.5244	(1.0000)	0	1
OVARY	B-CYSTADENOMA	(0.7769)	1.0000	1	1
OVARY	M-HEMANGIOSARCOMA	1.0000	(1.0000)	1	0
UTERUS	B-ENDOMETRIAL STROMAL POLYP	1.0000	(1.0000)	2	0
UTERUS	M-CARCINOMA	1.0000	(1.0000)	1	0
UTERUS	B-LEIOMYOMA	1.0000	(1.0000)	1	0
UTERUS, CERVIX	M-SQUAMOUS CELL CARCINOMA	1.0000	(1.0000)	1	0
HARDERIAN GLAND	B-ADENOMA	0.8924	(1.0000)	4	2

Note: An '*' indicates that the dose-tumor association may be significant for the selected dose pair because the p-value <= 0.05.

Table 6F

FEMALE MOUSE STUDY S366_102

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

BEST POSSIBLE COPY

Pairwise Comparisons

Dosage Pair: 0.00 vs 0.10

ANIMAL: MICE
SEX: FEMALE

HARDERIAN GLAND	M-CARCINOMA	1.0000	(1.0000)	1	0
MAMMARY GLAND	M-CARCINOMA	(0.7769)	1.0000	1	1
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, HISTIO	0.5427	(0.9991)	4	5
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, MIXED	0.8968	(1.0000)	2	1
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, LYMPHB	0.8382	(1.0000)	3	2
HEMATO NEOPLASIA	M-MALIGNANT LYMPHOMA, LYMPHC	0.3319	(1.0000)	1	3
HEMATO NEOPLASIA	M-HISTIOCYTIC SARCOMA	0.5244	(1.0000)	0	1
SKIN, OTHER	B-FIBROMA	1.0000	(1.0000)	1	0
SKIN, OTHER	M-MELANOMA	1.0000	(1.0000)	1	0
SKIN, OTHER	B-HEMANGIOMA	1.0000	(1.0000)	1	0
SKIN, OTHER	M-NEUROFIBROSARCOMA	0.5244	(1.0000)	0	1
SUBCUTANEOUS TIS	M-FIBROSARCOMA	(1.0000)	1.0000	1	0

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Note: An '*' indicates that the dose-tumor association may be significant for the selected dose pair because the p-value <= 0.05.

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Figure 1M

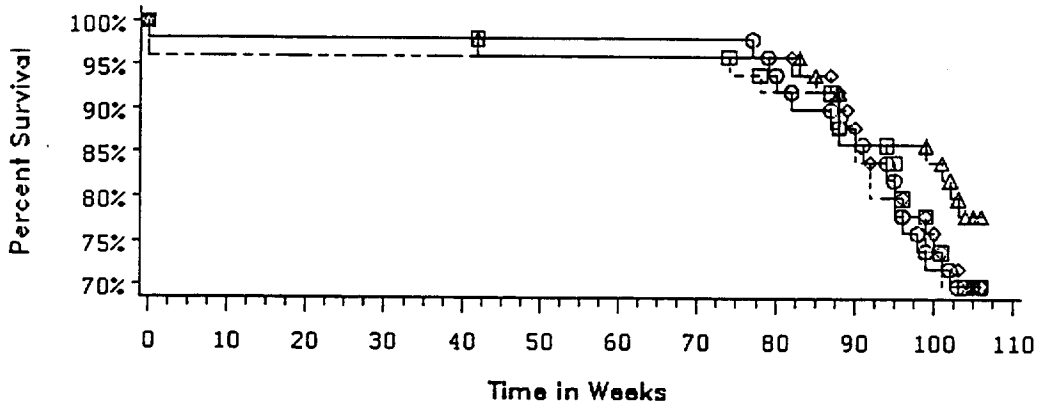
MALE RAT STUDY S366_103

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Kaplan – Meier Survival Function

Animal: RAT

Sex: MALE



Dose: Ctrl Low Med High

Figure 1F

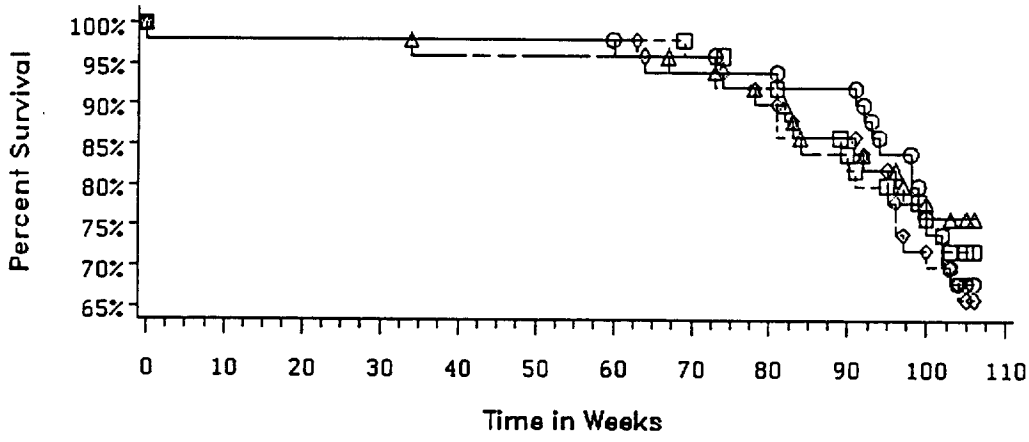
FEMALE RAT STUDY S366_103

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Kaplan – Meier Survival Function

Animal: RAT

Sex: FEMALE



Dose: Ctrl Low Med High

Figure 2M

MALE MOUSE STUDY S366_102

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Kaplan–Meier Survival Function

Animal: MOUSE

Sex: MALE

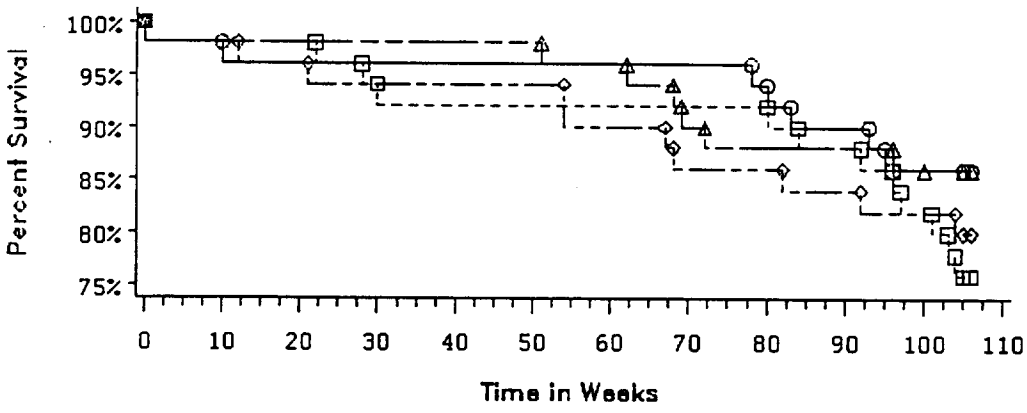


Figure 2F

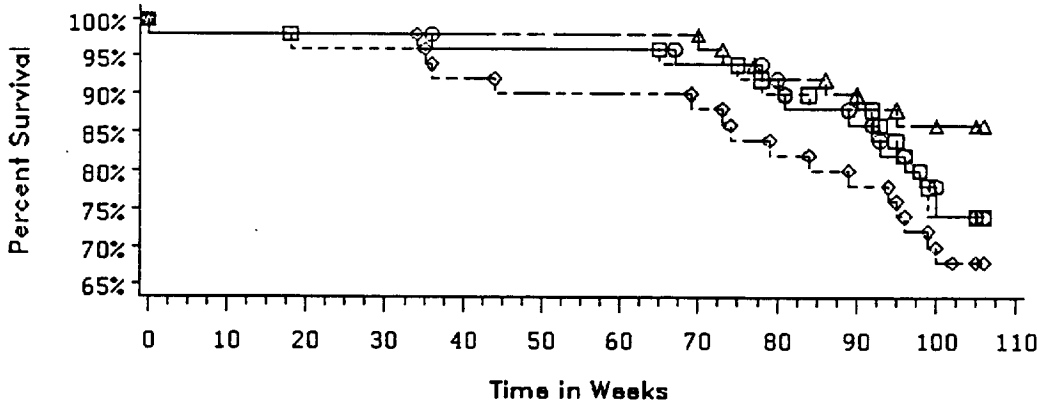
FEMALE MOUSE STUDY S366_102

[NDA20-706 EMADASTINE DIFUMARATE KG-2413]

Kaplan–Meier Survival Function

Animal: MOUSE

Sex: FEMALE



Hafwise

Statistical Review and Evaluation

SEP 16 1996

NDA:	**20-706 [Related IND]**
Drug Class:	**Topical Ophthalmic Solution**
Name of Drug:	**EMADINE ™ 0.05% [Emedastine Difumarate]**
Applicant:	**Alcon Laboratories, Inc., 6201 S. Freeway, Ft Worth, TX 76134**
Submission Date:	**March 26, 1996**
Indications:	**Relief within Minutes of Signs/Symptoms of Allergic Conjunctivitis**
Studies:	**Controlled Clinical: C93-19; C94-90; C95-71** **Clin Pharm: C93-12; C95-13; C95-35; C95-11; C93-16; C94-93** **Additional: C94-86 (Safety Data Only); C95-54 (In Planning)**
Statistical Reviewer:	**Lillian Patrician, MS, MBA**
Clinical Reviewer:	**Elizabeth Ludwig, MD**
Applicant Contact Persons:	**Susan Caballa (817) 568-6296 / Robert Roehrs (817) 551-8764**

I. Background

EMADINE ™ 0.05% has an active ingredient (Emedastine), which is a topically effective histamine H1 antagonist with a rapid onset of action. It is being submitted for the treatment of symptomatic relief (within minutes and for at least four hours) of allergic conjunctivitis. Efficacy was measured with a 4-point scoring system for ocular itching and redness. Redness of the eye was measured as the sum of redness scores for 3 regions of the eye (ciliary, episcleral, and conjunctival).

The sponsor reports having conducted ten total studies with Emedastine Ophthalmic Solution. Three were efficacy studies (C93-19; C94-90; C95-71) using the Conjunctival Allergen Challenge (CAC) model. A fourth efficacy study (C94-86), comparing Emedastine Ophthalmic solution with 2% cromolyn sodium, was initiated internationally and discontinued for reasons other than safety. Only safety data are being submitted. Six Clinical Pharmacology / Pharmacokinetics studies tested all concentrations of Emedastine Ophthalmic solution for comfort level after instillation in the eye. ***[Attachment # 1 - Page 13]***

Visit Schedule

Conjunctival Allergen Challenge Model (CAC)

V1	Screening Measures	Challenge #1		
V2	Challenge #2 (Confirmatory)	+3+10+20 minute Measures		
V3	Treatment	+ 10 min.	Challenge #3	+3+10+20 minute Measures
V4	Treatment	+ 4 hours	Challenge #4	+3+10+20 minute Measures

The study design includes Visit # 3 to demonstrate onset-of-action of study drug. Ten minutes following instillation of treatment into the randomized eye, the subject's allergic symptoms of conjunctivitis are provoked by an allergen challenge. Efficacy measures are then recorded at 3, 10, and 20 minutes post-challenge. Visit # 4 demonstrates the duration of action. Four hours after instillation of treatment, the allergen challenge is again administered and efficacy measures taken. Duration of action could not be adequately measured during Visit #3 due to the degradation of allergen effect on the vehicle eye (mast cell changes over 4 hour time period). To assure testing beyond the possible refractory period, the third visit was at least 14 days after the second visit, and the fourth was at least 14 days after the third.

Primary Efficacy Measures

Score	Itching	Redness
0	none	none
0.5	intermittent tickling / corner of eye	
1	intermittent tickling / more eye	mild
1.5	intermittent tickling all over sensation	
2	mild, continuous itch	moderate
2.5	moderate, diffuse, continuous itch	
3	severe itch	severe
3.5	severe itch improved with rubbing	
4	incapacitating itch requiring rubbing	extremely severe

There is no way to confirm that the allergen challenge was given 4 hours following instillation of drops. The case report form only provides record for the time of treatment instillation. Instructions to challenge four hours post-instillation do not include time of challenge. This is also the case for the onset-of-challenge visit where instructions to challenge 10 minutes following instillation do not include time of challenge, nor time efficacy measures were actually taken.

There appears to be no bias in enrollment for those subjects randomized to the treatment and vehicle groups. Even though the study design planned no stratification by antigen challenge threshold values, the randomization schema provides a balance across treatment arms for subjects with varying levels of antigen challenge thresholds. Through the contralateral administration of Emedastine and vehicle, the CAC model also assures that subjects requiring a higher antigen challenge are evenly assigned to both treatment and vehicle. ***[Attachment # 2 - Page 14]***

The subgroup distribution of subjects in Study C9319 shows a balance across treatment arms. For all studies, subjects were predominantly under 65 years of age, of brown or blue iris eye color, and Caucasian. ***[Attachment # 3 - Page 15]***

No statistical comparisons of subgroup results were made, however, the mean redness scores for females in all treatment arms and all studies are consistently lower than those for males. This also holds true for the vehicle-treated and Levocabastine female subjects. ***[Attachment # 4 - Page 16]*** Allergen data were not available for Study C9571, however, data from Studies C9319 and C9490 indicate that female subjects required higher doses of allergen challenge. After adjusting for the higher female enrollment (25% more than males with a 200:160 female:male ratio), the distribution of subjects by threshold allergen challenge shows more women than men challenged at the higher ranges of provocation dosing. ***[Attachment # 5 - Page 17].***

II. **CAC Efficacy Study C 9319**

Triple-masked, Placebo-controlled, Randomized, Parallel-Group Contralateral Eye Comparison Study

Treatment	# Subjects	Randomized OD or OS	Contralateral Eye
Group A	60	0.05% Emedastine	Emedastine Vehicle (Placebo)
Group B	60	0.10% Emedastine	Emedastine Vehicle (Placebo)
Group C	60	0.50% Emedastine	Emedastine Vehicle (Placebo)
Group D	60	Emedastine Vehicle (Placebo)	Emedastine Vehicle (Placebo)

1. Sponsor's Evaluation: C9319 was designed to compare three concentrations of Emedastine ophthalmic solution (0.05%, 0.10%, 0.50%) to vehicle control. The sponsor reports that all three concentrations of Emedastine showed statistically significant differences from vehicle in measurements of ocular itching and sum of scores for regional redness. The sponsor also reports that the 0.10% level showed a statistically significant difference from that of 0.50%, and that the 0.05% and 0.10% levels showed no statistically significant difference between each other. For reasons of optimum safety, the sponsor chose 0.05% level as the recommended dose concentration of use. Of 60 patients per group in Visit 1, all 60 had a positive confirmatory challenge at Visits 2, 3, and 4.

The following subjects did not complete study:

Investigator	Subject	Treatment Arm	Last Visit	Reason for Discontinuation
Abelson (1028)	102	0.50% EM [OS]	V4	BASELINE REDNESS > 1+ AT VISIT 4 BASELINE EXAM
Abelson (1028)	103	0.10% EM [OS]	V3	BASELINE REDNESS >1+ OU
Abelson (1028)	176	0.50% EM [OS]	V3	LOST TO FOLLOW UP - Missed V4 due to death in family
Abelson (1028)	179	0.05% EM [OD]	V3	LOST TO FOLLOW UP - Missed V4 due to death in family
Abelson (1028)	188	Vehicle [OD]	V3	LOST TO FOLLOW UP - Chose not to attend exit visit
Spitalny (1814)	340	0.50% EM [OD]	V3	LOST TO FOLLOW UP - Failed to take exit pregnancy test

Paired t-tests per treatment group were used as the statistical methodology in evaluating the comparisons between treated and vehicle eyes. To compare the different treatment levels, the sponsor also used an analysis of covariance model, ANOVA (SAS Proc Mixed), where the placebo contralateral eyes were a covariate. Group D, the vehicle-vehicle group, was used to confirm no carry-over effect by comparing the vehicle-treated eyes from each of Groups A, B, and C with the vehicle-treated eyes of Group D.

2. **Reviewer's Evaluation**:

Emedastine Carry-Over Effect: The comparison of vehicle-treated eyes per treatment arm A, B, and C (0.05%, 0.10%, and 0.50% Emedastine) with the vehicle-treated eyes of vehicle-vehicle arm D shows no evidence of statistically different values, with three exceptions. At Visit 4 +3 minutes post-challenge, the mean redness measure of 3.77 for vehicle eyes of the 0.05% Emedastine arm and 4.72 of vehicle arm D reveal a statistically significant difference at the 0.05 level with a p-value of 0.0257. At this same visit time (V4 +3), the mean itching measure of 1.36 for vehicle eyes of the 0.50% Emedastine arm and 1.82 of vehicle arm D show a statistically significant difference with a p-value of 0.0114. And, at Visit 4 +20 minutes post-challenge, the mean redness measure of 5.86 for vehicle eyes of the 0.10% Emedastine arm and 6.71 of vehicle arm D reveal a statistically significant difference with a p-value of 0.0454. There was no evidence of statistically significant differences between the vehicle eyes at any other time points.

When using this approach, the vehicle-treated eyes in treatment arms A, B, and C appear to show no systemic carry-over effect from the Emedastine-treated contralateral eyes at most time points. However, the mean scores for ocular itching and redness at Visit 2 (confirmatory allergen challenge visit prior to any dosing of study drug) are markedly higher than those same eyes assigned to vehicle treatment at Visits 3 and 4. ***[Attachment # 6 A-B - Page 18-19]***

To test beyond a possible refractory period, there was a 14-day interim between Visits 2 and 3, as well as Visits 3 and 4. Even so, the efficacy measures of the vehicle-treated eyes decrease from Visit 2 to Visit 3, and again to Visit 4. These decreases are more pronounced for ocular

itching scores. Comparisons between eyes measured at Visit 2 and those same eyes at Visits 3 and 4 (after instillation of study drug and provocation with allergen challenge) demonstrate at all time points, a statistically significant difference between all levels of Emedastine as compared to vehicle (placebo). Measures taken following administration of Emedastine show an improvement of more than 2 points for both the mean ocular itching and mean regional redness scores. The magnitude of these decreases is not realized when comparing differences between treated and contralateral vehicle eyes, as was planned in the protocol. There appears to be some influence of study drug on the contralateral vehicle eye. More probably, the cleansing effect of flushing the eye with study drug or vehicle helps to abate the signs and symptoms provoked by the allergen challenge. ***[Attachment # 7 A-B - Page 20-21]***

Comparative Results of Emedastine versus Vehicle: Paired t-tests were used to compare Emedastine-treated eyes with their contralateral vehicle control eyes. At each time point and for both ocular itching and sum of scores on regional redness, the results demonstrate statistically significant differences at the 0.05 level between all levels of Emedastine and vehicle, with 4 exceptions. There is no evidence of statistically significant differences in regional redness scores between 0.50% Emedastine and vehicle at Visit 3 +20, Visit 4 +10, and Visit 4 +20 minutes; an no evidence between 0.05% Emedastine and vehicle at Visit 4 +20 minutes (p=0.0646). ***[Attachment # 8 - Page 22]*** However, when comparing the difference between vehicle and treated eye for each treatment arm with that of the vehicle-vehicle arm, the results demonstrate statistically significant differences at the 0.05 level between all levels of Emedastine and vehicle. This is true at each time point and for both ocular itching and sum of scores on regional redness.

Comparative Results of Concentration Levels of Emedastine-treated Contralateral Eyes: The mean differences from vehicle contralateral eye were used to evaluate efficacy measures of ocular itching and regional redness for the 3 concentrations of Emedastine-treated eyes. When compared to each other, the results show no evidence of statistically significant differences among the 3 levels of 0.05%, 0.10% and 0.50% Emedastine, with 3 exceptions. At Visit 4 +3 minutes post-challenge, the mean difference in itching measure of 1.29 for 0.05% Emedastine-treated eyes and 0.91 for the 0.50% Emedastine-treated eyes reveal a statistically significant difference at the 0.05 level with a p-value of 0.0409. At this same V4 + 3 time point, the mean difference in itching measure of 1.42 for 0.10% Emedastine-treated eyes and 0.91 for 0.50% Emedastine-treated eyes show a statistically significant difference with a p-value of 0.0075. And, at Visit 3 +20 minutes post-challenge, the mean difference in redness measure of 1.42 for 0.10% Emedastine-treated eyes and 0.14 for 0.50% Emedastine-treated eyes reveal a statistically significant difference with a p-value of 0.0028.

Safety Summary: Of the adverse experiences reported as possibly, probably, or definitely related, 2 subjects experienced ocular discomfort where Emedastine was seen as the suspect drug. One report of eye pruritus was also attributed to Emedastine.

Number of Subjects with Adverse Experiences
(as Reported by Sponsor)
[Vol 20.8.1866]

C9319	0.05% EM + PBO	0.10% EM + PBO	0.50% EM + PBO	PBO + PBO	Relation
Experience	n = 12 of 60	n = 10 of 60	n = 16 of 60	n = 11 of 60	
Eye Pruritus	1 (1.7%)	0	0	0	Related
Eye Discomfort	0	1 (1.7%)	1 (1.7%)	0	Related
Decreased Visual Acuity	1 (1.7%)	0	0	0	Not Related
Foreign Body Sensation	1 (1.7%)	0	0	0	Not Related
Lid Edema	0	1 (1.7%)	0	0	Not Related
Headache	8 (13.3%)	5 (8.3%)	11 (18.3%)	4 (6.7%)	Not Related
Back Pain	1 (1.7%)	1 (1.7%)	0	0	Not Related
Cold Syndrome	0	3 (5.0%)	2 (3.3%)	3 (5.0%)	Not Related
Flu Syndrome	0	0	0	1 (1.7%)	Not Related
Periodontal Abscess	0	0	1 (1.7%)	0	Not Related
Dysmenorrhea	0	0	1 (1.7%)	0	Not Related
Nausea	0	0	0	1 (1.7%)	Not Related
Arthritis	0	0	0	1 (1.7%)	Not Related
Rhinitis	0	0	0	1 (1.7%)	Not Related
Bronchitis	0	0	0	1 (1.7%)	Not Related

III. **CAC Efficacy Study C9490**

Triple-masked, Placebo-controlled, Randomized, Parallel-Group
Contralateral Eye Comparison Study

Treatment	# Subjects	Randomized OD or OS	Contralateral Eye
Group A	60	0.005% Emedastine	Emedastine Vehicle (Placebo)
Group B	60	0.05% Emedastine	Emedastine Vehicle (Placebo)

1. **Sponsor's Evaluation**: C9490 was designed to compare two concentrations of Emedastine ophthalmic solution (0.005% and 0.05%) to contralateral vehicle control. The sponsor reports that the 0.05% concentration of Emedastine showed statistically significant differences from vehicle in measurements of ocular itching and sum of scores for regional redness. Of 60 patients per group in Visit 1, all 60 had a positive confirmatory challenge at Visits 2, 3, and 4. All subjects completed study.

Paired t-tests per treatment group were used as the statistical methodology in evaluating the comparisons between treated and vehicle eyes. To compare the different treatment levels, the sponsor also used an analysis of covariance model, ANOVA (SAS Proc Mixed), where the placebo contralateral eyes were a covariate.

2. **Reviewer's Evaluation:**

Comparative Results of Emedastine versus Vehicle: Paired t-tests were used to compare Emedastine-treated eyes with their contralateral vehicle control eyes. At each time point for ocular itching, the results demonstrate statistically significant differences at the 0.05 level between both levels of Emedastine and vehicle. Even though the ocular itching and redness scores for the 0.005% level of Emedastine were consistently lower than those of vehicle-treated eyes, there was no evidence of statistically significant differences in redness scores from contralateral vehicle control eyes at all time points of Visit 4. In this study at Visit 3 +20 minutes, the redness scores for 0.05% level of Emedastine also had insufficient evidence to demonstrate a statistical difference from vehicle. ***[Attachment # 9 - Page 23]***.

Comparative Results of 2 Concentration Levels of Emedastine-treated Contralateral Eyes: The mean differences from vehicle contralateral eye were used to compare efficacy measures of ocular itching and regional redness for 2 concentrations (0.005% and 0.05%) of Emedastine. The itching results demonstrate a statistically significant difference between the 2 levels of 0.005% and 0.05% Emedastine at Visit 4 +3 only. However, the mean differences in redness scores are statistically different at all time measures of Visit 4. ***[Attachment # 10 - Page 24]***

As was seen in Study C9319, the vehicle-treated eyes at Visits 3 and 4 show lower ocular itching scores than those same eyes measured during the confirmatory challenge Visit 2. The mean ocular redness scores for both 0.005% and 0.05% Emedastine are relatively consistent throughout all visits. ***[Attachment # 11 A-B - Page 25-26]*** The mean differences between Emedastine-treated eyes at Visits 3 and 4 and those same eyes prior to treatment at Visit 2 show more pronounced decreases than contralateral eye comparisons, but the improvement in redness scores seen at Visit 3 shows degradation at Visit 4, especially for the 0.005% Emedastine-treated subjects. ***[Attachment # 12 A-B - Page 27-28]***

Safety Summary: Only one subject reported an adverse experience (headache) as possibly, probably, or definitely related.

Number of Subjects with Adverse Experiences
(as Reported by Sponsor)
[Vol 21.8.2214]

C9490	0.005% EM + Placebo	0.05% EM + Placebo	Relation
Experience	n = 9 of 60	n = 0 of 60	
Headache	1 (1.7%)	0	Related
Headache	2 (3.3%)	0	Not Related
Back Pain	1 (1.7%)	0	Not Related
Cold Syndrome	2 (3.3%)	0	Not Related
Chest Pain	1 (1.7%)	0	Not Related
Rhinitis	3 (5.0%)	0	Not Related
Bronchitis	1 (1.7%)	0	Not Related

IV. **CAC Efficacy Study C 9571**

Triple-masked, Placebo-controlled, Randomized, Parallel-Group Contralateral Eye Comparison Study

Treatment	# Subjects	Randomized OD or OS	Contralateral Eye
Group A	64	0.05% Emedastine	0.05% Levocabastine
Group B	16	0.05% Emedastine	Emedastine Vehicle (Placebo)
Group C	17	0.05% Levocabastine	Emedastine Vehicle (Placebo)

1. **Sponsor's Evaluation:** C9571 was designed to compare 0.05% concentration of Emedastine ophthalmic solution to 0.05% Levocabastine Ophthalmic Suspension. The sponsor reports that Emedastine is superior to Levocabastine in alleviating ocular itching and statistically equivalent to Levocabastine (while numerically superior) in alleviating ocular redness.

Subject #174 enrolled in treatment arm "0.05% Emedastine (OS) - Vehicle (OD)" under Investigator Netland (1960) was dropped from study due to an adverse experience (Visit # 4 event was described as "SPK OU WITH BASELINE REDNESS > 1 OU").

Paired t-tests per treatment group were used as the statistical methodology in evaluating the

comparisons between Emedastine-treated and Levocabastine-treated eyes. The sponsor enrolled 96 subjects, 33 of whom were assigned to a parallel masking control group. The sponsor reports that they received either Emedastine Ophthalmic Solution 0.05% or Levocabastine Ophthalmic Suspension 0.05% in one eye, and placebo (Emedastine Ophthalmic Vehicle) in the other eye [Vol 2-0091].

The visit schedule in this study differs from that of C9319 and C9490. During Visit # 3, efficacy measures were taken 1, 3, and 5 minutes post-challenge. During Visit # 4, they were measured 3, 5, and 10 minutes post-challenge, and 2 hours following dosing of drug rather than 4 hours.

2. Reviewer's Evaluation:

Comparative Results of 0.05% Emedastine with 0.05% Levocabastine:

Paired t-tests were used to compare Emedastine-treated eyes with their contralateral Levocabastine control eyes. For ocular itching, the results demonstrate statistically significant differences at the 0.05 level between Emedastine and Levocabastine at Visit 3 +5 and Visit 4 +3 minutes. There was no evidence of statistically significant differences at any other time points, nor for any time points measuring sum of regional redness. Even though the number of subjects in the vehicle masking control group was small, the comparison of Levocabastine-treated eyes with the contralateral vehicle-treated eyes of these 17 subjects demonstrates statistically significant differences for itching (all time points) and for redness (Visit 3 + 5, V3 +10, V4 +5, and V4 +10 minutes). The Emedastine-Vehicle masking control group of 16 subjects also demonstrated significance for itching at all visits, but showed no evidence of statistically significant differences in redness. ***[Attachment # 13 - Page 29]***

Of the 17 subjects in the Levocabastine-vehicle masking control group, the vehicle-treated eyes at Visits 3 and 4 show scores comparable to those same eyes measured during the confirmatory challenge Visit 2. However, decreases in scores are seen more in the 16 Emedastine-vehicle subjects whose vehicle-treated eyes were contralateral to Emedastine treatment. Although the sample size of 17 is small, the Levocabastine contralateral vehicle eyes do not demonstrate that carry-over effect that is seen with Emedastine in all three studies.
[Attachment # 14 A-B - Page 30-31]

The graphical representation of scores for the 64 Emedastine-Levocabastine subjects shows a greater than 2 point decrease in both ocular itching and redness from Visit 2 to Visits 3 and 4. Levocabastine maintains its decreased redness scores throughout Visit 3 and Visit 4, whereas Emedastine redness scores degrade slightly at Visit 4 from Visit 3. ***[Attachment # 15 A-B - Page 32-33]*** The upper bound of 95 percent confidence intervals on the mean difference between Levocabastine and Emedastine ocular itching and redness scores (LEVO-EM) is less than the 0.8 maximum that the sponsor planned for equivalence testing in the protocol. The confidence interval on itching scores includes zero for all time points; it includes zero for 5 of 6 time points on redness scores, with a Visit 4 +3 lower limit of 0.00705. ***[Attachment # 16 - Page 34]***

Safety Summary: Of the adverse experiences reported as possibly, probably, or definitely related, 3 subjects experienced ocular discomfort in the Levocabastine-treated eye; 2 additional subjects experienced ocular discomfort in both the Emedastine and Levocabastine eyes; and 1 subject reported discomfort in both the Emedastine and vehicle eyes. One subject experienced pruritus in the Emedastine eye.

Number of Subjects with Adverse Experiences
(as Reported by Sponsor)
[Vol 21.8.2454]

C9571	0.05% EM + LEVO	0.05% EM + PBO	0.05% LEVO + PBO	Relation
Experience	n = 16 of 64	n = 4 of 16	n = 1 of 17	
Ocular Discomfort	5 (7.8%)	1 (6.3%)	0	Related
Pruritus	0	1 (6.3%)	0	Related
Keratopathy	0	1 (6.3%)	0	Not Related
Headache	7 (10.9%)	0	0	Not Related
Cold Syndrome	2 (3.1%)	0	0	Not Related
Flu Syndrome	1 (1.6%)	0	0	Not Related
Lymphadenopathy	1 (1.6%)	0	0	Not Related
Bronchitis	2 (3.1%)	0	0	Not Related
Rhinitis	1 (1.6%)	1 (6.3%)	0	Not Related
Pharyngitis	1 (1.6%)	0	0	Not Related
Increased Cough	0	0	1 (5.9%)	Not Related
Surg/Med Procedure	1 (1.6%)			

V. Other Studies

Three comfort studies (C93-12, C95-13, and C95-35) were apparently conducted in tandem with the sponsor's three comfort studies (C93-79, C95-12, and C95-18) for Opatanol ™ (Olopatadine Hydrochloride). Only safety data are being submitted for C94-86 (a comparative study against 2% cromolyn sodium), which was discontinued after enrolling 66 patients. Note that under a separate submission (NDA 20-688 - Olapatadine Hydrochloride vs 2% cromolyn sodium), the sponsor also conducted another comparative study using 2% cromolyn sodium for the treatment of allergic conjunctivitis. Again, only safety results were submitted for 200 patients.

VI. Reviewer's Overall Conclusions

1. The mean redness scores for females in all treatment arms and all studies are consistently lower than those for males. This also holds true for the vehicle-treated and Levocabastine female subjects. Allergen data was not available for Study C9571, however, data from Studies C9319 and C9490 indicate that female subjects required higher doses of allergen challenge. After adjusting for the higher female enrollment, the distribution of subjects by threshold allergen challenge shows more women than men challenged at the higher ranges of provocation dosing.

2. For Emedastine-vehicle subjects, the mean scores for ocular itching and redness at Visit 2 (confirmatory allergen challenge visit prior to any dosing of study drug) are markedly higher than those same eyes assigned to vehicle treatment at Visits 3 and 4. To test beyond a possible refractory period, there was a 14-day interim between Visits 2 and 3, as well as Visits 3 and 4. Even so, the efficacy measures of the vehicle-treated eyes decrease from Visit 2 to Visit 3, and again to Visit 4. These decreases are more pronounced for ocular itching scores.

Comparisons between eyes measured at Visit 2 and those same eyes at Visits 3 and 4 (after instillation of study drug and provocation with allergen challenge) demonstrate at all time points, a statistically significant difference between all levels of Emedastine as compared to vehicle (placebo). Measures taken following administration of Emedastine show an improvement of more than 2 points for both the mean ocular itching and mean regional redness scores. There appears to be some influence of study drug on the contralateral vehicle eye. More probably, the cleansing effect of flushing the eye with study drug or vehicle helps to abate the signs and symptoms provoked by the allergen challenge.

3. The overall safety is summarized by adverse experiences. Of 457 subjects enrolled in the three studies, seventy-nine reported adverse experiences, eleven of which were evaluated as possibly, probably, or definitely related to treatment. These include ocular discomfort (8 total reportings); eye pruritus (2 total reportings); and headache (1 reporting). Levocabastine 0.05% was the suspect drug in 3 of the ocular discomfort cases; the remaining 5 ocular discomforts, as well as the eye pruritus and headache, were from those receiving either 0.05%, 0.10%, or 0.50% Emedastine.

4. Disregarding the possible carry-over effect of Emedastine, which favors placebo at Visits 3 and 4 with lower efficacy scores, statistical comparisons of treated versus contralateral vehicle eyes still show statistically significant differences at most time points. In Study C9319, ocular itching scores for all concentrations of Emedastine (0.05%, 0.10% and 0.50%) were statistically different from contralateral vehicle. This was also demonstrated for the redness scores of 0.10% Emedastine, for 5 of 6 time points of 0.05% Emedastine, and for 3 of 6 time points of the 0.50% concentration level. In Study C9490, both 0.005% and 0.05% Emedastine demonstrated statistically significant differences in itching scores with those of contralateral vehicle. The redness scores for the 0.05% concentration were statistically different from vehicle at 5 of 6 time points. Those of the 0.005% concentration were statistically different at Visit 3 only. In Study C9571, 0.05% Emedastine showed no evidence of being statistically different from 0.05% Levocabastine following the tested 10 minute and 2 hour drug instillation periods.

In conclusion, as compared to the contralateral vehicle eye, Emedastine 0.05% statistically demonstrates efficacy in alleviating the signs and symptoms of allergic conjunctivitis. Measures taken following administration of Emedastine show an improvement of more than 2 points for both the mean ocular itching and mean regional redness scores from those taken at the confirmatory challenge visit. The equivalence of 0.05% Emedastine to 0.05% Levocabastine is confirmed for onset-of-action at Visit 3, and for a duration of 2 rather than 4 hours.

VII. There are No Reviewer Comments to be Conveyed to the Sponsor

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Archival: Orig. NDA 20-706

cc:
IND
HFD-340/Scientific Investigations
HFD-550/Division Files
HFD-550/DivDir/W. Chambers
HFD-550/MO/E. Ludwig
HFD-550/CSO/J. Holmes
HFD-725/DivDir/R. Harkins
HFD-725/TL/H. Leung
HFD-725/Stat/L. Patrician
HFD-725/File Copy

This report has a total of thirty-four [34] pages including sixteen attachments.

Summary Data for All Protocols

Study	Study Design	Investigators / Sites	Enrolled	Safety	Eligible for Efficacy	Study Duration	Date of Study Conduct
C93-19	CAC#1 (0.05%; 0.10%; 0.50%) vs PBO contralateral eye; Efficacy Study measuring 1) Ocular redness [scale range 0-12 summing 0-4 severity levels over 3 sections of eye: ciliary, episcleral, and conjunctival] and 2) Ocular itching	1028 Abelson, MA 1814 Spitalny, AZ	240	240	240	2 doses over 2 weeks	10/29/94 to 4/04/95
C94-90	CAC#2 (0.005%; 0.05%) vs PBO contralateral eye; Efficacy Study measuring 1) Ocular redness [scale range 0-12 summing 0-4 severity levels over 3 sections of eye: ciliary, episcleral, and conjunctival] and 2) Ocular itching	1735 Lawry, TX	120	120	120	2 doses over 2 weeks	03/04/95 to 4/09/95
C95-71	CAC#3 (0.05%) vs LIVOSTIN contralateral eye; Efficacy Study measuring 1) Ocular redness [scale range 0-12 summing 0-4 severity levels over 3 sections of eye: ciliary, episcleral, and conjunctival] and 2) Ocular itching	1960 Netland, MA	97	97	97	2 doses over 2 weeks	11/10/95 to 12/19/95
C93-12	Comfort #1 (0.01%; 0.05%; 0.1%; 0.5%) vs Acular & PBO; Pharm/Pharmacokinetic Study		30			single dose	
C95-13	Comfort #2 0.05% vs Acular and Livostin; Pharm/Pharmacokinetic Study		30			single dose	
C95-35	Comfort #3 0.05% vs Acular and Livostin; Pharm/Pharmacokinetic Study		30			single dose	
C95-11	Pupil Diameter 0.05% vs PBO; Pharm/Pharmacokinetic Study		40			single dose	
C93-16	Multidose Safety 0.01, 0.05, 0.1, 0.5%; Pharm/Pharmacokinetic Study		40			15 days	
C94-93	Long Term Safety 0.05% vs PBO; Pharm/Pharmacokinetic		362			6 weeks	
C94-86	Seasonal AKC 0.05% vs 2% cromolyn sodium [DISCONTINUED]; Safety data only		66			6 weeks	
C95-54	Seasonal AKC 0.05% vs Levocabastine 0.05% [IN PLANNING]	International: Australia; New Zealand; Africa				6 weeks	

Number of Subjects Randomized to Treatment Groups

Attachment # 2

By Challenge Threshold Values

THRESHOLD VALUES	C9319				C9490	
	0.05% EM-PBO	0.10% EM-PBO	0.50% EM-PBO	PBO-PBO	0.005% EM-PBO	0.05% EM-PBO
19	21	23	16	14	23	19
39	9	8	11	10	8	7
78-79	9	12	11	13	13	10
156	5	4	10	9	3	7
312	6	5	7	6	3	7
625	2	6	5	4	5	4
1250	8	2	0	4	5	6
Total Patients	60	60	60	60	60	60

Subgroup Distribution

Attachment # 3

Number of Subjects Per Study and Subgroup

[Reviewer's Results]

	C9319				C9490	C9571
	0.05% EM	0.10% EM	0.50% EM	Vehicle	0.005% - 0.05% EM	Emedastine - Levocabastine
Age						
< 65	58	57	58	58	56	64
GE 65	2	3	2	2	4	0
Iris Color						
Brown	20	25	20	21	37	26
Hazel	15	11	9	18	8	10
Green	3	6	5	5	8	7
Blue	22	18	26	16	7	21
Race						
Caucasian	58	59	58	60	34	61
Black	2	1	1	0	3	1
Other	0	0	1	0	23	2
Sex						
Male	20	31	31	25	27	27
Female	40	29	29	35	33	37

Mean Scores for Sum of Ocular Regional Redness

Attachment # 4

	Visit 3 +3		Visit 3 +10		Visit 3 +20		Visit 4 +3		Visit 4 +10		Visit 4 +20	
C9319	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
0.05% EM (60)	3.08	2.73	5.63	5.21	6.15	5.34	3.60	2.31	6.10	4.41	5.93	4.40
0.05% Contra Vehicle(60)	4.40	3.85	7.13	5.85	7.78	5.94	4.55	3.37	7.23	5.37	7.35	5.15
0.10% EM (60)	3.02	2.14	5.27	4.67	5.11	4.67	3.23	2.19	4.95	4.16	5.12	4.12
0.10% Contra Vehicle (60)	4.68	3.78	6.56	5.95	6.61	6.00	4.28	3.59	6.53	5.46	6.35	5.34
0.50% EM (60)	3.52	2.98	6.13	4.62	6.77	5.09	3.60	2.44	5.98	4.54	6.22	4.43
0.50% Contra Vehicle (60)	4.31	4.29	6.84	5.81	6.63	5.53	5.20	3.17	6.95	5.09	6.87	5.31
Vehicle Arm (60)	5.08	4.10	7.50	5.81	8.04	5.67	5.10	4.44	7.42	6.31	7.56	6.40
Vehicle Arm (60)	4.90	4.37	7.60	5.96	7.62	5.73	5.18	4.37	7.22	6.03	7.28	5.99
C9490												
0.005% EM (60)	3.43	3.15	5.69	4.94	6.07	5.09	4.64	3.26	6.91	6.32	7.31	6.47
0.005% Contra Vehicle (60)	5.00	3.98	7.15	5.91	7.15	5.82	5.54	4.08	7.39	6.48	7.46	6.41
0.05% EM (60)	3.35	2.65	5.65	4.75	6.04	4.72	3.67	2.72	6.25	5.37	6.58	5.31
0.05% Contra Vehicle (60)	4.58	4.68	6.79	6.07	6.42	5.69	5.42	5.01	7.25	6.50	7.37	6.09

	Visit 3 +1		Visit 3 +5		Visit 3 +10		Visit 4 +3		Visit 4 +5		Visit 4 +10	
C9571	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
0.05% Emedastine (64)	3.13	2.35	3.72	3.31	4.91	4.14	3.44	2.55	4.65	3.65	5.93	4.57
0.05% Levocabastine (64)	3.50	2.32	4.54	3.70	5.44	4.41	3.93	2.62	4.83	3.77	5.96	4.91
0.05% EM (16)	2.07	2.78	3.07	3.56	3.50	4.78	3.14	3.81	3.93	4.63	5.29	6.00
0.05% Contra Vehicle (16)	3.29	4.22	4.71	5.17	5.57	5.56	3.79	4.63	5.07	6.19	6.14	7.06
0.05% Levocabastine (17)	3.89	2.44	4.67	3.44	5.78	4.00	3.44	2.00	4.56	6.72	5.44	3.81
0.05% Contra Vehicle (17)	4.94	3.75	6.78	4.98	8.28	5.50	5.56	3.00	6.72	4.63	7.39	5.88

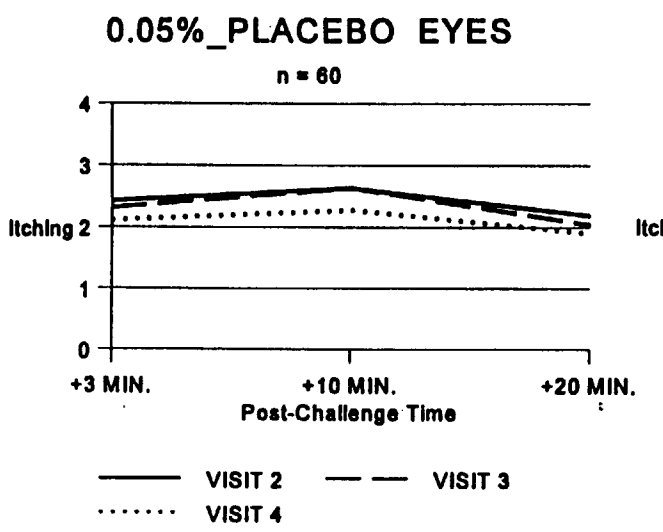
Distribution of Subjects by Allergen Threshold Values

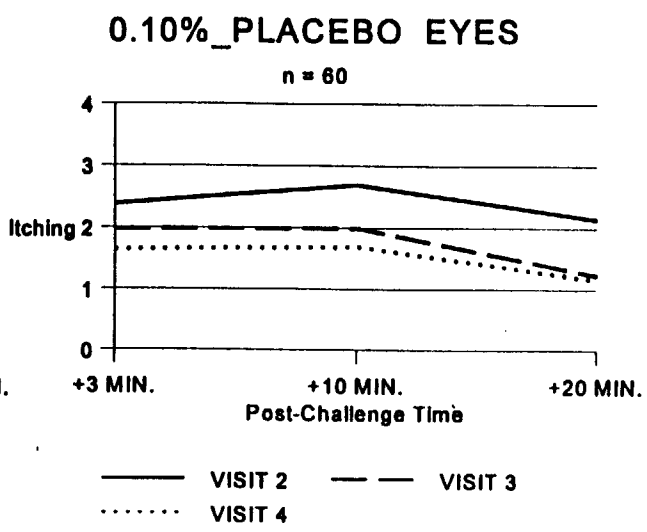
Attachment # 5

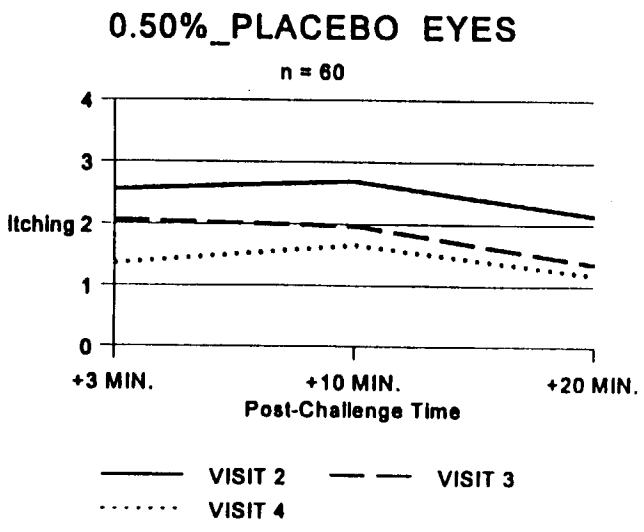
Studies C9319 and C9490

Allergen Threshold	Males Enrolled	Females Enrolled	Expected Female Distribution	Total
CAC Units	#	#	#	#
19	63	53	79	116
39	23	30	29	53
78	29	39	36	68
156	12	26	15	38
312	11	23	14	34
625	14	12	17	26
1250	8	17	10	25
TOTAL	160	200	200	360

Mean Ocular Itching Scores for C9319



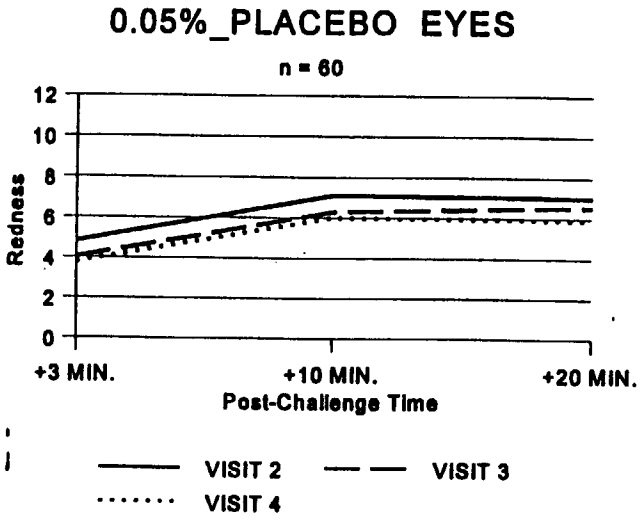


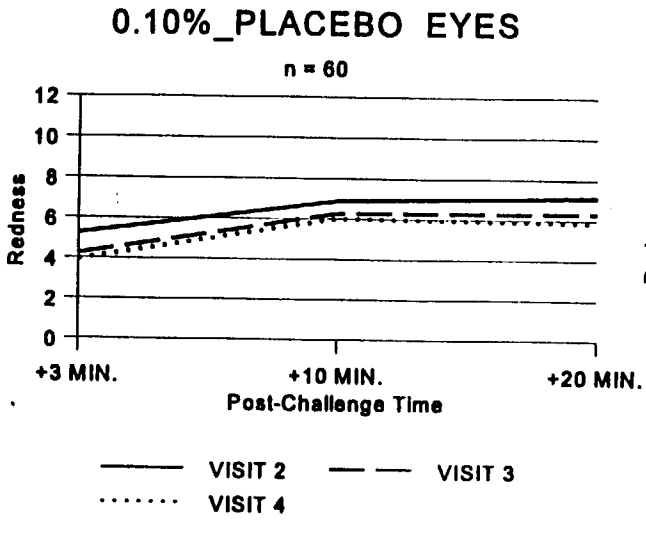


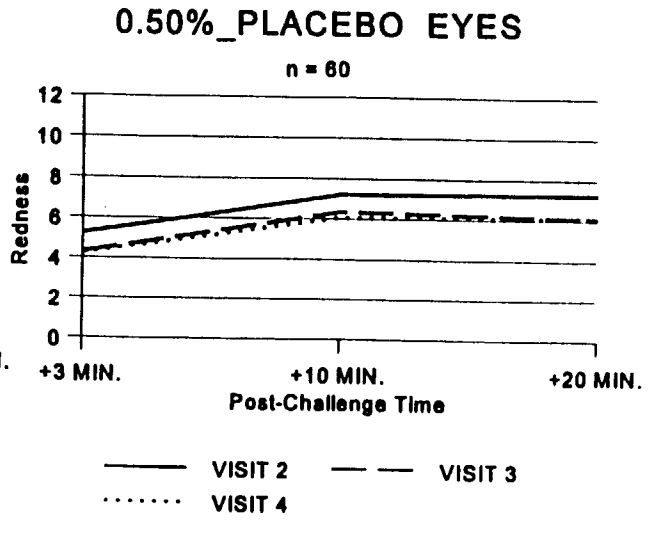
NDA 20-706 Emedastine Contralateral Vehicle (Placebo) Eyes

Attachment # 6 B

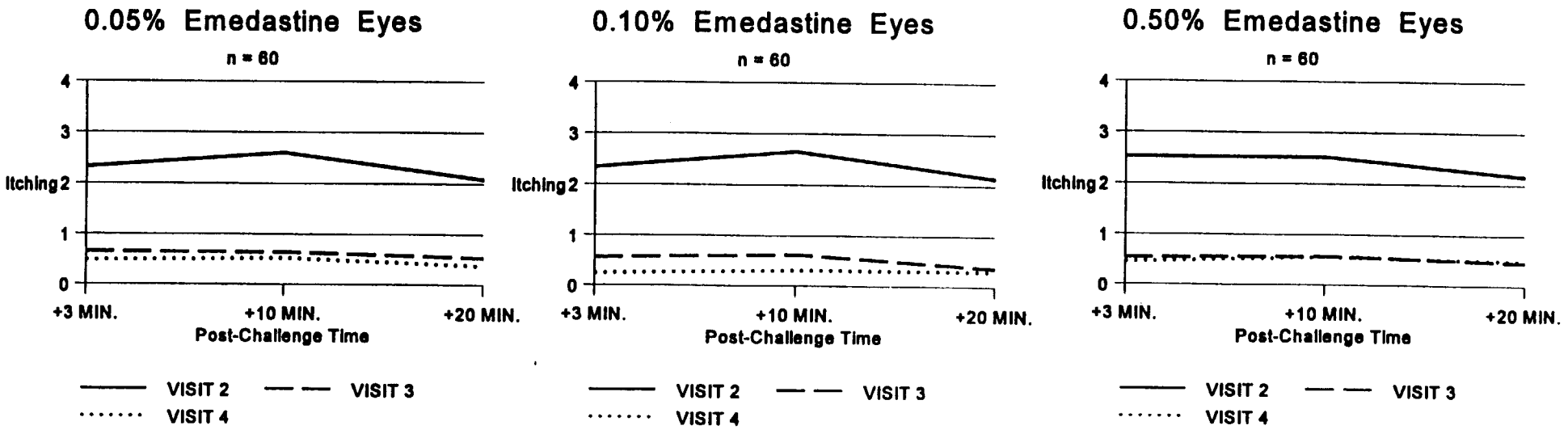
Mean Ocular Redness Scores for C9319







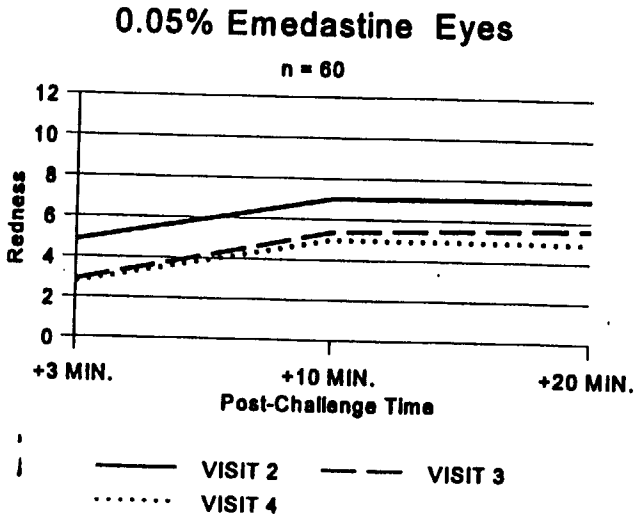
Mean Ocular Itching Scores for C9319

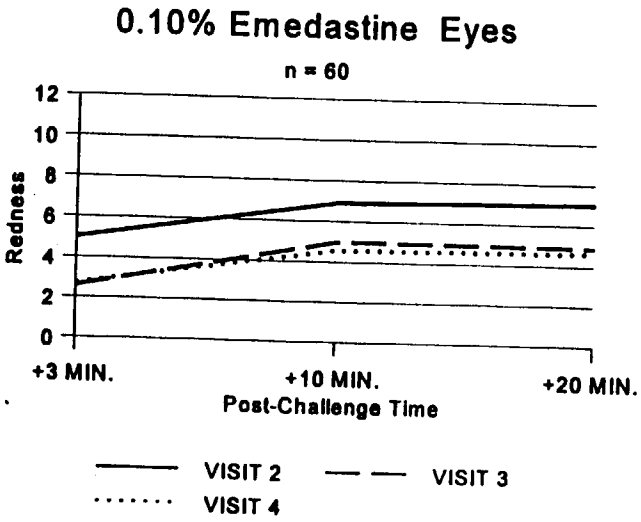


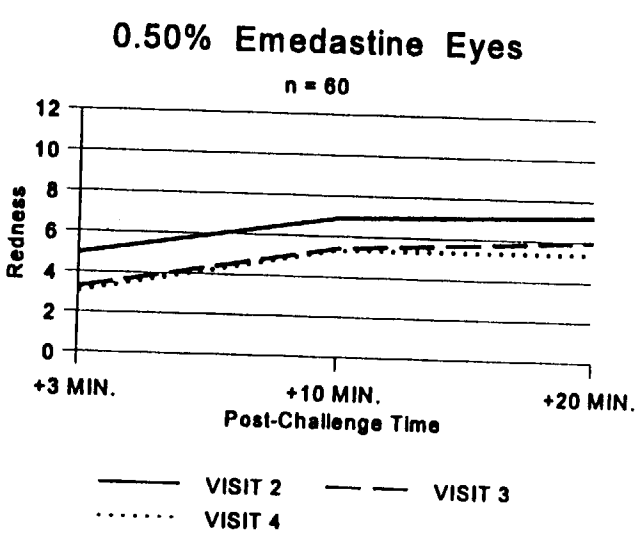
NDA 20-706 Emedastine Contralateral Treated Eyes

Attachment # 7 B

Mean Ocular Redness Scores for C9319







Contralateral Eye Comparison between 3 Concentrations of Emedastine and Vehicle (Placebo)
Mean Scores for Ocular Itching and Redness (Ciliary, Episcleral, and Conjunctival)

[Reviewer's Results]

C9319	0.05% Emedastine vs. Vehicle (Placebo)			0.10% Emedastine vs. Vehicle (Placebo)			0.50% Emedastine vs. Vehicle (Placebo)		
	0.05% EM Mean	PBO Mean	p-value	0.10% EM Mean	PBO Mean	p-value	0.50% EM Mean	PBO Mean	p-value
ITCHING	n = 60	n = 60		n = 60	n = 60		n = 60	n = 60	
Visit 2 + 3 minutes	2.32	2.42		2.33	2.38		2.52	2.55	
Visit 2 + 10 minutes	2.60	2.63		2.65	2.69		2.52	2.53	
Visit 2 + 20 minutes	2.08	2.19		2.14	2.14		2.16	2.12	
Visit 3 + 3 minutes	0.65	2.06	0.000 **	0.55	1.98	0.000 **	0.53	2.06	0.000 **
Visit 3 + 10 minutes	0.64	2.10	0.000 **	0.62	1.99	0.000 **	0.57	1.97	0.000 **
Visit 3 + 20 minutes	0.53	1.61	0.000 **	0.36	1.23	0.000 **	0.46	1.36	0.000 **
Visit 4 + 3 minutes	0.48	1.77	0.000 **	0.24	1.65	0.000 **	0.45	1.36	0.000 **
Visit 4 + 10 minutes	0.52	1.97	0.000 **	0.31	1.69	0.000 **	0.55	1.66	0.000 **
Visit 4 + 20 minutes	0.37	1.29	0.000 **	0.30	1.16	0.000 **	0.49	1.18	0.0001 **
REDNESS	n = 60	n = 60		n = 60	n = 60		n = 60	n = 60	
Visit 2 + 3 minutes	4.83	4.83		4.99	5.24		4.94	5.23	
Visit 2 + 10 minutes	6.99	7.10		6.90	6.88		6.89	7.20	
Visit 2 + 20 minutes	7.06	7.01		7.02	7.11		7.18	7.26	
Visit 3 + 3 minutes	2.87	4.03	0.0046 **	2.59	4.24	0.000 **	3.26	4.30	0.0165 **
Visit 3 + 10 minutes	5.35	6.28	0.0456 **	4.98	6.27	0.0025 **	5.40	6.34	0.0497 **
Visit 3 + 20 minutes	5.61	6.55	0.0481 **	4.90	6.32	0.0015 **	5.96	6.10	0.7754
Visit 4 + 3 minutes	2.75	3.77	0.0115 **	2.72	3.94	0.0029 **	3.05	4.24	0.0108 **
Visit 4 + 10 minutes	4.98	6.00	0.0316 **	4.56	6.01	0.0026 **	5.30	6.07	0.1411
Visit 4 + 20 minutes	4.92	5.90	0.0646	4.63	5.86	0.0089 **	5.37	6.13	0.1591

Contralateral Eye Comparison between 2 Concentrations of Emedastine and Vehicle (Placebo)
Mean Scores for Itching and Redness (Ciliary, Episcleral, and Conjunctival)

[Reviewer's Results]

C9490	0.005% Emedastine vs. Vehicle (Placebo)			0.05% Emedastine vs. Vehicle (Placebo)		
	0.005% EM Mean	Placebo Mean	p-value	0.05% EM Mean	Placebo Mean	p-value
ITCHING	n = 60	n = 60		n = 60	n = 60	
Visit 2 + 3 minute	2.58	2.53		2.52	2.58	
Visit 2 + 10 minutes	2.94	2.92		2.86	2.95	
Visit 2 + 20 minutes	2.68	2.72		2.63	2.67	
Visit 3 + 3 minute	1.11	2.31	0.000 **	0.83	2.30	0.000 **
Visit 3 + 10 minutes	0.97	2.63	0.000 **	0.95	2.41	0.000 **
Visit 3 + 20 minutes	0.66	2.04	0.000 **	0.83	1.98	0.000 **
Visit 4 + 3 minutes	1.17	2.11	0.000 **	0.78	2.32	0.000 **
Visit 4 + 10 minutes	1.12	2.28	0.000 **	0.85	2.40	0.000 **
Visit 4 + 20 minutes	0.92	1.90	0.000 **	0.73	1.88	0.000 **
REDNESS	n = 60	n = 60		n = 60	n = 60	
Visit 2 + 3 minute	4.45	4.40		3.97	4.14	
Visit 2 + 10 minutes	6.24	1.56		6.25	6.33	
Visit 2 + 20 minutes	6.43	6.42		6.35	6.21	
Visit 3 + 3 minute	3.28	4.44	0.0070 **	2.95	4.63	0.000 **
Visit 3 + 10 minutes	5.28	6.47	0.0043 **	5.14	6.38	0.0024 **
Visit 3 + 20 minutes	5.53	6.42	0.0382 **	5.29	6.01	0.1137
Visit 4 + 3 minutes	3.88	4.73	0.0774	3.13	5.19	0.000 **
Visit 4 + 10 minutes	6.58	6.89	0.4259	5.75	6.83	0.0036 **
Visit 4 + 20 minutes	6.85	6.88	0.9341	5.86	6.64	0.0441 **

Contralateral Eye Comparison between 0.005% and 0.05% Emedastine

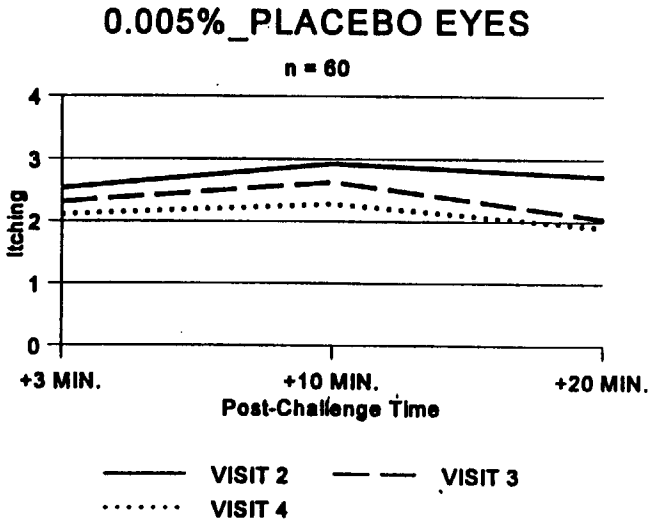
Mean Difference in Vehicle and Treated Scores

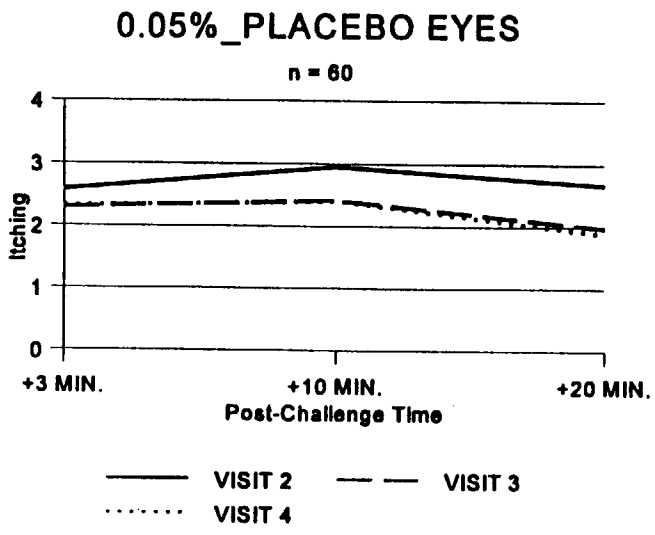
Itching and Redness (Ciliary, Episcleral, and Conjunctival)

[Reviewer's Results]

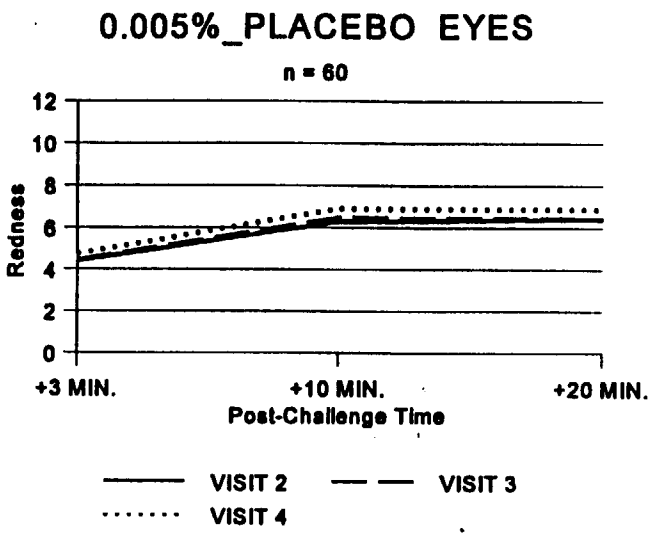
C9490	0.005% Emedastine versus 0.05% Emedastine		
	n = 60		
	0.005% Emedastine Mean Difference	0.05% Emedastine Mean Difference	p-value
ITCHING			
Visit 3 + 3 minute	1.20	1.47	0.1651
Visit 3 + 10 minutes	1.66	1.46	0.3156
Visit 3 + 20 minutes	1.38	1.15	0.2063
Visit 4 + 3 minutes	0.94	1.53	0.0056 **
Visit 4 + 10 minutes	1.67	1.55	0.0812
Visit 4 + 20 minutes	0.98	1.15	0.3772
REDNESS			
Visit 3 + 3 minute	1.67	1.68	0.1022
Visit 3 + 10 minutes	1.19	1.24	0.8956
Visit 3 + 20 minutes	0.88	0.72	0.6556
Visit 4 + 3 minutes	0.85	2.06	0.0005 **
Visit 4 + 10 minutes	0.31	1.08	0.0183 **
Visit 4 + 20 minutes	0.03	0.78	0.0161 **

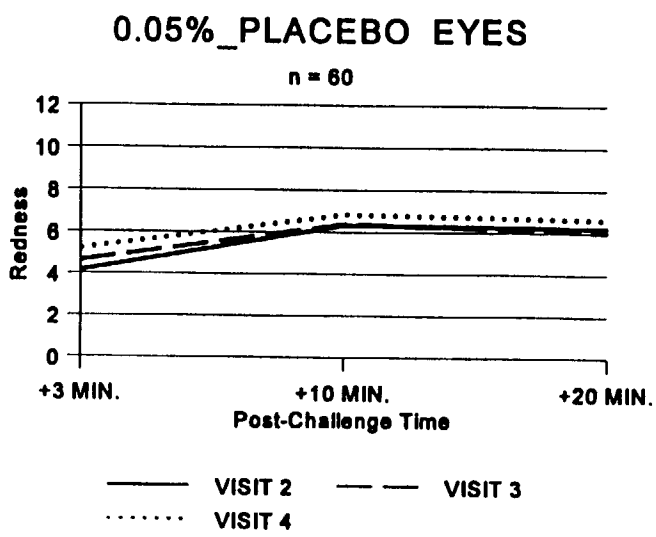
Mean Ocular Itching Scores for C9490



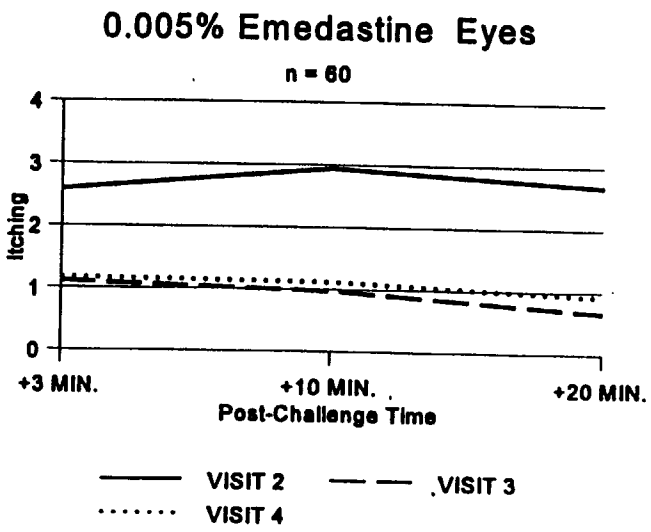


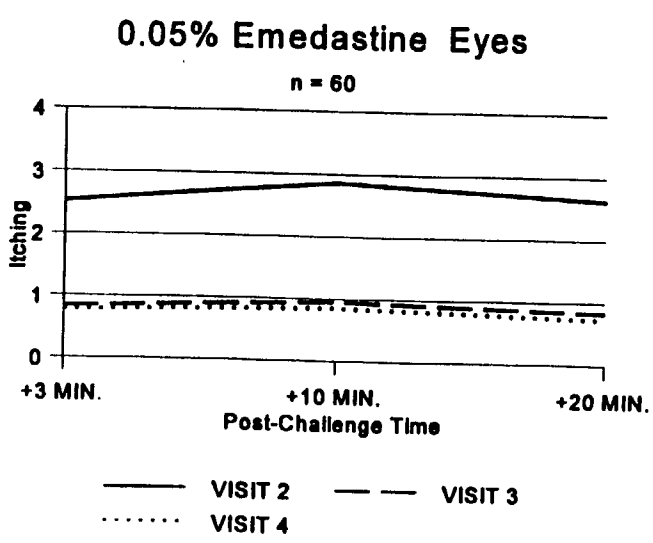
Mean Ocular Redness Scores for C9490



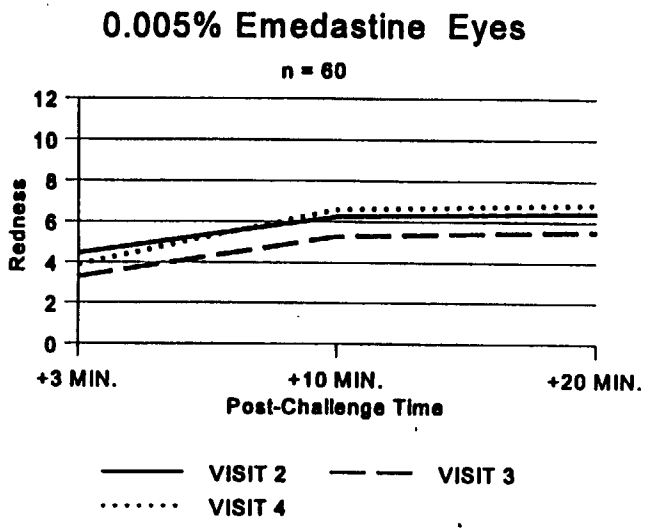


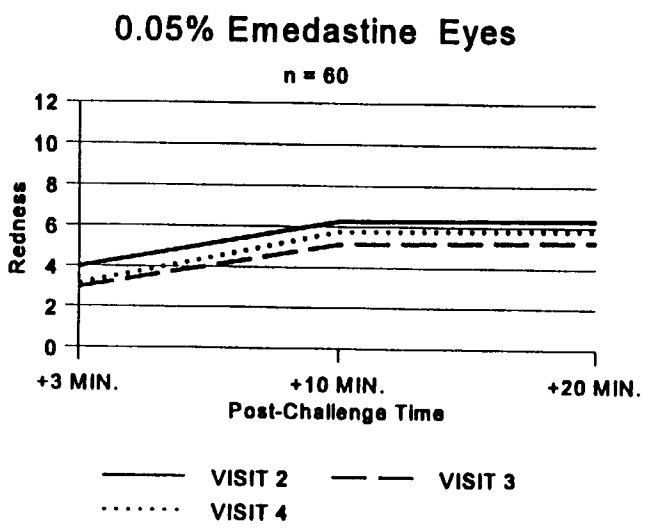
Mean Ocular Itching Scores for C9490





Mean Ocular Redness Scores for C9490



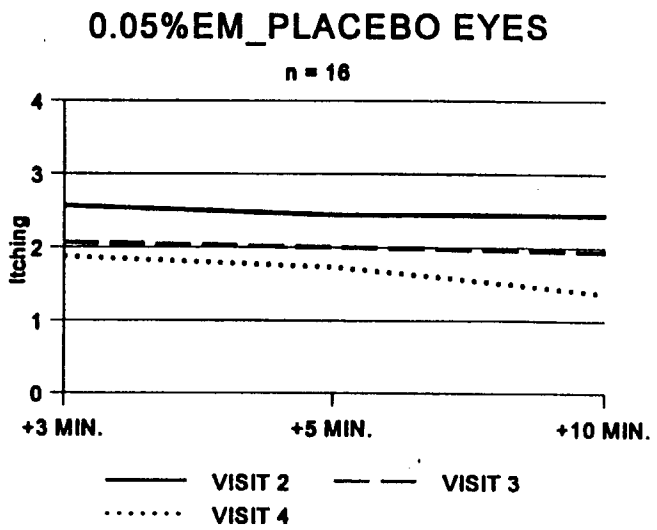


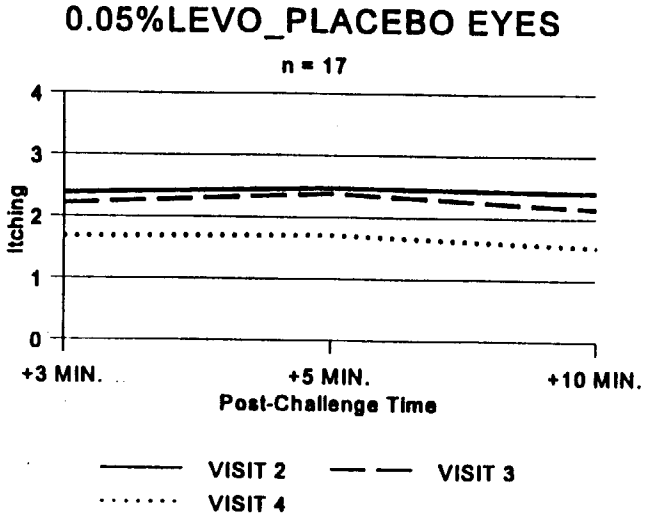
Contalateral Eye Comparison between Emedastine and Levocabastine with Placebo Masking Control Mean Scores for Ocular Itching and Redness (Ciliary, Episcleral, and Conjunctival)

[Reviewer's Results of Intent-to-treat Subjects]

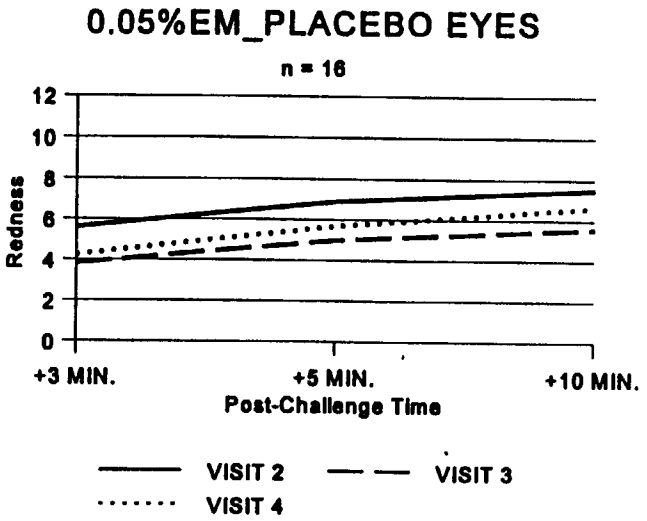
C9571	Emedastine vs. Levocabastine			Emedastine vs. Vehicle (Placebo)			Levocabastine vs. Vehicle (Placebo)		
	EM Mean	LEV Mean	p-value	EM Mean	PBO Mean	p-value	LEV Mean	PBO Mean	p-value
ITCHING	n = 64	n = 64		n = 16	n = 16		n = 17	n = 17	
Visit 2 + 1 minute	2.36	2.32		2.53	2.56		2.32	2.38	
Visit 2 + 5 minutes	2.62	2.53		2.44	2.44		2.32	2.47	
Visit 2 + 10 minutes	2.48	2.46		2.38	2.44		2.24	2.41	
Visit 3 + 1 minute	0.86	1.18	0.0617	0.81	2.06	0.0009 **	1.21	2.21	0.0112 **
Visit 3 + 5 minutes	0.88	1.32	0.0103 **	0.81	2.00	0.0012 **	1.15	2.38	0.0007 **
Visit 3 + 10 minutes	0.91	1.14	0.1606	0.66	1.94	0.0002 **	0.76	2.15	0.0003 **
Visit 4 + 3 minutes	0.54	0.82	0.0437 **	0.20	1.87	0.0000 **	0.79	1.68	0.0044 **
Visit 4 + 5 minutes	0.61	0.86	0.0736	0.10	1.73	0.0000 **	0.56	1.71	0.0009 **
Visit 4 + 10 minutes	0.66	0.89	0.1246	0.20	1.37	0.0002 **	0.71	1.53	0.0209 **
REDNESS	n = 64	n = 64		n = 16	n = 16		n = 17	n = 17	
Visit 2 + 1 minute	5.02	5.05		5.25	5.59		4.76	4.59	
Visit 2 + 5 minutes	6.63	6.73		7.09	6.88		6.56	6.59	
Visit 2 + 10 minutes	7.43	7.41		7.84	7.50		7.29	7.26	
Visit 3 + 1 minute	2.68	2.82	0.6824	2.47	3.81	0.0715	3.21	4.38	0.2044
Visit 3 + 5 minutes	3.48	4.05	0.1198	3.34	4.97	0.0576	4.09	5.88	0.0409 **
Visit 3 + 10 minutes	4.47	4.84	0.3378	4.22	5.56	0.1134	4.94	6.97	0.0187 **
Visit 4 + 3 minutes	2.93	3.17	0.4838	3.50	4.23	0.3441	2.76	4.35	0.0862
Visit 4 + 5 minutes	4.07	4.22	0.7051	4.30	5.67	0.0925	3.53	5.74	0.0137 **
Visit 4 + 10 minutes	5.14	5.35	0.6105	5.67	6.63	0.2088	4.68	6.68	0.0261 **

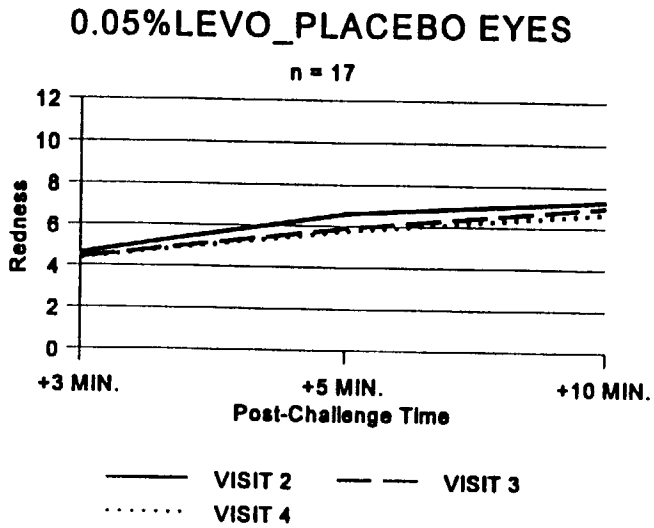
Mean Ocular Itching Scores for C9571



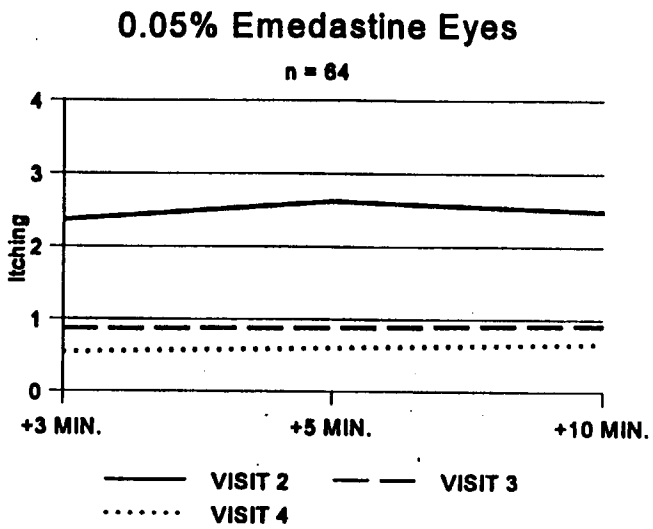


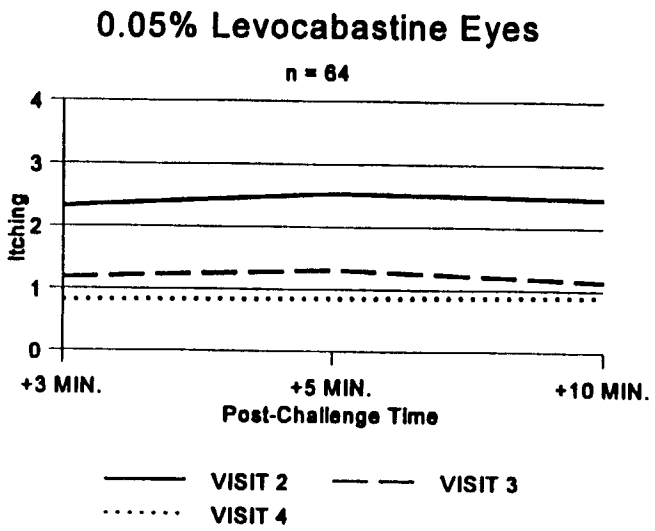
Mean Ocular Redness Scores for C9571



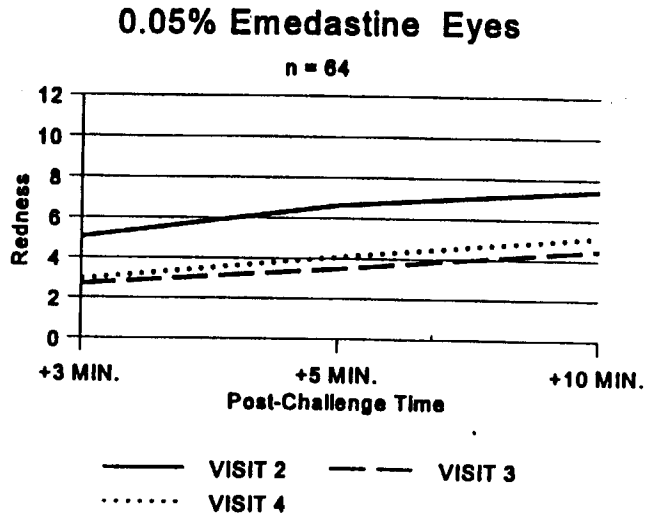


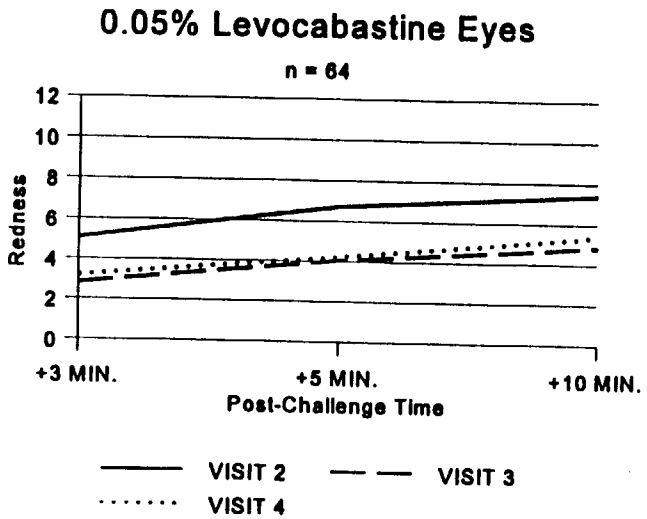
Mean Ocular Itching Scores for C9571





Mean Ocular Redness Scores for C9571





NDA 20-706 Emedastine vs.Levocabastine Attachment # 16

Contralateral Study C9571

95% Confidence Intervals
Mean Differences [Levocabastine - Emedastine] in Ocular Itching and Redness Scores

[Reviewer's Results of Intent-to-treat Dataset]

C9571	EM Mean	LEV Mean	n_{trt} [lower P_{trt} , upper P_{trt}] mean difference $_{trt}$
ITCHING			
Visit 3 + 1 minutes	0.86	1.18	64 [-0.18, 0.25] 0.04
Visit 3 + 5 minutes	0.88	1.32	64 [-0.19, 0.27] 0.04
Visit 3 + 10 minutes	0.91	1.14	64 [-0.18, 0.24] 0.03
Visit 4 + 3 minutes	0.54	0.82	64 [-0.19, 0.19] 0.00
Visit 4 + 5 minutes	0.61	0.86	64 [-0.28, 0.11] -0.08
Visit 4 + 10 minutes	0.66	0.89	64 [-0.40, 0.02] -0.19
REDNESS			
Visit 3 + 1 minute	2.68	2.82	64 [-0.17, 0.32] 0.08
Visit 3 + 5 minutes	3.48	4.05	64 [-0.33, 0.44] 0.05
Visit 3 + 10 minutes	4.47	4.84	64 [-0.48, 0.36] -0.06
Visit 4 + 3 minutes	2.93	3.17	64 [0.007, 0.51] 0.26
Visit 4 + 5 minutes	4.07	4.22	64 [-0.14, 0.59] 0.23
Visit 4 + 10 minutes	5.14	5.35	64 [-0.41, 0.27] -0.07