CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-861s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

SECONDARY STATISTICAL REVIEW

NDA/Serial Number:	21-861/000
Drug Name:	Olopatadine Hydrochloride (Patanase) Nasal Spray 0.6%
Indication(s):	Proposed for seasonal allergic rhinitis in patients 12 years of age and older
Applicant:	Alcon Inc.
Date(s):	Submitted: September 26, 2007
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
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Project Manager:	Miranda Raggio

Introduction

Olopatadine hydrochloride nasal spray (olopatadine HCl), a selective H1 antihistamine, was first submitted to the agency in December, 2004 for the indications of treating seasonal (b) (4) allergic rhinitis (SAR (b) (4) An approvable action was taken primarily due to unacceptable safety concerns in nasal septal perforation, nasal ulceration, and epistaxis observed in clinical studies. In responding to this concern, in this resubmission the sponsor reformulated the drug product by removing povidone, an excipient in the original formulation. In this resubmission, the sponsor only pursued SAR indication in patients 12 years of age and older with two sprays per nostril twice a day. (b) (4)

Prior to the resubmission, agreements were reached between the medical division and the sponsor that the efficacy of SAR in povidone-free formulation could be established in studies using povidone-containing formulation, if an environmental exposure chamber (EEC) study with povidone-free formulation shows similar treatment effect to EEC studies conducted with povidone-containing formulation. In addition, it was agreed that a one-year safety study with povidone-free formulation will be conducted and the 6-month interim data can be used for the safety assessment for the new formulation.

In the original submission, two efficacy trials (C0210 and C0237), one 1-year safety study (C0192), and two EEU studies (C0183 and C0352), were included. The primary statistical review for the original submission, conducted by Dr. Ted Guo, evaluated the efficacy information in Studies C0210 and C0237. The primary statistical review was concurringly reviewed by Dr. Sue-Jane Wang.

Since the original submission, five studies had been conducted and were submitted in this resubmission. Among the 5 studies, Study C0569 -- a 1-year safety study in PAR patients and Study C0564 -- an EEC study in SAR patients were conducted with povidone-free formulation. Study C0470 -- a phase 3 efficacy study in SAR patients, Study C0349 – a taste comparing study, and Study C0445 – a safety and pharmacokinetic study in healthy subjects were conducted with povidone-containing formulation. The primary statistical review was again assigned to Dr. Ted Guo, who provided detailed evaluation for Studies C0569 and C0564, and partially evaluated Study C0470. In addition, Dr. Guo provided analyses of certain secondary endpoints in Studies C0210 and C0237, submitted in the original submission, in this review cycle for labeling purposes.

SAR indication

The efficacy claim for SAR in the label was supported by two phase III studies, Studies C0210 and C0237, conducted with povidone-containing formulation and submitted in the original submission. Study C0470, submitted in this resubmission, was also a phase III randomized, double-blind, placebo vehicle and active- controlled study conducted with povidone-containing formulation. Agreement was made in the review team that there was no need to review the efficacy information of this study. Therefore the efficacy information of this study was not covered in the primary statistical review of this cycle.

Studies C0210 and C0237 were randomized, double-blind, placebo vehicle controlled, parallel group, and multi-center studies. Patients 12 years of age and older with SAR were randomized to olopatadine HCI 0.6%, 0.4%, or placebo and received 2 weeks of treatment. The nasal symptoms, including runny nose, itchy nose, stuffy nose, and sneezing, were assessed twice daily in the morning (AM) and evening (PM) reflectively and instantaneously. The individual symptom was rated on a scale of 0-3, with 0 as no symptom and 3 as the worse symptom. The average of the AM and PM total nasal symptom score (AM/PM TNSS) was used for the efficacy assessment. The primary endpoint was defined as the average percent change from baseline in the AM/PM TNSS over the 2-week treatment period. There were three key secondary efficacy endpoints:

- The percent change from baseline in the average of AM and PM instantaneous TNSS;
- Changes from baseline in the AM and PM individual symptoms of runny nose, stuffy nose, itchy nose, sneezing, itchy eyes, and watery eyes, as well as the total ocular symptom scores (TOSS) ;

(b) (4)

Study C0237 randomized 562 patients, of which 191 in vehicle, 188 in olopatadine HCI 0.4%, and 183 in olopatadine HCI 0.6%. Study C0210 randomized 671 patients, of which 223 in vehicle, 228 in olopatadine HCI 0.4%, and 220 in olopatadine HCI 0.6%. The results of the percent changes from baseline in reflective TNSS and reflective TOSS are displayed in Table 1. Both doses of olopatadine showed statistical significant better effect in reducing nasal symptom scores compare with vehicles in both studies. Both olopatadine dose groups also showed significant larger reduction in ocular symptoms compared with vehicle in both studies. Overall olopatadine 0.6% was numerically better than olopatadine 0.4%.

Table 1: Mean percent change from baseline in reflective TNSS and TOSS averaged over 14 days of treatment.

Treatment	N	Baseline	Change from baseline	Difference from placebo		
				Estimate	95% CI	p-value
Study C0237 (N=562) in reflective TNSS						
Vehicle	191	8.75	-27%			
olopatadine 0.6%	183	8.71	-38%	-11%	(-16.9%, -6.2%)	<0.001
olopatadine 0.4%	188	8.9	-35%	-8%	(-13.5%, -2.9%)	0.003
Study C0210 (N=671) in reflective TNSS						
Vehicle	223	9.07	-19%			
olopatadine 0.6%	220	9.17	-30%	-11%	(-15.5%, -6.7%)	<0.001
olopatadine 0.4%	228	9.26	-27%	-8%	(-12.7%, -3.9%)	<0.001

Study C0237 (N=562) in reflective TOSS				
Vehicle	191	-31.7%		
olopatadine 0.6%	183	-43.0%	-11.3%	(-20.1%, -2.5%)
olopatadine 0.4%	188	-37.7%	-6.0%	(-14.8%, 2.8%)
Study C0210 (N=671) in reflective TOSS				
Vehicle	223	-16.6%		
olopatadine 0.6%	220	-36.0%	-14.0%	(-22.7%, -5.4%)
olopatadine 0.4%	228	-33.2%	-11.3%	(-19.8%, -2.8%)

Sources: Dr. Ted Guo's primary statistical reviews.

(b) (4)

Safety study

Two long term safety studies, Study C0192 and Study C0569, were submitted in the original submission and this resubmission, respectively. Study C0192 was conducted with povidone-containing formulation. Therefore, the safety information of this study was no longer relevant. Study C0569 was conducted with povidone-free formulation and was an on-going study at the time of this resubmission to evaluate the safety of long term use of olopatadine over one year. The 6-month interim information in safety and efficacy was included in this submission. This study was a randomized, double-blind, vehicle-controlled, parallel group, and multicenter study conducted in PAR patients. Patients were randomized to olopatadine HCI 0.6% or vehicle to receive treatment 2-spray per nostril twice daily. The efficacy information was collected in this study primarily as the assay sensitivity in the evaluation of safety as a measure of study medication compliance.

The efficacy evaluation was based on patient-rated relief assessment at Day 30. This assessment was rated on a 4-point scale (1=complete relief, 2=moderate relief, 3=mild relief, 4=no relief). Among 890 randomized patients (445 patients in each treatment group), 861 patients (431 in olopatadine and 430 in vehicle) provided the patient-rated relief assessment. Based on Dr. Guo's analysis, the olopatadine HCI 0.6% group reported statistically significantly better symptom relief compared with placebo. The mean score were 2.5 and 2.7 in olopatadine HCI 6% and vehicle, respectively.

In safety evaluation, the primary statistical reviewer noted the differences of the reported occurrence of epistaxis in Studies C0569 and C0192. In Study C0569, there were 19.3% and 23.4% of epistaxis reported in olopatadine and vehicle, respectively, over 6-month treatment period. While in Study C0192, there were 19.2% and 12.0% of epistaxis reported in olopatadine and vehicle, respectively over one-year treatment period. The high occurrence of epistaxis in the vehicle group in Study C0569 was believed to be the result of more careful ascertainment at this adverse event because of the safety concern raised in povidone-containing formulation and

shown in Study C0192. As the rate of epistaxtis in olopatadine was comparable to the vehicle group in Study C0569, it was concluded that excess epistaxtis has not been identified in povidone-free formulation compared with vehicle.

Onset of action

The sponsor submitted three EEU studies, Studies C0183, C0352 and C0564. The first two studies were submitted in the original submission and conducted with povidone-containing formulation. The two studies were reviewed in the medical officer's review and no covered in the primary statistical review. Study C0564 was submitted in this resubmission and was conducted with povidone-free formulation. This primary statistical reviewer performed a detailed statistical evaluation for this study. In addition, the results of this study was cross compared with the two EEU studies conducted with povidone-containing formulation for the purposes of bridging the efficacy information obtained from povidone-containing formulation to povidone-free formulation.

The EEC studies were single dose, randomized, double-blind, placebo vehicle controlled, and parallel group studies conducted in SAR patients. The instantaneous nasal symptom scores were assessed in patients after the exposure to pollen, every 30 minutes post-dose for 3 hours and hourly up to 12 hours. Change from baseline in instantaneous TNSS was analyzed with t-tests at each time points of the assessment.

Studies C0564 and C0352 showed statistical significant treatment difference at 30 minutes post-dose and Study C0183 at 60 minutes post-dose. The statistical significant difference was maintained through the 12-hour treatment period. The onset of action of olopatadine HCI 6% was concluded at 30 minutes post-dose.

The treatment effect of olopatadine HCI 0.6% with povidone-free formulation in Study C0564 was considered comparable to the effect of olopatadine HCI 0.6% with povidone-containing formulation in Studies C0352 and C0183. Therefore, the efficacy information of the povidone-free formulation could be established from the studies with povidone-containing formulation.

Conclusion

Based on the information submitted in the original submission and this resubmission, olopatadine HCI 0.6% with povidone-free formulation had demonstrated statistically significant effect in symptom reduction compared with placebo in SAR patients 12 years of age and above. The greater symptom reductions in olopatadine HCI 6% in comparison to vehicle were observed in both nasal and ocular symptoms. The onset of action of olopatadine HCI 6% was shown to be 30 minutes post-dose. (b) (4)

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Qian Li
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation
Clinical Studies

NDA/Serial Number:	NDA 21861
Drug Name:	Patanase (olopatadine HCl nasal spray)
Indication(s):	The proposed indication is for the treatment of the symptoms of seasonal allergic rhinitis (SAR) (b) (4) in patients 12 years of age and older
Applicant:	Alcon
Date(s):	Applicant's submission date: 9/26/2007 Date last updated:
Review Priority:	Standard
Biometrics Division:	Biometrics Division 2
Statistical Reviewer:	Ted Guo, Ph.D., Biometrics Division 2
Concurring Reviewers:	Qian Li, Sc. D., Team Leader, Biometrics Division 2
Medical Division:	Division of Pulmonary and Allergy Products (ODE II, HFD-570)
Clinical Team:	James Kaiser, M.D., Medical Officer (ODE II, HFD-570)
Project Manager:	Miranda Raggio (ODE II, HFD-570)
Keywords:	NDA review, clinical studies

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Executive Summary

Introduction

Overview

Olopatadine (Patanase®) Nasal Spray is proposed to treat the symptoms of seasonal allergic rhinitis (SAR) (b) (4) in patients 12 years of age and older. Olopatadine is given to the patient two sprays per nostril bid.

Over time the sponsor has conducted clinical studies to assess the safety and effectiveness of olopatadine with formulations with and without povidone. In 2005, I performed a statistical evaluation of the effectiveness of olopatadine based on pivotal studies C0237 and C0210 in which olopatadine contained povidone. These studies demonstrated that olopatadine was statistically superior to placebo in treating SAR. Because of the safety concern, in particular, the toxic characteristics to the nasal mucosa membrane, this drug was not approved. Upon the recommendation from the Division, the sponsor developed a new formulation without povidone. Some studies of the new formulation were then submitted to the Agency. Studies C0569 and C0564 were two of them. This report includes the efficacy and safety evaluations of olopatadine in the povidone- free formulation.

The efficacy of olopatadine in treating patients with SAR has been established in the formulation with povidone in Studies C0237 and C0210 submitted in the original submission. My evaluations of Studies C0569 and C0564 in this re-submission shows that olopatadine in the povidone-free formulation is superior to placebo based on either patient-rated relief assessment (PRRA) or instantaneous TNSS in the Environment Exposure Chamber (EEC). Study C0564 also demonstrated a 30-minute onset-of-action and 12-hour duration-of-action. (b) (4)

Adverse reactions in Costart terms found in 2%+ of the patients evaluated for safety include: allergy, arthralgia, asthma, bronchitis, cold syndrome, conjunctivitis, cough inc, dermatitis, diarrhea, discomfort nasal, dysmenorrheal, dyspepsia, epistaxis, flu syndrome, gastroenteritis, GI discomfort, headache, hypertension, infect, infect urine tract, injury accident, insomnia, myalgia, nausea, otitis med, pain back, pharyngitis, rhinitis, sinusitis, surgical/medical proc, taste perverse, ulcer nasal, toothache, pain, extremity, pain, ear, depression, and dry nosed. Adverse reaction findings may vary while evaluated in MedDRA preferred terms or organ class terms.

Note that epistaxis occurred in 19.3% of the povidone-free-olopatadine-treated patients (n=86) in Study C0569, representing a similar percentage of the povidone-containing-olopatadine-treated patients (19.2%, n=88) with epistaxis in Study C0192 submitted in the original submission. The percentage of patients on placebo with epistaxis increased from 12% in Study C0192 to 23.4% in Study C0569. Furthermore, the percentage of patients with epistaxis on placebo was greater than the percentage of patients with epistaxis on the povidone-free olopatadine treatment. The new formulation of the povidone-free olopatadine hydrochloride nasal spray did not appear to decrease the occurrence rate of epistaxis.

Scope of Statistical Review

Study C0569, entitled Safety Study of Olopatadine Nasal Spray 0.6%, is an ongoing study and was submitted for regulatory evaluation as an interim report. I evaluated the **safety** based on AEs. I also evaluated the **effectiveness** of the drug based on patient-reported outcome (the only efficacy endpoint defined by the sponsor).

Study C0564, entitled Olopatadine Nasal Spray 0.6% vs. Vehicle in Treating Seasonal Allergic Rhinitis Patients in an EEC, was conducted in 2006. I evaluated the **effectiveness** of the drug based on instantaneous TNSS.

Studies C0183 and C0352 were EEC studies of olopatadine (with povidone) were submitted in the previous submission and reviewed by the medical reviewer. In consultation with the medical reviewer, the results of these studies are mentioned in this review, but they are not worthy for a re-evaluation.

(b) (4)

Study C0470, submitted under category of Other Study Reports, was a Phase-3 randomized, multi-center, double-blind, double-dummy, active control, parallel group safety and efficacy study of olopatadine which contained povidone. In consultation with the medical reviewer, I did not perform an in-depth evaluation of this study. (b) (4)

Data Sources

The sponsor submitted its study reports in paper and its data in electronic format on CDs. All the data were submitted either as SAS data sets or as SAS v.5 transport files, which were converted to SAS data sets for statistical evaluations.

Statistical Evaluation

Study C0569

Evaluation of Efficacy

Study Designs and Endpoints

Study C0569, a safety study of olopatadine, is an ongoing study and was submitted for regulatory evaluation as an interim report. The study is a Phase-3 randomized, double-blind, **multi-center**, parallel-grouped clinical study. This is a one-year safety study with an efficacy component. In this report, the last enrolled patient has been on treatment for 6 months.

The objective of the study is to "describe and compare the safety and efficacy of Olopatadine HCl Nasal Spray 0.6% versus Vehicle when given as **2 sprays** per nostril **twice daily** (BID) for up to 12 months in patients with perennial allergic rhinitis (PAR)."

Though this is primarily a safety study, the primary **statistical** objective is to demonstrate the superiority of olopatadine to vehicle based on a patient-reported outcome. The efficacy evaluation is based on the primary efficacy variable: the mean response to the patient-rated relief assessment at Day 30 (Visit 2). Such an assessment is rated on a 4-point scale (1=complete relief, 2=moderate relief, 3=mild relief, and 4=no relief). In addition to the above primary efficacy variable, secondary efficacy variables included (1) the mean response from Visit 2 to the end of the study, and (2) the average number of days when rescue medications are used.

Per the suggestion from the medical reviewer, Dr. James Kaiser, for Study C0569, this report is focused on both the safety and the efficacy evaluations.

Analysis Patient Populations

Patient Distributions of Demographic and Baseline Characteristics

All randomized patients (890) were included in the safety evaluation. These patients were also intent-to-treat (ITT) patients. According to the sponsor's study report, there were a small number of patients (30 in olopatadine and 27 in vehicle placebo, 57 in total) who had protocol violations. The per-protocol (PP) patient population consisted of the ITT patients excluding these 57 patients.

Table 1 Patient disposition (Study C0569)

	Olopatadine0.6%		Vehicle	
	N	%	N	%
-- Remaining in study --	353	79.3	362	81.3
-- Discontinued --				
Adverse Event	22	4.9	16	3.6
Lost to Follow-Up	16	3.6	15	3.4
Decision Unrelated to an Adverse Event	19	4.3	21	4.7
Treatment Failure	20	4.5	16	3.6
Protocol Violation	7	1.6	6	1.3
Other	8	1.8	9	2.0
Total	445	100.0	445	100.0

Source: C0569_saf

Since this is an ongoing study, the number of future dropouts is unknown. The available data show that there were about 80% of the patients remaining in the study at interim analysis.

Table 2 Patient distributions by sex, race, and age group (Study C0569)

	Olopatadine0.6%		Vehicle	
	N	%	N	%
Caucasian	359	80.7	361	81.1
Black	43	9.7	39	8.8
Asian	4	0.9	6	1.3
Hispanic	32	7.2	37	8.3
Other	7	1.6	2	0.4
Male	163	36.6	149	33.5
Female	282	63.4	296	66.5
65+	11	2.5	9	2.0
<65	434	97.5	436	98.0
Total	445	100.0	445	100.0

Source: C0569_saf

Among the randomized patients, more than 80% were white, more than 60% were female, and about 98% were under age 65. The patients were equally distributed between olopatadine and vehicle placebo.

Statistical Methodology

Two-sample t-tests were applied to the comparison between the olopatadine and vehicle placebo groups for the primary efficacy variable: the mean response at Day 30 to the patient-rated relief assessment (PRRA) which was rated on a 4-point scale (1=complete relief, 2=moderate relief, 3=mild relief and 4=no relief). This study included an efficacy component to evaluate the assay sensitivity. The efficacy analysis was conducted to ensure that the patients received study drug while they were evaluated for the safety.

Note that the sponsor did not use TNSS as the outcome variable as is commonly used for seasonal rhinitis. PRRA may provide some evidence for efficacy and is seen to be used as secondary efficacy variable. Although the use PRRA cannot be legitimately rejected, it is not the best choice for the efficacy endpoint.

Missing data handling

LOCF was used for the missing PRRA. That is, for a missing visit, the last non-missing visit data were used to fill in the missing data. Note that the efficacy assessment was based on the 30-day **v**isit (Visit 2), all available data for Visit 2 were included in the analysis. There were a total of 861 patients with available PRRA data for the efficacy evaluation. Note that the 30-day visit was the first post-randomization visit; LOCF did not apply here, however applied to the subsequent visits.

Efficacy Results

Analyses of the primary efficacy variable

Table 3 Descriptive statistics of PRRA (Study C0569)

	N	MIN	MAX	MEAN	STD
Olopatadine	431	1.0	4.0	2.5	0.9
Vehicle	430	1.0	4.0	2.7	0.9

Source: C0569_ITT

Table 4 Two-sample t-test (Study C0569)

Method	Variances	t-statistic	P-value
Pooled	Equal*	-3.27	0.0011

Source: C0569_ITT
*: The variances of the two groups were tested to be equal.

The above analysis demonstrates that olopatadine 0.6% was superior to vehicle placebo in the treatment of patients with PAR (P=0.001). This result validated that the patients received their assigned medication and demonstrated the significant effect of olopatadine.

Analyses of secondary efficacy variables

Not available.

Evaluation of Safety

This report includes the evaluation of the safety of Patanase for Study C0569 alone. The purpose of the safety evaluation was to facilitate the medical reviewer for regulatory decisions. Because of the different standards over time for AEs, this report use MedDRA's preferred and organ class terms, in addition to the older Costart terms. No inferential statistical analyses were performed. I made comments from the perspective of a statistician.

I analyzed the AEs occurring in patients in the safety population. To compile a concise report, in this section, I only list the AEs occurred in 2% of the patients or more. A complete list of AEs can be found in the Appendix.

Table 5 provides the numbers and percentages of AEs using MedDRA preferred terms. Table 6 shows the numbers and percentages of AEs using MedDRA system organ class terms.

Table 5 AEs based on MedDRA preferred terms (Study C0569)

AEs presented as: AEPTTXT; Group totals: 445, 445 in Olopatadine, Vehicle	Treatment			
	Olopatadine		Vehicle	
	N	%	N	%
NO AE	112	25.17	99	22.25
Epistaxis	86	19.33	104	23.37
Rhinitis	65	14.61	55	12.36
Upper respiratory tract infection	55	12.36	55	12.36
Nasopharyngitis	52	11.69	51	11.46
Sinusitis	43	9.66	45	10.11
Headache	42	9.44	45	10.11
Rhinitis allergic	35	7.87	45	10.11
Nasal ulcer	39	8.76	26	5.84
Injury	19	4.27	32	7.19
Seasonal allergy	19	4.27	20	4.49
Pharyngolaryngeal pain			19	4.27
Asthma	18	4.04		
Dysgeusia	29	6.52		
Influenza			19	4.27

Source: C0569_AE (in 2%+)

Table 6 AEs based on MedDRA system organ class terms (Study C0569)

AEs presented as: AESOCTXT; Group totals: 445, 445 in Olopatadine, Vehicle	Treatment			
	Olopatadine		Vehicle	
	N	%	N	%
NO AE	112	25.17	99	22.25
Infections and infestations	218	48.99	214	48.09
Respiratory, thoracic and mediastinal disorders	176	39.55	186	41.80
Nervous system disorders	91	20.45	71	15.96
Gastrointestinal disorders	51	11.46	48	10.79

AEs presented as: AESOCTXT; Group totals: 445, 445 in Olopatadine, Vehicle	Treatment			
	Olopatadine		Vehicle	
	N	%	N	%
Musculoskeletal and connective tissue disorders	43	9.66	46	10.34
Injury, poisoning and procedural complications	30	6.74	40	8.99
Skin and subcutaneous tissue disorders	26	5.84	28	6.29
Immune system disorders	25	5.62	25	5.62
Psychiatric disorders	18	4.04		
Eye disorders			18	4.04
Reproductive system and breast disorders			18	4.04

Source: C0569_AE (in 2%+)

AEs also can be reported in terms of Costart terms. Table 7 provides the numbers and percentages of patients with specified AEs using Costart terms. I only list the AEs occurred in 2% or more of the patients. A complete list of AEs can be found in Table 28 of the appendix.

Table 7 AEs based on Costart terms (Study C0569)

presented as: Costart**;** **Group totals: 445,445**	**Treatment**			
	Olopatadine		**Vehicle**	
	N	**%**	**N**	**%**
NO AE	112	25.17	99	22.25
Allergy	19	4.27	20	4.49
Arthralgia	10	2.25	17	3.82
Asthma	19	4.27	17	3.82
Bronchitis	15	3.37	10	2.25
Cold synd	52	11.69	52	11.69
Conjunctivitis	10	2.25		
Cough inc	16	3.60	14	3.15
Dermatitis			9	2.02
Diarrhea	11	2.47		
Discomfort nasal	12	2.70	13	2.92
Dysmenorrhea			11	2.47
Dyspepsia	9	2.02		
Epistaxis	86	19.33	104	23.37
Flu synd	13	2.92	19	4.27
Gastroenteritis	11	2.47	12	2.70
Gi dis	9	2.02		
Headache	55	12.36	59	13.26
Hypertens	13	2.92	15	3.37
Infect	67	15.06	65	14.61
Infect urin tract	9	2.02		
Injury accid	19	4.27	32	7.19
Insomnia			9	2.02
Myalgia	9	2.02	10	2.25
Nausea			9	2.02
Otitis med			9	2.02
Pain back	12	2.70	12	2.70
Pharyngitis	35	7.87	30	6.74
Rhinitis	104	23.37	103	23.15

presented as: Costart**; Group totals: 445,445**	**Treatment**			
	Olopatadine		**Vehicle**	
	N	**%**	**N**	**%**
Sinusitis	47	10.56	47	10.56
Surgical/medical proc	13	2.92	14	3.15
Taste pervers	29	6.52		
Ulcer nasal	39	8.76	26	5.84

Source: C0569_AE (in 2%+)

Table 8 includes the numbers and percentages of patients with specified AEs by sex. This table was created per the advice from the medical reviewer. I only list the AEs occurred in 2% or more of the patients. A complete list of AEs can be found in Table 29 in the appendix.

Table 8 AEs based on Costart terms by sex (Study C0569)

	Olopatadine				**Vehicle**			
	Female		**Male**		**Female**		**Male**	
	N=282	**%**	**N=163**	**%**	**N=296**	**%**	**N=149**	**%**
No AE	66	23.4	46	28.2	65	22.0	34	22.8
Allergy	17	6.0			14	4.7	6	4.0
Arthralgia	8	2.8			11	3.7	6	4.0
Asthma	15	5.3	4	2.5	10	3.4	7	4.7
Bronchitis	13	4.6			9	3.0		
Cold synd	35	12.4	17	10.4	35	11.8	17	11.4
Conjunctivitis	7	2.5						
Cough inc	13	4.6			8	2.7	6	4.0
Dermatitis					8	2.7		
Diarrhea	8	2.8					3	2.0
Discomfort nasal	6	2.1	6	3.7	12	4.1		
Dizziness					7	2.4		
Dry nose	6	2.1						
Dysmenorrhea					11	3.7		
Dyspepsia	7	2.5						
Epistaxis	52	18.4	34	20.9	63	21.3	41	27.5
Flu synd	8	2.8	5	3.1	15	5.1	4	2.7
Gastroenteritis	9	3.2			8	2.7	4	2.7
Gi dis	7	2.5			7	2.4		
Headache	43	15.2	12	7.4	41	13.9	18	12.1
Hypertens	6	2.1	7	4.3	11	3.7	4	2.7
Infect	44	15.6	23	14.1	43	14.5	22	14.8
Infect urin tract	8	2.8			6	2.0		
Injury accid	12	4.3	7	4.3	19	6.4	13	8.7
Insomnia					7	2.4		
Migraine					6	2.0		
Myalgia	6	2.1			9	3.0		
Nausea					8	2.7		
Otitis med							5	3.4
Pain back	9	3.2			9	3.0	3	2.0
Pain ear					7	2.4		
Pharyngitis	24	8.5	11	6.7	23	7.8	7	4.7

	Olopatadine				Vehicle			
	Female		Male		Female		Male	
	N=282	%	N=163	%	N=296	%	N=149	%
Rhinitis	62	22.0	42	25.8	61	20.6	42	28.2
Sinusitis	28	9.9	19	11.7	38	12.8	9	6.0
Surgical/medical proc	10	3.5			7	2.4	7	4.7
Taste pervers	21	7.4	8	4.9				
Tooth dis							3	2.0
Toothache	8	2.8			6	2.0		
Ulcer nasal	21	7.4	18	11.0	16	5.4	10	6.7

Source: C0569_AE (in 2%+)

More discussions can be found in the section, COMMENTS ON LABELING under section **Adverse Reactions**.

Findings in Special/Subgroup Populations

No analyses on special populations or subgroups were performed for this report.

Study C0564

Evaluation of Efficacy

Study Designs and Endpoints

Study C0564 was an efficacy study comparing olopatadine nasal spray 0.6% vs. vehicle in treating patients with SAR in an EEC (where the patients were exposed to short ragweed pollen). It was a Phase-3 randomized, double-blind, parallel-grouped, **single center** clinical study. Olopatadine nasal spray used in this study was povidone free. The treatment was administered **2 sprays** per nostril **once daily**. The study started on January 16, 2006 and ended on March 11, 2006. The study randomized 406 patients who were also in the ITT population. The ITT patient was defined by the sponsor as the patient who received randomized drug.

The objective of the study was to demonstrate the superiority of olopatadine to vehicle in patients with SAR receiving a treatment of 12 hours in an EEC.

The primary efficacy variable was the **change from baseline in instantaneous TNSS**, the sum of the nasal symptom scores: runny nose, itchy nose, congestion, and sneezing. Each individual nasal symptom was rated on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe). Two secondary efficacy variables were (1) the change from baseline in individual instantaneous nasal symptom score and (2) patient global rating scale. Two-sample t-tests were used to compare olopatadine and placebo in the change

from baseline in TNSS and individual nasal symptom scores. The baseline was referred to the Priming Visits: Visits 2a and 2b; and the post dose visit was Visit 3. After dosing, patients rated their instantaneous symptoms on diary cards every 30 minutes for 4 hours, then every hour for another 8 hours. Patients also completed the global assessment question at 4 hours and 12 hours pose dosing using a 5-point scale (0=very much better, 1=moderate better, 2=a little better, 3=unchanged, 4=a little worse, 5=moderately worse, 6=very much worse).

Per the suggestion from the medical reviewer, Dr. James Kaiser, for Study C0564, this report is focused on the efficacy evaluation alone.

Analysis Patient Populations

Distributions of Demographic and Baseline Characteristics

All randomized patients (406) were included in the intent-to-treat (ITT) population. There were a small number of patients (3) who had protocol violations. The per-protocol (PP) patient population consisted of the ITT patients without these 3 patients. There were no discontinued patients.

Table 9 Patient distributions by sex, race, and age group (Study C0564)

	Olopatadine0.6%		**Vehicle**	
	N	**%**	**N**	**%**
Caucasian	96	47.1	106	52.5
Asian	30	14.7	19	9.4
Black	49	24.0	50	24.8
Hispanic	11	5.4	9	4.5
Other	18	8.8	18	8.9
Female	97	47.5	102	**50.5**
Male	107	52.5	100	**49.5**
<65	197	96.6	198	**98.0**
65+	7	3.4	4	**2.0**
Total	**204**	**100.0**	**202**	**100.0**

Source: Analysis_itt

Among all the patients, more than 47% were white, about 50% were female, and more than 96% were under age 65. The patients were equally distributed between olopatadine and vehicle placebo.

Table 10 Baseline distribution of TNSS (Study C0564)

Treatment	**#Patients**	**Median TNSS**	**25th Percentile**	**75th Percentile**	**Mean**	**Std.**
Olopatadine	204	10.00	8.50	11.00	9.77	1.84
Vehicle	202	9.50	8.00	11.00	9.51	1.84

Source: Analysis_itt

The difference in mean or median TNSS between the two groups appears to be small.

Statistical Methodology

Two-sample t-tests were applied to the comparison between the olopatadine and vehicle placebo groups for the primary efficacy variable: the change from baseline to each time point of Visit 3 in instantaneous TNSS. The same analysis was done for individual symptom scores as well.

Missing data handling

The sponsor pre-specified that for the ITT data set, LOCF was used for missing data. In particular, data only from 4 hours post dose onward were carried forward to fill in the missing data. The data showed that there were no missing data before 4 hours post-dose. Note that in this ITT patient population, no patients were discontinued from the study.

Efficacy Results

Analyses of the primary efficacy variable

Table 11 Descriptive statistics of change in TNSS from baseline by time point (Study C0564)

Time in minutes	Treatment									
	vehicle					olopatadine				
	N	MIN	MAX	MEAN	STD	N	MIN	MAX	MEAN	STD
30	202	-8.5	2.5	-1.4	2.2	204	-10.0	2.5	-2.4	2.3
60	202	-7.5	4.0	-1.5	2.3	204	-11.0	2.5	-2.5	2.4
90	202	-7.5	4.5	-1.6	2.4	204	-11.0	3.5	-3.0	2.7
120	202	-8.5	4.0	-1.6	2.4	204	-10.0	3.5	-3.2	2.7
150	202	-10.5	3.5	-1.9	2.5	204	-11.0	3.5	-3.4	2.7
180	202	-10.0	3.0	-2.1	2.7	204	-12.0	3.5	-3.5	2.9
210	202	-10.0	3.5	-2.2	2.7	204	-12.0	3.0	-3.7	2.9
240	202	-10.0	4.0	-2.2	2.8	204	-12.0	3.5	-3.8	2.8
300	202	-9.0	4.5	-2.0	2.9	204	-12.0	3.5	-3.6	2.8
360	202	-9.0	5.5	-1.7	2.9	204	-11.0	2.5	-3.4	2.8
420	202	-9.0	4.5	-1.5	2.8	204	-11.0	2.5	-3.2	2.7
480	202	-9.0	4.5	-1.4	2.8	204	-10.0	3.5	-2.9	2.7
540	202	-10.0	4.5	-1.3	2.8	204	-11.5	3.5	-2.8	2.6
600	202	-8.5	4.5	-1.3	2.9	204	-11.5	4.0	-2.9	2.8
660	202	-9.5	4.5	-1.4	2.9	204	-11.5	4.0	-2.9	2.8
720	202	-8.5	4.0	-1.3	2.9	204	-10.5	4.0	-2.8	2.8

Source: Analysis_itt

Table 12 Two-sample t-test based on change in TNSS from baseline (Study C0564)

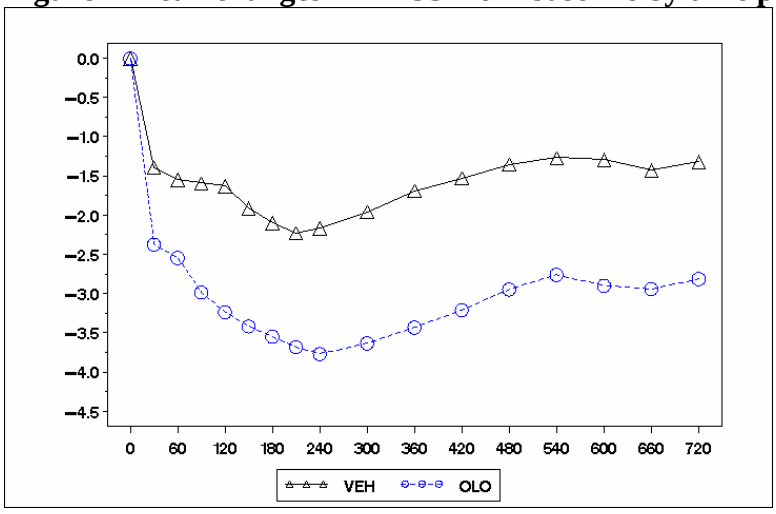
Time point	T-statistic	P-value
30	4.33	<.0001
60	4.26	<.0001
90	5.51	<.0001
120	6.31	<.0001
150	5.78	<.0001
180	5.28	<.0001
210	5.30	<.0001
240	5.72	<.0001
300	5.89	<.0001
360	6.22	<.0001
420	6.10	<.0001
480	5.82	<.0001
540	5.50	<.0001
600	5.72	<.0001
660	5.41	<.0001
720	5.26	<.0001

Source: Analysis_itt

The above analysis demonstrates that olopatadine 0.6% is superior to vehicle placebo in the treatment of patients with SAR, which have been consistently demonstrated from 30 to 720 minutes post dose. Furthermore, the positive findings support the claim the sponsor made that this drug had "an onset-of-action as early as 30 minutes and a minimum duration-of-action of 12 hours (page 65, study report, volume 20)".

Figure 1 shows the mean changes in TNSS from baseline. For all the time points considered, there is a clear separation between the treatment groups. Olopatadine had a greater reduction in TNSS than vehicle placebo across the time points. The first time point on the graph is 30 minutes post dose.

Figure 1 Mean changes in TNSS from baseline by time point (Study C064)

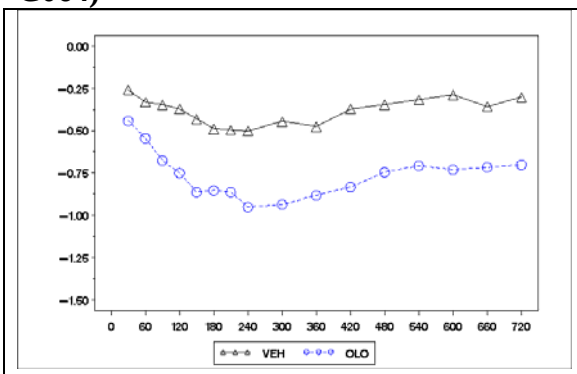


Source: Analysis_itt1

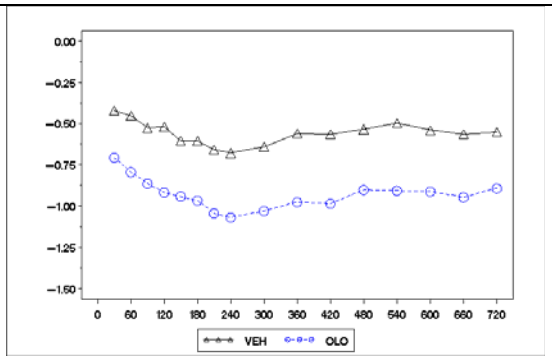
Analyses of secondary efficacy variables

The secondary efficacy variables are the changes from baseline in individual scores for the symptoms of: runny nose, itchy nose, sneezing and stuffy nose. From 30 minutes post dose onward, olopatadine was superior to placebo except that at 60 minutes, for **stuffy nose**, the difference between olopatadine and placebo was not statistically significant. I confirmed that the graphs drawn using the sponsor's data and those in the sponsor's study report were very similar. I also verified the statistical tests at all time points. My findings are in agreement with the sponsor's findings. The statistical tables from these analyses are omitted from this report.

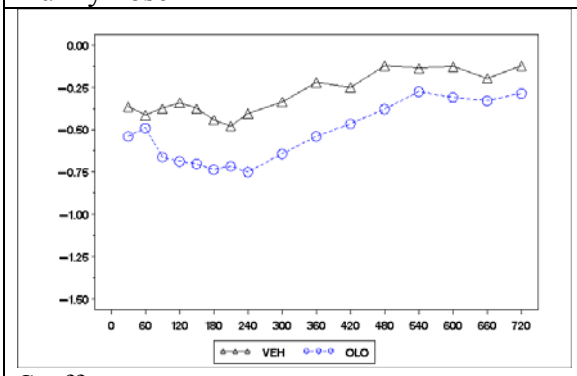
Figure 2 Change from baseline by treatment in individual symptom scores (Study C064)



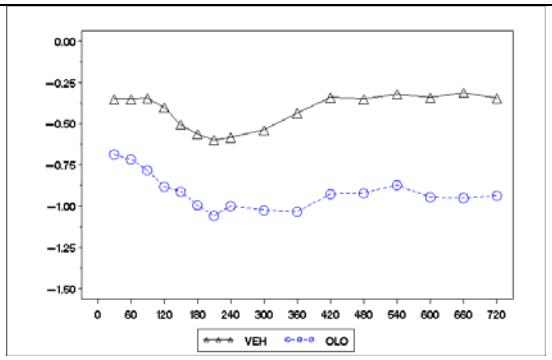
Runny nose



Itchy nose



Stuffy nose



Sneezing

The other secondary efficacy endpoint, patients' global ratings, was not evaluated for this report.

Evaluation of Safety

Evaluation of safety was not done for this study.

Study C0470

Evaluation of Efficacy

Study Designs and Endpoints

Study C0470 was an efficacy and safety study aimed to compare olopatadine nasal spray 0.6% to olopatadine vehicle and azelastine HCl nasal spray 0.1% in treating patients with SAR. It was a Phase-3 randomized, double-blind, parallel-grouped, vehicle- and active-controlled clinical study. Olopatadine used in this study contained povidone.

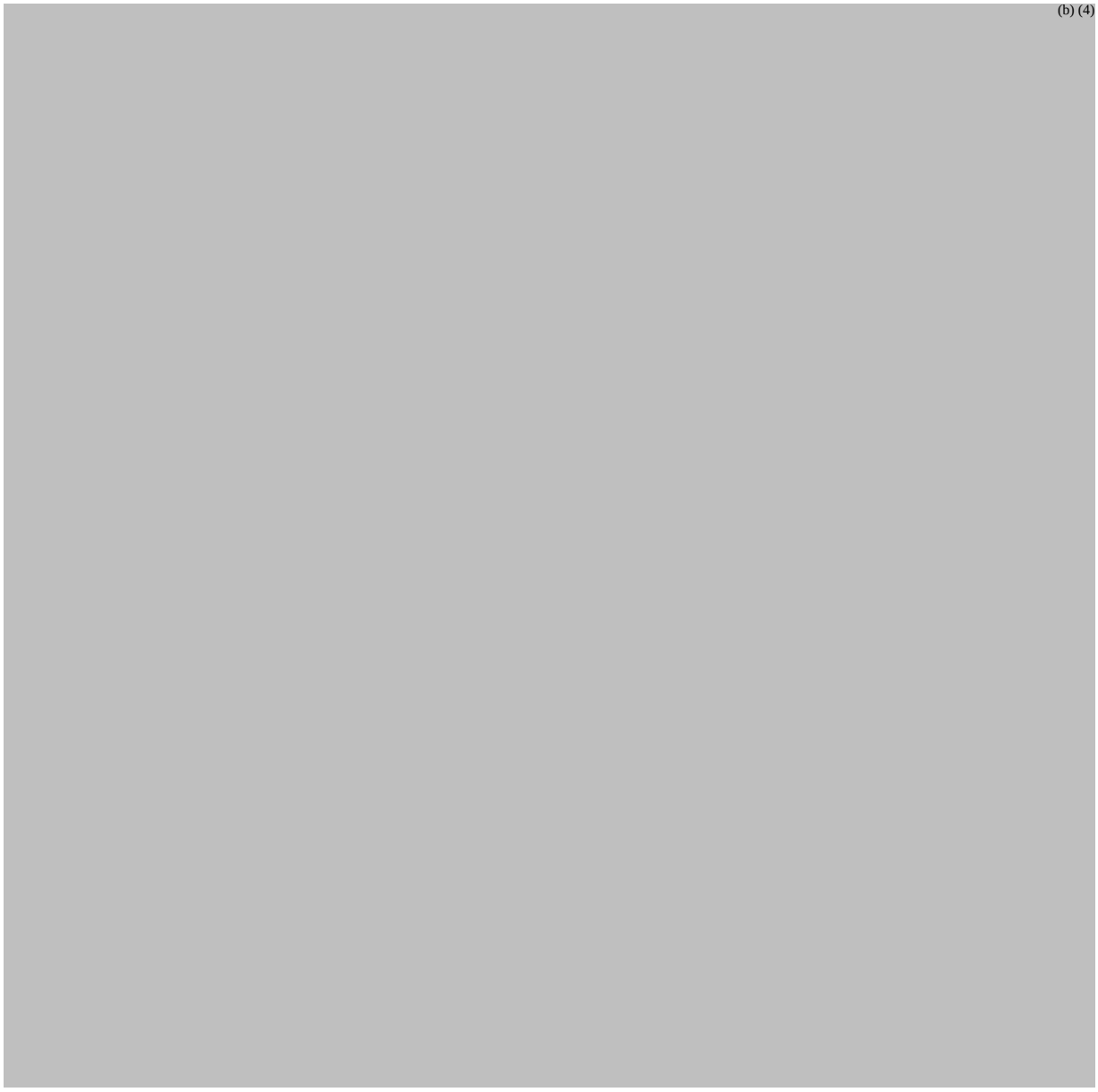
The patient was randomized to one of the three treatment arms: olopatadine 0.6%, azelastine 0.1%, or vehicle placebo. The treatment was administered 2 sprays per nostril bid for 16+7 days following a 14-day vehicle run-in period. The measurement for the change from baseline in this study means the change from baseline visit, Visit 2 (randomization) to Visit 4 (Day 16+7).

The primary efficacy variable was the percent change from baseline to Visit 4 in reflective TNSS defined as the average of the AM and PM reflective total of the nasal symptom scores including runny nose, itchy nose, sneezing and congestion.

The secondary efficacy variables included (1) the percent change from baseline in the AM (awakening) and PM (bedtime) individual reflective eye symptom scores including itchy and watery eyes, (b) (4)

Efficacy Results

(b) (4)



Findings in Special/Subgroup Populations

No analyses on special populations or subgroups were performed for this report.

Summary and Conclusions

Statistical issues and Collective Evidence

Efficacy evaluation

Onset of action
Study C0564 provided evidence for the superiority of olopatadine to vehicle placebo based on the change from baseline in TNSS. The onset-of-action of olopatadine was demonstrated as early as 30 minutes and the duration-of-action was demonstrated to have maintained for at least 12 hours.

Studies C0183 and C0352 were evaluated by the medical reviewer for onset-of-action. and not evaluated by the statistical reviewer. The medical reviewer concluded, "The results of the applicant's EEU studies support an onset of action claim. The data demonstrate, in replicate, an onset of action at 90 minutes post-dose for olopatadine 0.6%. A statistically significant difference from vehicle placebo in TNSS was noted at 90 minutes postdose for olopatadine 0.6% in study C0183 and at 30 minutes in study C0352, and these differences were maintained at each of the remaining time points in the studies."

In conclusion, Studies C0352 and C0564 supported a 30-minute onset-of-action and a 12-hour duration-of-action.

Efficacy
The effectiveness of (povidone-free) olopatadine 0.6% was established based on the data from Studies C0569 and C0564.

(b) (4)

Safety evaluation based on AE findings

The AEs based on MedDRA and Costart terms are listed and summarized to facilitate the medical review for regulatory decisions. More discussions can be found in the section, COMMENTS ON LABELING under section **Adverse Reactions**.

Conclusions and Recommendations

In conclusion, olopatadine (povidone-free) was demonstrated to be superior to placebo in terms of either patient-rated relief assessment (PRRA) or instantaneous TNSS in EEC. Olopatadine (povidone-free) was also demonstrated a 30-minute onset-of-action and 12-hour duration-of-action. (b) (4)

COMMENTS ON LABELING

Clinical Studies

Study C0564 provided evidence of statistically superiority of povidone-free olopatadine to vehicle placebo.

Studies C0564 and C0352 demonstrated an onset-of-action as early as 30 minutes and a minimum duration-of-action of 12 hours.

(b) (4)

My reanalysis of the sponsor's data lead to the following results (Table 16 to Table 21). The findings will be compared with those of the sponsor. The analyses include Studies C0237 and C0210.

Table 16 Analysis of symptom score of itchy eye in percent change from baseline (Study C0237)

Treatment (N)	LS-Mean	Lower CL	Upper CL	Difference	Lower CL	Upper CL
Placebo (191)	-0.29	-0.35	-0.23			
Olopatadine 0.4 pct (188)	-0.34	-0.40	-0.28	-0.05	-0.14	0.05
Olopatadine 0.6 pct (183)	-0.41	-0.47	-0.35	-0.11	-0.21	-0.02

Table 17 Analysis of symptom score of watery eye in percent change from baseline (Study C0237)

Treatment (N)	LS-Mean	Lower CL	Upper CL	Difference	Lower CL	Upper CL
Placebo (191)	-0.37	-0.43	-0.31			
Olopatadine 0.4 pct (188)	-0.43	-0.49	-0.37	-0.06	-0.16	0.03
Olopatadine 0.6 pct (183)	-0.45	-0.51	-0.39	-0.09	-0.18	0.01

Table 18 Analysis of symptom score of reflective total ocular symptom score (rTOSS) in percent change from baseline (Study C0237)

Treatment (N)	LS-Mean	Lower CL	Upper CL	Difference	Lower CL	Upper CL
Placebo (191)	-31.68	-37.13	-26.22			
Olopatadine 0.4 pct (188)	-37.65	-43.21	-32.09	-5.97	-14.77	2.83
Olopatadine 0.6 pct (183)	-42.99	-48.57	-37.41	-11.31	-20.13	-2.50

Table 19 Analysis of symptom score of itchy eye in percent change from baseline (Study C0210)

Treatment (N)	LS-Mean	Lower CL	Upper CL	Difference	Lower CL	Upper CL
Placebo (223)	-0.13	-0.19	-0.07			
Olopatadine 0.4 pct (228)	-0.25	-0.31	-0.20	-0.12	-0.22	-0.03
Olopatadine 0.6 pct (220)	-0.30	-0.36	-0.24	-0.17	-0.26	-0.08

Table 20 Analysis of symptom score of watery eye in percent change from baseline (Study C0210)

Treatment (N)	LS-Mean	Lower CL	Upper CL	Difference	Lower CL	Upper CL
Placebo (223)	-0.19	-0.24	-0.13			
Olopatadine 0.4 pct (228)	-0.30	-0.36	-0.24	-0.11	-0.21	-0.02
Olopatadine 0.6 pct (220)	-0.31	-0.37	-0.25	-0.12	-0.22	-0.03

Table 21 Analysis of symptom score of reflective total ocular symptom score (rTOSS) in percent change from baseline (Study C0210)

Treatment (N)	LS-Mean	Lower CL	Upper CL	Difference	Lower CL	Upper CL
Placebo (223)	-16.56	-21.94	-11.18			
Olopatadine 0.4 pct (228)	-27.87	-33.16	-22.58	-11.31	-19.82	-2.79
Olopatadine 0.6 pct (220)	-30.60	-36.01	-25.20	-14.04	-22.65	-5.43

The findings in Table 16 through Table 21 are summarized in Table 21.

Table 22 Summary of effectiveness of olopatadine based on ocular symptom scores

Treatment Vs. placebo	Superiority shown Itchy eye C0237/C0210	Superiority shown Watery eye C0237/C0210	Superiority shown rTOSS C0237/C0210
Olopatadine 0.4 pct (188)	No/Yes	No/Yes	No/Yes
Olopatadine 0.6 pct (183)	Yes/Yes	No/Yes	Yes/Yes

In conclusion, olopatadine 0.6 appeared to improve itchy eye and rTOSS better than placebo but not watery eye. This conclusion contradicts Figure 3, above, of the proposed label.

Adverse Reactions

The sponsor presented the AEs based on short-term SAR clinical trials in addition to the AE findings based on long-term PAR clinical studies. My inclination is that the AE findings based on short-term SAR studies should be superseded by the long-term PAR studies.

AEs from earlier submitted long-term Study C0192 are listed in Table 23. Note that Study C0192 included olopatadine with povidone.

Table 23 AEs based on Study C0192

Adverse event	Olopatadine NS 0.6% (N = 459)		Vehicle placebo (N = 465)	
Patients with adverse events	367	80.0	382	82.1
All adverse events	1253	273.0	1232	264.9
Epistaxis	88	19.2	56	12.0
Cold syndrome	76	16.6	75	16.1
Taste perversion	44	9.6	4	0.9
Arthralgia	23	5.0	12	2.6
Cough increased	22	4.8	15	3.2
Otitis media	15	3.3	14	3.0
Dyspepsia	14	3.1	9	1.9
Toothache	13	2.8	7	1.5
Diarrhea	13	2.8	6	1.3
Dermatitis	12	2.6	9	1.9
Injury, accidental	11	2.4	7	1.5
Pain, extremity	11	2.4	7	1.5
Pain, ear	10	2.2	8	1.7
Depression	9	2.0	3	0.6
Dry nose	9	2.0	2	0.4

Source: Sponsor's Table 96 Adverse events occurring at a frequency greater than 2% and more frequently in olopatadine 0.6% than vehicle placebo, C-01-92 [Module 5, Volume 67, pages 779-793, 917]

Also, incorporated findings of AEs from recently submitted long-term Study C0569, the proposed label states,

(b) (4)

Such a presentation lacks coherent standard and clarity. I summarized the AE findings from C0569 in Table 24, below. It is the same as Table 7 displayed previously. Note that Study C0569 included olopatadine without povidone.

Table 24 AEs based on Costart terms (Study C0569)

presented as: Costart; **Group totals: 445,445**	**Treatment**			
	Olopatadine		**Vehicle**	
	N	**%**	**N**	**%**
NO AE	112	25.17	99	22.25
Allergy	19	4.27	20	4.49
Arthralgia	10	2.25	17	3.82
Asthma	19	4.27	17	3.82
Bronchitis	15	3.37	10	2.25
Cold synd	52	11.69	52	11.69
Conjunctivitis	10	2.25		
Cough inc	16	3.60	14	3.15
Dermatitis			9	2.02
Diarrhea	11	2.47		
Discomfort nasal	12	2.70	13	2.92
Dysmenorrhea			11	2.47
Dyspepsia	9	2.02		
Epistaxis	86	19.33	104	23.37
Flu synd	13	2.92	19	4.27
Gastroenteritis	11	2.47	12	2.70
Gi dis	9	2.02		
Headache	55	12.36	59	13.26
Hypertens	13	2.92	15	3.37
Infect	67	15.06	65	14.61
Infect urin tract	9	2.02		
Injury accid	19	4.27	32	7.19
Insomnia			9	2.02
Myalgia	9	2.02	10	2.25
Nausea			9	2.02
Otitis med			9	2.02
Pain back	12	2.70	12	2.70
Pharyngitis	35	7.87	30	6.74
Rhinitis	104	23.37	103	23.15
Sinusitis	47	10.56	47	10.56
Surgical/medical proc	13	2.92	14	3.15
Taste pervers	29	6.52		
Ulcer nasal	39	8.76	26	5.84

Source: C0569_AE (in 2%+). This table is identical to Table 7.

To explore the similarity in the percentages of patients with specific AEs resulting from the two olopatadine formulations, I combined Table 23 and Table 24, above, and created Table 25.

Table 25 Adverse reaction in Costart terms: Studies C0569 and C0192 compared

Study C0569	Olopatadine (N=445)		Vehicle (N=445)		Study C0192	Olopatadine (N=459)		Vehicle (N=465)	
	N	%	N	%		N	%	N	%
NO AE	112	25.2	99	22.3					
Allergy	19	4.3	20	4.5					
Arthralgia	10	2.3	17	3.8		23	5.0	12	2.6
Asthma	19	4.3	17	3.8					
Bronchitis	15	3.4	10	2.3					
Cold synd	52	11.7	52	11.7		76	16.6	75	16.1
Conjunctivitis	10	2.3							
Cough inc	16	3.6	14	3.2		22	4.8	15	3.2
Dermatitis			9	2.0		12	2.6	9	1.9
Diarrhea	11	2.5				13	2.8	6	1.3
Discomfort nasal	12	2.7	13	2.9					
Dysmenorrhea			11	2.5					
Dyspepsia	9	2.0				14	3.1	9	1.9
Epistaxis	86	19.3	104	23.4		88	19.2	56	12.0
Flu synd	13	2.9	19	4.3					
Gastroenteritis	11	2.5	12	2.7					
Gi dis	9	2.0							
Headache	55	12.4	59	13.3					
Hypertens	13	2.9	15	3.4					
Infect	67	15.1	65	14.6					
Infect urin tract	9	2.0							
Injury accid	19	4.3	32	7.2		11	2.4	7	1.5
Insomnia			9	2.0					
Myalgia	9	2.0	10	2.3					
Nausea			9	2.0					
Otitis med			9	2.0		15	3.3	14	3.0
Pain back	12	2.7	12	2.7					
Pharyngitis	35	7.9	30	6.7					
Rhinitis	104	23.4	103	23.2					
Sinusitis	47	10.6	47	10.6					
Surgical/medical proc	13	2.9	14	3.2					
Taste pervers	29	6.5				44	9.6	4	0.9
Ulcer nasal	39	8.8	26	5.8					
Toothache						13	2.8	7	1.5
Pain, extremity						11	2.4	7	1.5
Pain, ear						10	2.2	8	1.7
Depression						9	2.0	3	0.6
Dry nose						9	2.0	2	0.4

Note that epistaxis occurred in 19.3% of the povidone-free-olopatadine-treated patients (n=86) in Study C0569, representing a similar percentage of the povidone-containing-olopatadine-treated patients (19.2%, n=88) with epistaxis in the earlier Study C0192. The

percentage of patients on placebo with epistaxis increased from 12% in Study C0192 to 23.4% in Study C0569. Furthermore, the percentage of patients with epistaxis on placebo is greater than the percentage of patients with epistaxis on the povidone-free olopatadine treatment. The new formulation of the povidone-free olopatadine hydrochloride nasal spray does not appear to decrease the occurrence rate of epistaxis.

APPENDIX

Table 26 Complete list of AEs based on MedDRA preferred terms (Study C0569)

AEs presented as: AEPTTXT; Group totals: 445, 445 in Olopatadine, Vehicle	Treatment			
	Olopatadine		Vehicle	
	N	%	N	%
NO AE	112	25.17	99	22.25
Epistaxis	86	19.33	104	23.37
Rhinitis	65	14.61	55	12.36
Upper respiratory tract infection	55	12.36	55	12.36
Nasopharyngitis	52	11.69	51	11.46
Sinusitis	43	9.66	45	10.11
Headache	42	9.44	45	10.11
Rhinitis allergic	35	7.87	45	10.11
Nasal ulcer	39	8.76	26	5.84
Injury	19	4.27	32	7.19
Seasonal allergy	19	4.27	20	4.49
Pharyngolaryngeal pain	16	3.60	19	4.27
Asthma	18	4.04	15	3.37
Dysgeusia	29	6.52	3	0.67
Influenza	13	2.92	19	4.27
Cough	16	3.60	14	3.15
Nasal discomfort	14	3.15	15	3.37
Arthralgia	10	2.25	17	3.82
Sinus headache	12	2.70	15	3.37
Bronchitis	15	3.37	10	2.25
Back pain	12	2.70	12	2.70
Nasal congestion	11	2.47	9	2.02
Pharyngitis streptococcal	12	2.70	7	1.57
Myalgia	8	1.80	10	2.25
Diarrhoea	11	2.47	5	1.12
Insomnia	7	1.57	9	2.02
Hypertension	6	1.35	9	2.02
Urinary tract infection	9	2.02	6	1.35
Dizziness	6	1.35	8	1.80
Nausea	5	1.12	9	2.02
Toothache	8	1.80	6	1.35
Gastroenteritis viral	4	0.90	9	2.02
Migraine	6	1.35	7	1.57
Otitis media	4	0.90	9	2.02
Dysmenorrhoea	1	0.22	11	2.47
Ear pain	5	1.12	7	1.57
Rash	3	0.67	8	1.80
Viral infection	6	1.35	5	1.12
Gastroenteritis	7	1.57	3	0.67
Hypersensitivity	5	1.12	5	1.12
Tension headache	7	1.57	3	0.67
Depression	4	0.90	5	1.12
Dyspepsia	6	1.35	3	0.67

AEs presented as: AEPTTXT; Group totals: 445, 445 in Olopatadine, Vehicle	Treatment			
	Olopatadine		Vehicle	
	N	%	N	%
Eye pruritus	3	0.67	6	1.35
Gastrooesophageal reflux disease	4	0.90	5	1.12
Nasal dryness	7	1.57	2	0.45
Procedural pain	4	0.90	5	1.12
Abdominal pain	3	0.67	5	1.12
Anxiety	5	1.12	3	0.67
Dermatitis contact	3	0.67	5	1.12
Fatigue	4	0.90	4	0.90
Herpes simplex	6	1.35	2	0.45
Pain in extremity	3	0.67	5	1.12
Pharyngitis	5	1.12	3	0.67
Conjunctivitis	5	1.12	2	0.45
Dyspnoea	2	0.45	5	1.12
Vomiting	5	1.12	2	0.45
Abdominal pain upper	3	0.67	3	0.67
Constipation	2	0.45	4	0.90
Fungal infection	3	0.67	3	0.67
Muscle spasms	4	0.90	2	0.45
Neck pain	6	1.35		
Pyrexia	3	0.67	3	0.67
Rhinitis seasonal	3	0.67	3	0.67
Arthropod bite	4	0.90	1	0.22
Blood pressure increased	3	0.67	2	0.45
Dry mouth	3	0.67	2	0.45
Pruritus	5	1.12		
Sinus congestion	3	0.67	2	0.45
Throat irritation	4	0.90	1	0.22
Tooth abscess	2	0.45	3	0.67
Tooth fracture	2	0.45	3	0.67
Upper respiratory tract congestion	3	0.67	2	0.45
Weight increased	5	1.12		
Acne	2	0.45	2	0.45
Blood pressure systolic increased	3	0.67	1	0.22
Cystitis	2	0.45	2	0.45
Dry skin	3	0.67	1	0.22
Lymphadenopathy	1	0.22	3	0.67
Nasal polyps	3	0.67	1	0.22
Respiratory tract infection	3	0.67	1	0.22
Stomach discomfort	2	0.45	2	0.45
Urticaria	2	0.45	2	0.45
Vertigo	2	0.45	2	0.45
Anaemia	1	0.22	2	0.45
Blood pressure diastolic increased	1	0.22	2	0.45
Ear congestion	1	0.22	2	0.45
Eczema	2	0.45	1	0.22
Eyelid oedema	2	0.45	1	0.22
Food poisoning	2	0.45	1	0.22
Heart rate increased	2	0.45	1	0.22
Hordeolum	2	0.45	1	0.22

AEs presented as: AEPTTXT; Group totals: 445, 445 in Olopatadine, Vehicle	Treatment			
	Olopatadine		Vehicle	
	N	%	N	%
Localised infection	1	0.22	2	0.45
Lower respiratory tract infection	2	0.45	1	0.22
Nephrolithiasis	2	0.45	1	0.22
Osteopenia	2	0.45	1	0.22
Otitis externa	1	0.22	2	0.45
Palpitations	1	0.22	2	0.45
Pneumonia	1	0.22	2	0.45
Systolic hypertension	1	0.22	2	0.45
Uterine leiomyoma	2	0.45	1	0.22
Vaginal infection	3	0.67		
Vulvovaginal mycotic infection	2	0.45	1	0.22
Wheezing	1	0.22	2	0.45
Abdominal discomfort	1	0.22	1	0.22
Aphthous stomatitis	1	0.22	1	0.22
Appendicitis	1	0.22	1	0.22
Arthritis			2	0.45
Blepharospasm	1	0.22	1	0.22
Carpal tunnel syndrome	1	0.22	1	0.22
Cellulitis	2	0.45		
Cerumen impaction	2	0.45		
Cervical dysplasia	1	0.22	1	0.22
Chest pain			2	0.45
Cholecystectomy	1	0.22	1	0.22
Cholecystitis acute			2	0.45
Colonic polyp	1	0.22	1	0.22
Conjunctivitis allergic	1	0.22	1	0.22
Conjunctivitis bacterial	1	0.22	1	0.22
Conjunctivitis infective	2	0.45		
Dehydration	2	0.45		
Dermatitis	1	0.22	1	0.22
Diverticulitis	1	0.22	1	0.22
Dry throat	1	0.22	1	0.22
Eye irritation			2	0.45
Gastritis			2	0.45
Hypothyroidism			2	0.45
Menometrorrhagia	1	0.22	1	0.22
Menorrhagia	1	0.22	1	0.22
Metrorrhagia			2	0.45
Muscle twitching			2	0.45
Night sweats			2	0.45
Ocular hyperaemia	1	0.22	1	0.22
Oral candidiasis			2	0.45
Ovarian cyst	1	0.22	1	0.22
Pneumonia primary atypical	1	0.22	1	0.22
Pruritus generalised	1	0.22	1	0.22
Rhinalgia	1	0.22	1	0.22
Rhinitis perennial	1	0.22	1	0.22
Rhinorrhoea			2	0.45
Rosacea	1	0.22	1	0.22

AEs presented as: AEPTTXT; Group totals: 445, 445 in Olopatadine, Vehicle	Treatment			
	Olopatadine		Vehicle	
	N	%	N	%
Sneezing			2	0.45
Staphylococcal infection	1	0.22	1	0.22
Sunburn	1	0.22	1	0.22
Tendonitis			2	0.45
Tooth extraction			2	0.45
Tooth impacted	2	0.45		
Tooth infection	1	0.22	1	0.22
Vaginal haemorrhage	1	0.22	1	0.22
Wisdom teeth removal	2	0.45		
Abscess			1	0.22
Anaphylactic reaction	1	0.22		
Angioneurotic oedema	1	0.22		
Aortic valve incompetence			1	0.22
Attention deficit/hyperactivity disorder	1	0.22		
Benign breast neoplasm	1	0.22		
Biopsy breast			1	0.22
Biopsy cervix			1	0.22
Body tinea			1	0.22
Bone disorder	1	0.22		
Breast disorder	1	0.22		
Breast pain	1	0.22		
Bruxism	1	0.22		
Bursitis			1	0.22
Carpal tunnel decompression			1	0.22
Cataract operation	1	0.22		
Cervical conisation	1	0.22		
Cervix haemorrhage uterine			1	0.22
Chapped lips			1	0.22
Chest discomfort			1	0.22
Cholecystitis chronic			1	0.22
Cholelithiasis			1	0.22
Chronic obstructive pulmonary disease	1	0.22		
Chronic sinusitis	1	0.22		
Colonoscopy	1	0.22		
Colposcopy	1	0.22		
Conjunctival haemorrhage			1	0.22
Corneal abrasion	1	0.22		
Cyst	1	0.22		
Cyst removal			1	0.22
Cystocele	1	0.22		
Dental caries	1	0.22		
Dermatitis atopic			1	0.22
Diabetes mellitus			1	0.22
Diarrhoea haemorrhagic			1	0.22
Diarrhoea infectious			1	0.22
Disturbance in attention	1	0.22		
Ear pruritus	1	0.22		
Electrolyte imbalance			1	0.22
Endodontic procedure	1	0.22		

AEs presented as: AEPTTXT; Group totals: 445, 445 in Olopatadine, Vehicle	Treatment			
	Olopatadine		Vehicle	
	N	%	N	%
Endometrial ablation	1	0.22		
Endometriosis			1	0.22
Erythema			1	0.22
Erythema multiforme	1	0.22		
Eustachian tube dysfunction			1	0.22
Exostosis			1	0.22
Eye discharge			1	0.22
Eye disorder	1	0.22		
Eye infection	1	0.22		
Eye laser surgery	1	0.22		
Eye swelling			1	0.22
Feeling jittery	1	0.22		
Folliculitis			1	0.22
Furuncle			1	0.22
Gastrointestinal ulcer			1	0.22
Genital prolapse			1	0.22
Giardiasis			1	0.22
Gingival disorder	1	0.22		
Glossitis	1	0.22		
Glossodynia			1	0.22
Gout	1	0.22		
Haematuria	1	0.22		
Heat rash			1	0.22
Herpes zoster			1	0.22
Hiatus hernia			1	0.22
Hip dysplasia	1	0.22		
Hot flush			1	0.22
Hypercholesterolaemia	1	0.22		
Hyperlipidaemia	1	0.22		
Hypertriglyceridaemia	1	0.22		
Hypoaesthesia			1	0.22
Hypokalaemia			1	0.22
Hyponatraemia	1	0.22		
Incision site complication			1	0.22
Incontinence	1	0.22		
Injection site reaction			1	0.22
Intervertebral disc degeneration			1	0.22
Intervertebral disc operation			1	0.22
Irritable bowel syndrome	1	0.22		
Knee arthroplasty	1	0.22		
Labyrinthitis	1	0.22		
Laryngitis	1	0.22		
Laryngospasm	1	0.22		
Libido decreased	1	0.22		
Liver function test abnormal	1	0.22		
Local reaction	1	0.22		
Lung neoplasm malignant	1	0.22		
Lymph gland infection	1	0.22		
Lymphadenitis	1	0.22		

AEs presented as: AEPTTXT; Group totals: 445, 445 in Olopatadine, Vehicle	Treatment			
	Olopatadine		Vehicle	
	N	%	N	%
Macular degeneration			1	0.22
Malaise			1	0.22
Medical device implantation			1	0.22
Meniscus operation			1	0.22
Menopause	1	0.22		
Menstruation irregular			1	0.22
Mole excision			1	0.22
Mood swings	1	0.22		
Mouth ulceration	1	0.22		
Multiple sclerosis	1	0.22		
Musculoskeletal chest pain	1	0.22		
Musculoskeletal stiffness			1	0.22
Nasal septum deviation			1	0.22
Neuralgia			1	0.22
Neuritis	1	0.22		
Obesity			1	0.22
Oedema peripheral			1	0.22
Oesophageal achalasia			1	0.22
Oral pain	1	0.22		
Oral pruritus			1	0.22
Oral surgery			1	0.22
Pain	1	0.22		
Parvovirus infection			1	0.22
Periodontal disease			1	0.22
Peripheral embolism	1	0.22		
Pharyngeal oedema			1	0.22
Photophobia	1	0.22		
Piriformis syndrome	1	0.22		
Pityriasis rosea	1	0.22		
Platelet disorder	1	0.22		
Pleurisy	1	0.22		
Pneumothorax			1	0.22
Pollakiuria	1	0.22		
Procedural complication	1	0.22		
Prostatitis	1	0.22		
Pulmonary embolism	1	0.22		
Pulmonary granuloma	1	0.22		
Rash papular	1	0.22		
Rectocele	1	0.22		
Renal failure acute	1	0.22		
Schizophrenia	1	0.22		
Seborrhoeic keratosis	1	0.22		
Sensitivity of teeth			1	0.22
Septoplasty			1	0.22
Skin chapped			1	0.22
Skin infection			1	0.22
Skin irritation			1	0.22
Skin lesion	1	0.22		
Skin ulcer			1	0.22

AEs presented as: AEPTTXT; Group totals: 445, 445 in Olopatadine, Vehicle	Treatment			
	Olopatadine		Vehicle	
	N	%	N	%
Sleep apnoea syndrome	1	0.22		
Small intestinal obstruction	1	0.22		
Somnolence	1	0.22		
Squamous cell carcinoma			1	0.22
Stress			1	0.22
Subcutaneous abscess			1	0.22
Tachycardia	1	0.22		
Tendon repair			1	0.22
Therapeutic procedure	1	0.22		
Toe deformity			1	0.22
Tonsillitis			1	0.22
Tooth disorder	1	0.22		
Tympanic membrane disorder	1	0.22		
Tympanic membrane hyperaemia	1	0.22		
Tympanic membrane perforation			1	0.22
Ulcerative keratitis			1	0.22
Urinary incontinence			1	0.22
Uterine prolapse	1	0.22		
Vaginal candidiasis	1	0.22		
Vaginitis bacterial			1	0.22
Viral pharyngitis	1	0.22		

Table 27 Complete list of AEs based on MedDRA system organ class terms (Study C0569)

AEs presented as: AESOCTXT; Group totals: 445, 445 in Olopatadine, Vehicle	Treatment			
	Olopatadine		Vehicle	
	N	%	N	%
NO AE	112	25.17	99	22.25
Infections and infestations	218	48.99	214	48.09
Respiratory, thoracic and mediastinal disorders	176	39.55	186	41.80
Nervous system disorders	91	20.45	71	15.96
Gastrointestinal disorders	51	11.46	48	10.79
Musculoskeletal and connective tissue disorders	43	9.66	46	10.34
Injury, poisoning and procedural complications	30	6.74	40	8.99
Skin and subcutaneous tissue disorders	26	5.84	28	6.29
Immune system disorders	25	5.62	25	5.62
Psychiatric disorders	18	4.04	17	3.82
Eye disorders	15	3.37	18	4.04
Reproductive system and breast disorders	9	2.02	18	4.04
Ear and labyrinth disorders	11	2.47	13	2.92
Investigations	16	3.60	6	1.35
Surgical and medical procedures	10	2.25	12	2.70
General disorders and administration site conditions	10	2.25	11	2.47
Vascular disorders	8	1.80	12	2.70
Metabolism and nutrition disorders	6	1.35	4	0.90
Blood and lymphatic system disorders	4	0.90	5	1.12
Renal and urinary disorders	6	1.35	2	0.45
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	1.12	2	0.45
Cardiac disorders	2	0.45	3	0.67

AEs presented as: AESOCTXT; Group totals: 445, 445 in Olopatadine, Vehicle	Treatment			
	Olopatadine		Vehicle	
	N	%	N	%
Endocrine disorders			2	0.45
Hepatobiliary disorders			2	0.45
Congenital, familial and genetic disorders	1	0.22		
Social circumstances	1	0.22		

Table 28 Complete list of AEs based on Costart terms (Study C0569)

Aes presented as: costart; Group totals: 445,445	Treatment			
	Olopatadine		Vehicle	
	N	%	N	%
No ae	112	25.17	99	22.25
Abscess			2	0.45
Abscess periodont	2	0.45	3	0.67
Acne	3	0.67	4	0.90
Allerg react	6	1.35	5	1.12
Allergy	19	4.27	20	4.49
Anaphyl	1	0.22		
Anemia	1	0.22	2	0.45
Angioedema	1	0.22		
Anxiety	5	1.12	4	0.90
Apnea	1	0.22		
Appendicitis	1	0.22	1	0.22
Arthralgia	10	2.25	17	3.82
Arthritis			2	0.45
Arthropod bite	4	0.90	1	0.22
Asthma	19	4.27	17	3.82
Atrophy breast	1	0.22		
Bone dis	1	0.22	2	0.45
Bronchitis	15	3.37	10	2.25
Bursitis			1	0.22
Carcinoma lung	1	0.22		
Carcinoma skin			1	0.22
Cardiospasm			1	0.22
Cardiovasc dis			1	0.22
Cellulitis	2	0.45		
Cervix dis	1	0.22	1	0.22
Cholecyst			2	0.45
Cholelith			1	0.22
Cold synd	52	11.69	52	11.69
Colitis	1	0.22	1	0.22
Conjunctivitis	10	2.25	4	0.90
Constip	2	0.45	4	0.90
Corneal abrasion	1	0.22		
Cough inc	16	3.60	14	3.15
Cramps leg	3	0.67	1	0.22
Cyst	2	0.45	1	0.22
Cystitis	2	0.45	2	0.45
Dehydrat	2	0.45		
Depression	4	0.90	5	1.12

Aes presented as: costart; **Group totals: 445,445**	**Treatment**			
	Olopatadine		**Vehicle**	
	N	**%**	**N**	**%**
Derm contact	3	0.67	5	1.12
Dermatitis	4	0.90	9	2.02
Diabetes mell			1	0.22
Diarrhea	11	2.47	6	1.35
Diarrhea bloody			1	0.22
Discharge eye nos			1	0.22
Discomfort eye			1	0.22
Discomfort nasal	12	2.70	13	2.92
Dizziness	6	1.35	8	1.80
Dry mouth	4	0.90	3	0.67
Dry nose	7	1.57	2	0.45
Dysmenorrhea	1	0.22	11	2.47
Dyspepsia	9	2.02	6	1.35
Dyspnea	2	0.45	5	1.12
Ear congestion	1	0.22	2	0.45
Ear debris	2	0.45		
Ear dis			1	0.22
Eardrum per			1	0.22
Eczema	2	0.45	2	0.45
Edema eardrum	1	0.22		
Edema eye			1	0.22
Edema lid	2	0.45	1	0.22
Edema periph			1	0.22
Electrolyte abnorm			1	0.22
Emb	1	0.22		
Emb pulm	1	0.22		
Emotion labil	1	0.22		
Endometr dis			1	0.22
Epistaxis	86	19.33	104	23.37
Erythema			1	0.22
Erythema mult	1	0.22		
Eye dis	1	0.22		
Fatigue	4	0.90	4	0.90
Fever	3	0.67	3	0.67
Flu synd	13	2.92	19	4.27
Furunculosis			1	0.22
Gastritis			2	0.45
Gastroenteritis	11	2.47	12	2.70
Gi dis	9	2.02	7	1.57
Gingivitis	1	0.22	1	0.22
Glossitis			1	0.22
Gout	1	0.22		
Granuloma	1	0.22		
Headache	55	12.36	59	13.26
Hem conjunct			1	0.22
Hem vaginal	1	0.22	1	0.22
Hematuria	1	0.22		
Hernia			1	0.22
Herpes simplex	6	1.35	2	0.45

Aes presented as: costart; **Group totals: 445,445**	**Treatment**			
	Olopatadine		**Vehicle**	
	N	**%**	**N**	**%**
Herpes zoster			1	0.22
Hordeolum	2	0.45	1	0.22
Hypercholesterem	1	0.22		
Hyperemia eardrum	1	0.22		
Hyperemia eye	1	0.22	1	0.22
Hyperlipem	2	0.45		
Hypertens	13	2.92	15	3.37
Hypertonia	2	0.45	2	0.45
Hypertrophy skin	1	0.22		
Hypesthesia			1	0.22
Hypokalem			1	0.22
Hyponatrem	1	0.22		
Hypothyr			2	0.45
Incontin urin	1	0.22	1	0.22
Infect	67	15.06	65	14.61
Infect nail			1	0.22
Infect prostat	1	0.22		
Infect skin	1	0.22	2	0.45
Infect tooth	1	0.22	1	0.22
Infect urin tract	9	2.02	6	1.35
Inject site react			1	0.22
Injury accid	19	4.27	32	7.19
Insomnia	7	1.57	9	2.02
Irritation eye			1	0.22
Irritation nose	1	0.22	3	0.67
Irritation skin			1	0.22
Irritation throat	4	0.90	1	0.22
Joint dis	1	0.22	1	0.22
Kidney calculus	2	0.45	1	0.22
Kidney fail	1	0.22		
Laryngismus	1	0.22		
Laryngitis	1	0.22		
Libido dec	1	0.22		
Liver func abnorm	1	0.22		
Lung dis	4	0.90	2	0.45
Lymphadeno	3	0.67	3	0.67
Macular degenerat			1	0.22
Malaise			1	0.22
Menopause	1	0.22		
Menorrhagia	1	0.22	1	0.22
Metrorrhagia	1	0.22	4	0.90
Migraine	6	1.35	7	1.57
Miliaria			1	0.22
Monilia oral			2	0.45
Monilia vagina	2	0.45		
Myalgia	9	2.02	10	2.25
Nasal septum dis			1	0.22
Nausea	5	1.12	9	2.02
Neopl	3	0.67	1	0.22

Aes presented as: costart; **Group totals: 445,445**	**Treatment**			
	Olopatadine		**Vehicle**	
	N	**%**	**N**	**%**
Neopl breast	1	0.22		
Neopl skin	1	0.22		
Nervousness	1	0.22		
Neuralgia	1	0.22	1	0.22
Neuritis	1	0.22		
Obesity			1	0.22
Obstruct intest	1	0.22		
Osteoporosis	2	0.45	1	0.22
Otitis ext	1	0.22	2	0.45
Otitis med	5	1.12	9	2.02
Pain	6	1.35	6	1.35
Pain abdo	6	1.35	7	1.57
Pain back	12	2.70	12	2.70
Pain breast	1	0.22		
Pain chest			3	0.67
Pain ear	5	1.12	7	1.57
Pain extremity	3	0.67	5	1.12
Pain neck	5	1.12		
Pain throat			1	0.22
Palpitat	1	0.22	2	0.45
Person dis	1	0.22		
Pharyngitis	35	7.87	30	6.74
Photophobia	1	0.22		
Photosensitivity	1	0.22	1	0.22
Plat abnorm	1	0.22		
Pleural dis	1	0.22		
Pneumonia	2	0.45	3	0.67
Pneumothorax			1	0.22
Pruritus	6	1.35	2	0.45
Pruritus ear	1	0.22		
Pruritus eye	3	0.67	6	1.35
Pruritus nasal	1	0.22	1	0.22
Rash mac pap	2	0.45		
Rhinitis	104	23.37	103	23.15
Schizophrenic react	1	0.22		
Sclerosis mult	1	0.22		
Sinusitis	47	10.56	47	10.56
Skin dry	3	0.67	3	0.67
Sneezing			2	0.45
Somnolence	1	0.22		
Spasm lid	1	0.22	1	0.22
Stomatitis aphth	2	0.45	1	0.22
Surgical/medical proc	13	2.92	14	3.15
Sweat			2	0.45
Tachycardia	3	0.67	1	0.22
Taste pervers	29	6.52	3	0.67
Tendon dis			2	0.45
Tenosynovitis	1	0.22	1	0.22
Thinking abnorm	1	0.22		

Aes presented as: costart; **Group totals: 445,445**	**Treatment**			
	Olopatadine		**Vehicle**	
	N	**%**	**N**	**%**
Tongue dis	1	0.22		
Tooth caries	1	0.22		
Tooth dis	6	1.35	4	0.90
Toothache	8	1.80	6	1.35
Twitch			2	0.45
Ulcer corneal			1	0.22
Ulcer nasal	39	8.76	26	5.84
Ulcer skin			1	0.22
Ulcer stomach			1	0.22
Urin frequency	1	0.22		
Urin tract dis	1	0.22		
Urticaria	2	0.45	2	0.45
Uter atony	1	0.22		
Uter dis			1	0.22
Uter fibroid enlarge	2	0.45	1	0.22
Vaginitis	2	0.45	1	0.22
Vasodilat			1	0.22
Vertigo	2	0.45	2	0.45
Vomit	5	1.12	2	0.45
Weight inc	5	1.12		

Table 29 Complete list of AEs based on Costart terms by sex (Study C0569)

	Olopatadine				**Vehicle**			
	Female		**Male**		**Female**		**Male**	
	N=282	**%**	**N=163**	**%**	**N=296**	**%**	**N=149**	**%**
No AE	66	23.4	46	28.2	65	22.0	34	22.8
Abscess					2	0.7		
Abscess periodont	2	0.7			2	0.7	1	0.7
Acne	3	1.1			4	1.4		
Allerg react	5	1.8	1	0.6	4	1.4	1	0.7
Allergy	17	6.0	2	1.2	14	4.7	6	4.0
Anaphyl	1	0.4						
Anemia	1	0.4			2	0.7		
Angioedema			1	0.6				
Anxiety	4	1.4	1	0.6	2	0.7	2	1.3
Apnea	1	0.4						
Appendicitis			1	0.6			1	0.7
Arthralgia	8	2.8	2	1.2	11	3.7	6	4.0
Arthritis					2	0.7		
Arthropod bite	3	1.1	1	0.6	1	0.3		
Asthma	15	5.3	4	2.5	10	3.4	7	4.7
Atrophy breast	1	0.4						
Bone dis	1	0.4			2	0.7		
Bronchitis	13	4.6	2	1.2	9	3.0	1	0.7
Bursitis					1	0.3		
Carcinoma lung	1	0.4						
Carcinoma skin					1	0.3		
Cardiospasm							1	0.7

	Olopatadine				Vehicle			
	Female		Male		Female		Male	
	N=282	%	N=163	%	N=296	%	N=149	%
Cardiovasc dis							1	0.7
Cellulitis	2	0.7						
Cervix dis	1	0.4			1	0.3		
Cholecyst					1	0.3	1	0.7
Cholelith					1	0.3		
Cold synd	35	12.4	17	10.4	35	11.8	17	11.4
Colitis	1	0.4			1	0.3		
Conjunctivitis	7	2.5	3	1.8	2	0.7	2	1.3
Constip	2	0.7			4	1.4		
Corneal abrasion	1	0.4						
Cough inc	13	4.6	3	1.8	8	2.7	6	4.0
Cramps leg	3	1.1			1	0.3		
Cyst	2	0.7			1	0.3		
Cystitis	1	0.4	1	0.6	2	0.7		
Dehydrat			2	1.2				
Depression	4	1.4			4	1.4	1	0.7
Derm contact	2	0.7	1	0.6	5	1.7		
Dermatitis	4	1.4			8	2.7	1	0.7
Diabetes mell							1	0.7
Diarrhea	8	2.8	3	1.8	3	1.0	3	2.0
Diarrhea bloody					1	0.3		
Discharge eye nos					1	0.3		
Discomfort eye					1	0.3		
Discomfort nasal	6	2.1	6	3.7	12	4.1	1	0.7
Dizziness	4	1.4	2	1.2	7	2.4	1	0.7
Dry mouth	2	0.7	2	1.2	1	0.3	2	1.3
Dry nose	6	2.1	1	0.6	2	0.7		
Dysmenorrhea	1	0.4			11	3.7		
Dyspepsia	7	2.5	2	1.2	4	1.4	2	1.3
Dyspnea	1	0.4	1	0.6	3	1.0	2	1.3
Ear congestion			1	0.6	2	0.7		
Ear debris	2	0.7						
Ear dis					1	0.3		
Eardrum per					1	0.3		
Eczema	1	0.4	1	0.6	2	0.7		
Edema eardrum	1	0.4						
Edema eye					1	0.3		
Edema lid	2	0.7					1	0.7
Edema periph					1	0.3		
Electrolyte abnorm					1	0.3		
Emb	1	0.4						
Emb pulm	1	0.4						
Emotion labil	1	0.4						
Endometr dis					1	0.3		
Epistaxis	52	18.4	34	20.9	63	21.3	41	27.5
Erythema					1	0.3		
Erythema mult			1	0.6				
Eye dis	1	0.4						
Fatigue	2	0.7	2	1.2	3	1.0	1	0.7

	Olopatadine				Vehicle			
	Female		Male		Female		Male	
	N=282	%	N=163	%	N=296	%	N=149	%
Fever	1	0.4	2	1.2	3	1.0		
Flu synd	8	2.8	5	3.1	15	5.1	4	2.7
Furunculosis					1	0.3		
Gastritis					1	0.3	1	0.7
Gastroenteritis	9	3.2	2	1.2	8	2.7	4	2.7
Gi dis	7	2.5	2	1.2	7	2.4		
Gingivitis	1	0.4			1	0.3		
Glossitis					1	0.3		
Gout			1	0.6				
Granuloma	1	0.4						
Headache	43	15.2	12	7.4	41	13.9	18	12.1
Hem conjunct					1	0.3		
Hem vaginal	1	0.4			1	0.3		
Hematuria	1	0.4						
Hernia					1	0.3		
Herpes simplex	5	1.8	1	0.6	2	0.7		
Herpes zoster							1	0.7
Hordeolum	1	0.4	1	0.6			1	0.7
Hypercholesterem	1	0.4						
Hyperemia eardrum	1	0.4						
Hyperemia eye			1	0.6			1	0.7
Hyperlipem	1	0.4	1	0.6				
Hypertens	6	2.1	7	4.3	11	3.7	4	2.7
Hypertonia	1	0.4	1	0.6	1	0.3	1	0.7
Hypertrophy skin	1	0.4						
Hypesthesia							1	0.7
Hypokalem					1	0.3		
Hyponatrem			1	0.6				
Hypothyr					2	0.7		
Incontin urin	1	0.4			1	0.3		
Infect	44	15.6	23	14.1	43	14.5	22	14.8
Infect nail							1	0.7
Infect prostat			1	0.6				
Infect skin	1	0.4			2	0.7		
Infect tooth	1	0.4			1	0.3		
Infect urin tract	8	2.8	1	0.6	6	2.0		
Inject site react					1	0.3		
Injury accid	12	4.3	7	4.3	19	6.4	13	8.7
Insomnia	4	1.4	3	1.8	7	2.4	2	1.3
Irritation eye					1	0.3		
Irritation nose	1	0.4			3	1.0		
Irritation skin					1	0.3		
Irritation throat	3	1.1	1	0.6			1	0.7
Joint dis	1	0.4			1	0.3		
Kidney calculus	2	0.7			1	0.3		
Kidney fail			1	0.6				
Laryngismus	1	0.4						
Laryngitis	1	0.4						
Libido dec	1	0.4						

	Olopatadine				Vehicle			
	Female		Male		Female		Male	
	N=282	%	N=163	%	N=296	%	N=149	%
Liver func abnorm	1	0.4						
Lung dis	3	1.1	1	0.6	2	0.7		
Lymphadeno	3	1.1			2	0.7	1	0.7
Macular degenerat							1	0.7
Malaise					1	0.3		
Menopause	1	0.4						
Menorrhagia	1	0.4			1	0.3		
Metrorrhagia	1	0.4			4	1.4		
Migraine	5	1.8	1	0.6	6	2.0	1	0.7
Miliaria					1	0.3		
Monilia oral							2	1.3
Monilia vagina	2	0.7						
Myalgia	6	2.1	3	1.8	9	3.0	1	0.7
Nasal septum dis							1	0.7
Nausea	4	1.4	1	0.6	8	2.7	1	0.7
Neopl			3	1.8			1	0.7
Neopl breast			1	0.6				
Neopl skin			1	0.6				
Nervousness	1	0.4						
Neuralgia	1	0.4			1	0.3		
Neuritis			1	0.6				
Obesity					1	0.3		
Obstruct intest	1	0.4						
Osteoporosis	2	0.7			1	0.3		
Otitis ext			1	0.6	2	0.7		
Otitis med	3	1.1	2	1.2	4	1.4	5	3.4
Pain	4	1.4	2	1.2	4	1.4	2	1.3
Pain abdo	5	1.8	1	0.6	5	1.7	2	1.3
Pain back	9	3.2	3	1.8	9	3.0	3	2.0
Pain breast	1	0.4						
Pain chest					2	0.7	1	0.7
Pain ear	5	1.8			7	2.4		
Pain extremity	2	0.7	1	0.6	4	1.4	1	0.7
Pain neck	5	1.8						
Pain throat					1	0.3		
Palpitat	1	0.4			1	0.3	1	0.7
Person dis			1	0.6				
Pharyngitis	24	8.5	11	6.7	23	7.8	7	4.7
Photophobia	1	0.4						
Photosensitivity	1	0.4			1	0.3		
Plat abnorm	1	0.4						
Pleural dis			1	0.6				
Pneumonia	2	0.7			3	1.0		
Pneumothorax					1	0.3		
Pruritus	5	1.8	1	0.6	2	0.7		
Pruritus ear	1	0.4						
Pruritus eye	2	0.7	1	0.6	5	1.7	1	0.7
Pruritus nasal	1	0.4			1	0.3		
Rash mac pap	2	0.7						

	Olopatadine				Vehicle			
	Female		Male		Female		Male	
	N=282	%	N=163	%	N=296	%	N=149	%
Rhinitis	62	22.0	42	25.8	61	20.6	42	28.2
Schizophrenic react	1	0.4						
Sclerosis mult	1	0.4						
Sinusitis	28	9.9	19	11.7	38	12.8	9	6.0
Skin dry	2	0.7	1	0.6	2	0.7	1	0.7
Sneezing					2	0.7		
Somnolence	1	0.4						
Spasm lid	1	0.4			1	0.3		
Stomatitis aphth	2	0.7			1	0.3		
Surgical/medical proc	10	3.5	3	1.8	7	2.4	7	4.7
Sweat					2	0.7		
Tachycardia	3	1.1			1	0.3		
Taste pervers	21	7.4	8	4.9	1	0.3	2	1.3
Tendon dis					2	0.7		
Tenosynovitis	1	0.4			1	0.3		
Thinking abnorm			1	0.6				
Tongue dis			1	0.6				
Tooth caries	1	0.4						
Tooth dis	4	1.4	2	1.2	1	0.3	3	2.0
Toothache	8	2.8			6	2.0		
Twitch					1	0.3	1	0.7
Ulcer corneal					1	0.3		
Ulcer nasal	21	7.4	18	11.0	16	5.4	10	6.7
Ulcer skin					1	0.3		
Ulcer stomach					1	0.3		
Urin frequency	1	0.4						
Urin tract dis	1	0.4						
Urticaria	1	0.4	1	0.6	2	0.7		
Uter atony	1	0.4						
Uter dis					1	0.3		
Uter fibroid enlarge	2	0.7			1	0.3		
Vaginitis	2	0.7			1	0.3		
Vasodilat					1	0.3		
Vertigo	1	0.4	1	0.6	2	0.7		
Vomit	5	1.8			1	0.3	1	0.7
Weight inc	5	1.8						

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/s/

Ted Guo
3/3/2008 12:54:55 PM
BIOMETRICS
Stat review

Qian Li
3/5/2008 09:47:29 AM
BIOEQUIVALENCE STATISTICIAN
I concur. A secondary statistical review is writtern.

Statistical Review and Evaluation
(Carcinogenicity Studies)

NDA Number: 21-861

Drug Name: Patanase Nasal Spray (olopatadine HCl)

Sponsor: Alcon

Pharm/tox Reviewer: Jean Wu, M.D., Ph.D., Division of Pulmonary and Allergy Products

Pharm/tox Supervisory Reviewer: Joseph Ching-Long Sun, Ph.D., Division of Pulmonary and Allergy Products

Statistical Reviewer: Karl K. Lin, Ph.D., Division of Biometrics 6

Document Reviewed: Survival and tumor data included in Dr. Wu's January 24, 2008 request for a statistical review and evaluation of the two p53+/- transgenic mouse studies.

Summary

The Tarone trend test is used to analyze the survival data and the survival-unadjusted Peto trend test, and the Fisher exact test are used to analyze of the tumor data of the two 26 week p53+/- transgenic mouse studies.

The dose-response trend in mortality is statistically significant at 0.05 significance level in p53+/-male mice, but is not statistically significant in p53+/- female mice of the study 1.

The pair-wise comparisons in tumor incidence between sham and vehicle groups are statistically significant differences at two-sided 0.05 level of significance in total animal with skin sarcoma at SOI (site of injection) in females, and in total animal with skin sarcoma in females in study 1.

The survival-unadjusted dose-responses in tumor incidence are not statistically significant at 0.05 level of significance in both males and females for the tumor types tested in study 1.

The dose-response trend in mortality is statistically significant at 0.05 significance level in both p53+/- male and female mice of study 2.

The pair-wise comparisons in tumor incidence between sham and vehicle groups are statistically significant differences in tumor incidence at two-sided 0.05 level in total animals with skin sarcoma at SOI in both males and females, and in skin SOI (not last*) sarcoma in males in study 2.

The pairwise comparison in difference in tumor incidence between the vehicle control and the high dose groups is statistically significant at 0.05 level of significance in skin SOI (not last*) sarcoma in females in study 2.

In study 2, the survival-unadjusted dose-responses in skin SOI (last site) sarcoma in males, and in skin SOI (not last*) sarcoma, in skin SOI (generalized) sarcoma, and in total animals with skin sarcoma at SOI in females are statistically significant at 0.05 level in study 2.

If a survival-unadjusted test of dose response or a survival-unadjusted pair-wise comparison in incidence of a tumor type is statistically significant, then a corresponding survival-adjusted trend test or survival-adjusted pair-wise comparison will show a more significant result in these two studies if there are complete tumor data available for performing such a survival-adjusted analysis.

If a survival-unadjusted test of dose response or a survival-unadjusted pair-wise comparison in incidence of a tumor type is not statistically significant, then a corresponding survival-adjusted trend test or survival-adjusted pair-wise comparison may

show a significant result in these two studies if there are complete tumor data available for performing such a survival-adjusted analysis.

Background Information

There were two 26-week p53+/- transgenic mouse studies included in this NDA submission. The two studies were (1) 26-Week Repeated Subcutaneous Dose Carcinogenicity Study In $p53^{+/-}$ Mice with A Toxicokinetic Study in C57BL/6 Mice with (b) (4), and (2) 26-Week Repeated Subcutaneous Dose Carcinogenicity Study In $p53^{+/-}$ Mice with A Toxicokinetic Study in C57BL/6 Mice with (b) (4) The purpose of the transgenic mouse studies was to evaluate the carcinogenic potential of two degradants (b) (4) and (b) (4) of drug product (olopatadine HCl) when they were administered to p53+/- transgenic mice for 26 weeks.

Jean Wu, M.D., Ph.D. of the Division of Pulmonary and Allergy Products, the reviewing pharmacologist/toxicologist of this submission, has requested that the Pharm/Tox Statistics Team of the Office of Biostatistics perform a statistical review of the two transgenic mouse studies. The survival and tumor data used in this statistical review were provided by Dr. Wu. This reviewer has worked closely with Dr. Wu on this review project regarding the most appropriate ways to analyze the available but not complete mortality and tumor data provided by her.

I. Provided Survival and Tumor Data of the Two Studies

The following tables (Tables 1 and 2) contain the survival data, and the tumor data of the first transgenic mouse study, respectively. The information about the design of the study regarding the experimental groups, doses used, number of mice used per gender/group is also included in the tables.

Table 1

Survival Data of Study 1: 26-Week Repeated Subcutaneous Dose Carcinogenicity Study In $p53^{+/-}$ Mice with A Toxicokinetic Study in C57BL/6 Mice with (b) (4)

Mortality	Males						Females					
Dose (mg/kg/day)	Sham	Veh	3	10	30	PC	Sham	Veh	3	10	30	PC
p53 mice Total	**1/25**	**2/25**	**1/25**	**0/25**	**5/25**	**#1/25**	**0/25**	**1/25**	**0/25**	**1/25**	**2/25**	**9/25**
Days 43-91	0	1	0	0	0	0	0	0	0	0	0	2
Days 91-184	1	1	1	0	5	1	0	1	0	1	2	7
C57BL/6 mice Total	**0/25**	**1/37**	***0/26**	**0/26**	**3/51**	**NA**	**0/25**	**0/37**	**0/26**	**2/26**	**2/51**	**NA**
Days 39-83	0	1	0	0	3	NA	0	0	0	2	2	NA

Sham—Sham control group; Veh---Vehicle control group; PC---positive control group *one male accidentally killed was not included; #4 males died of dosing accident are not included

Table 2

Tumor Data of Study 1: 26-Week Repeated Subcutaneous Dose Carcinogenicity Study In $p53^{+/-}$ Mice with A Toxicokinetic Study in C57BL/6 Mice with (b) (4)

Findings	Males					Females				
Dose (mg/kg/day)	Sham	Veh	3	10	30	Sham	Veh	3	10	30
Total animal with skin sarcoma at SOI (site of injection)	**0**	**3**	**4**	**9**	**6**	**0**	**6**	**1**	**5**	**1**
Skin, untreated, non-SOI, sarcoma	0	1	1	2*	0	0	2	0	0	0
Total animal with skin sarcoma	**0**	**4**	**5**	**11**	**6**	**0**	**7**	**1**	**5**	**1**
Total animals with leukemia	**0**	**0**	**0**	**0**	**1**	**0**	**2**	**1**	**3**	**1**

The number in the table indicates the incidence of N=25 examined animals. Sham = sham control group, Veh. = vehicle control group; *animal #7720 sarcoma noted in spinal cord and abdominal activity, animal#7721 sarcoma noted in spinal cord;

Tables 3 and 4 below contain the survival data, and the tumor data of the second transgenic mouse study, respectively. The design of the second study was about the same as that of the first study except that doses used were not exactly the same in the two studies.

Table 3

Survival Data of Study 2: 26-Week Repeated Subcutaneous Dose Carcinogenicity Study In $p53^{+/-}$ Mice with A Toxicokinetic Study in C57BL/6 Mice with (b) (4)

Mortality	Males						Females					
Dose (mg/kg/day)	Sham	Veh	1	5	12.5/8	PC	Sham	Veh	1	5	12.5/8	PC
p53 mice	**0/25**	**1/25**	**2/25**	**2/25**	**10/25***	**1/25**	**1/25**	**0/25**	**2/25**	**5/25#**	**9/25***	**0/25**
Days 1-62 M/56F	0	0	0	0	4	0	0	0	0	1	4	0
Days 62M/56F-91	0	0	1	1	2	0	0	0	0	0	0	0
Days 91-185	0	1	1	1	4	1	1	0	2	4	5	0
C57BL/6 mice	**0/25**	**1/37**	**1/20**	**2/20**	**11/45***	**NA**	**0/25**	**1/37**	**0/20**	**1/20**	**5/45**	**NA**
Days 1-62 M/56F	0	0	0	1	6	NA	0	0	0	1	2	NA
Days 62M/56F-91	0	1	1	0	1	NA	0	0	0	0	0	NA
Days 91-185	0	0	0	1	4	NA	0	1	0	0	3	NA

Sham—Sham control group; Veh---Vehicle control group; PC---positive control group

Table 4

Tumor Data of Study 2: 26-Week Repeated Subcutaneous Dose Carcinogenicity Study In $p53^{+/-}$ Mice with A Toxicokinetic Study in C57BL/6 Mice with (b) (4)

Findings	Males					Females				
Dose (mg/kg/day)	Sham	Veh	1	5	12.5/8	Sham	Veh	1	5	12.5/8
Skin, SOI (last site), sarcoma	0	2	0	0	6	0	1	1	0	0
Skin, SOI (not last*) , sarcoma	0	7	6	4	11	0	5	3	5	12
Skin, SOI (generalized), sarcoma	0	1	0	0	1	0	0	0	0	3
Total animal with skin sarcoma at SOI	**0**	**10**	**6**	**4**	**11**	**0**	**6**	**3**	**5**	**12**
Skin, untreated, non-SOI, sarcoma	0	0	0	0	0	0	0	0	0	0

The number in the table indicates the incidence of N=25 examined animals. Sham = sham control group, Veh. = vehicle control group;

II. Dr. Wu's Comments on and Concerns over the Survival and Tumor Data of the Two Studies

In both studies, sarcomas at skin, injection sites were observed in vehicle control and treated groups but not in the sham group.

Slight mortality was observed in study 1 and significant test article related mortality at high dose was observed in study 2.

In the first study, mortality was observed in p53 mice and C57BL/6 mice. She is interested in knowing if the mortality was test article-related.

In Study 1, sarcoma was only observed in p53 mice. The positive control, p-cresidine, produced expected tumor findings in the urinary bladder. The sarcoma was observed in both vehicle and test article-treated groups. The sponsor indicated that the sarcoma was due to the vehicle-related repeated subcutaneous injection at injection site of the skin. She is interested in knowing if there is a significant difference between sham and vehicle control groups, and if there is a significant dose trend in the incidence among the vehicle control and treated groups excluding the positive control group in this tumor type.

In Study 2, the mortality in high dose group was significant. The initial high dose of 12.5 mg/kg was changed to 8 mg/kg on day 62 for male and day 56 for females due to early death observed. She is interested in knowing if the mortality in mid-dose female was test article-related too.

Also in the second study, sarcoma at the injection site was observed only in p53 mice. The positive control, p-cresidine, produced expected tumor findings in the urinary

bladder. She is interested in knowing if this is only vehicle-related repeated subcutaneous injection trauma.

III. Reviewer's Statistical Analysis of the Survival and Tumor Data of the Two Studies

The statistical methods used by this reviewer in the analysis of the survival and tumor data of the two studies, and some statistical issues related to analysis of carcinogenicity study data in general and to analysis of transgenic mouse study data in particular are discussed in this section of the report.

III.1 Methods of Analysis

The Tarone trend tests (Cox 1959; Peto et al. 1980; Tarone 1975; Lin 2000; Lin and Ali 1994 and 2006) are used to test the significant dose-response relationships (trends) in survival among the vehicle control, low, medium, and high dose groups. The survival data of the sham and the positive control groups were not included in the analysis.

Like human beings, older rodents have a many fold higher probability of developing or dying of tumors than those of a younger age. Therefore, in the analysis of tumor data, it is essential to identify and adjust for possible differences in intercurrent mortality among treatment groups to eliminate or reduce biases caused by these differences. It has been pointed out that "the effects of differences in longevity on numbers of tumor-bearing animals can be very substantial, and so, whether or not they (the effects) appear to be, they should routinely be corrected when presenting experimental results" (Peto et al. 1980). The death-rate method, the prevalence method, and the onset-rate methods are commonly used tests for dose-response trend in incidence rate in a fatal tumor, a incidental tumor, and a mortality independent tumor, respectively. Detailed discussions of these statistical methods can be found in Peto et al. 1980, Lin 2000, Lin and Ali 1994, and Lin and Ali 2006.

To perform mortality-adjusted analysis on the tumor data, additional information about the tumor data is needed. For each tumor type, the information about the breakdowns of the overall incidence rates in each of the time interval Dr. Wu specified in the mortality tables is needed. For example, for total animals with skin sarcomas at SOI for p53 males in Study 1, the overall incidence rates 0, 3, 4, 9, and 6 for the untreated, vehicle, low, medium, and high groups, respectively need to be broken down into incidence rates for each of the individual intervals, i.e., 0-42, 43-91, 92-184, and terminal sacrifice.

As mentioned above, if the high group in both males and females in both studies showed statistically higher mortalities than those of the remaining groups, then survival-adjusted analysis will be more appropriate. Under the above situation, for a given tumor type, if the survival-unadjusted analysis is statistically significant, then the survival-adjusted analysis will definitely be statistically more significant if there are complete tumor data available for performing such a survival-adjusted analysis. However, the converse will not be true. A non-statistically significant result from a survival-unadjusted analysis may

result in a statistically significant result in a survival-adjusted analysis because the high group will have more animals developed the type of tumor than those observed if the animals did not die early.

However, with the available data (overall tumor incidence rates only) contained in the e-mail that Dr. Wu sent this reviewer earlier, only mortality-unadjusted (i.e., survival-unadjusted) trend tests can be performed on the tumor data.

Because of the lack of complete information about the tumor data available for this statistical review, it was agreed between Dr. Wu and this reviewer to do the following sets of statistical analysis: (1) Tests of dose-response trend in mortality in vehicle, low, medium, and high dose groups of the drug, (2), survival-unadjusted tests of dose-response trend in tumor incidence in vehicle, low, medium, and high dose groups of the drug, (3) survival-unadjusted pairwise comparison tests between the sham and vehicle control groups, and (4) survival-unadjusted pairwise comparison tests between the vehicle control and the high dose group of the drug.

III.2 Statistical Issues in Analysis of Tumor Data

There are some statistical issues in the statistical analysis of data of carcinogenicity studies using transgenic mice of various models. One of them is the appropriateness of the use of the size of 25 animals for each gender/group. The second of the issues is the decision rules (i.e., levels of significance) to be used in the determination if a trend or a pairwise difference in tumor incidence is statistically significant.

The used group size of 25 in both studies will have things to do with the power of a statistical test (i.e., the probability of detecting a true effect). In general, the larger the group size, the higher the power will be. However, the power of a statistical test is also a function of the delta of effect (the difference in an endpoint between treated and untreated groups) an investigator would like to detect, and the variability in the study population being studied. The larger the delta effect to be detected, and the smaller the variability of the population, the higher the power will be.

The reason of using smaller group size in a transgenic mouse study than that in a two-year study is the biological assumption that a compound with carcinogenic effect will cause many more transgenic mice to develop a given tumor types much earlier than the negative control. Therefore, the delta effect to be detected will be large, and, therefore, only a smaller group size is needed to achieve a desired level of power. We did some sample size and power calculations a while ago to check if the group size of 10 used in studies conducted in very early time was appropriate or not. Our study results showed that the group size of 10 was too small. We recommended that the group size to be changed from 10 used in the early days to 25 currently used by most sponsors. With the group size of 25 and a delta effect of 15%-20% to be detected, a statistical test for drug effect will have a reasonable power of around 80%.

In a standard two-species-two-gender two-year study, the levels of significance of 0.025, and 0.005 are used in tests for dose-response trend for rare tumors, and common tumors, respectively, and the levels of significance of 0.05 and 0.01 are used for control-high groups pairwise comparison tests for difference in incidence for rare tumors, and common tumors, respectively (U.S. Department of Health and Human Services 2001). A tumor type is considered as rare if the spontaneous rate of the tumor type is 1% or lower. The above decision rules were developed by the Pharm/Tox Statistics Team of the Office of Biostatistics based on the research results of the team on this issue (Lin and Rahman 1998a and 1998b). In order to have reasonable levels of statistical power in detecting true a carcinogen, it was considered as appropriate in regulatory setting to assume about 10% overall false positive. The above decision rules were developed basing on this overall false positive rate, and were concurred by the CDER management.

The decision rules used in statistical analysis of data of carcinogenicity studies using transgenic mice are different from those used in two-year studies. The significance level of 0.05 is used in both tests for dose-response trend and tests for pairwise comparison difference in tumor incidence regardless of common or rare tumors. The main reasons for the use of this single level of significance in the data analysis of transgenic mouse studies are as follows: (1) Only 25 instead of 50 or more animals per gender/group are used. With a smaller group size, it is necessary to use a larger level of significance in a statistical test in order to achieve a reasonable level of power of the test. (2) Because of the nature of the transgenic mouse studies, only a small number of tumor types developed in the tested animals. The total number of statistical tests performed in a transgenic mouse study is much smaller than that of a standard two-year-two-species-two-gender study. The statistical issue of multiple tests is much less a problem in a transgenic mouse study than in the standard two year study.

The p-values calculated by the prevalence method, the death rate method, and the onset rate method are based on normal approximation (i.e., based on asymptotic calculations) in the test for the positive trend in tumor incidence rates. It is also well known that the approximation results may not be stable and reliable, and tend to underestimate the exact p-values when the total numbers of tumor occurrence across treatment groups are small (Ali 1990). In this situation, the exact permutation trend test should be used to test for the positive trend (Gart et al. 1986; Goldberg 1985, Lin 2000, Lin and Ali 1994, and Lin and Ali 2006).

III.3 Reviewer's Analysis Results

Results of the reviewer's analyses using the statistical procedures described in the previous subsections are presented in this subsection.

Results of Tests of Dose Response in Mortality Using Vehicle, 3, 10, and 30 Groups of p53+/- Mice of Study 1

The mortality data of p53+/- transgenic mice of study 1 used in the reviewer's analysis are presented in Table 5 below.

Table 5
Study 1: Tests of Dose Response in Mortality Using
Vehicle, 3, 10, and 30 Groups of p53+/- Mice

Mortality	Males				Females			
Dose (mg/kg/day)	Veh	3	10	30	Veh	3	10	30
p53 mice Total	**2/25**	**1/25**	**0/25**	**5/25**	**1/25**	**0/25**	**1/25**	**2/25**
Days 43-91	1	0	0	0	0	0	0	0
Days 91-184	1	1	0	5	1	0	1	2

Sham—Sham control group; Veh---Vehicle control group; PC---positive control group *one male accidentally killed was not included; #4 males died of dosing accident are not included

The following are the p-values of the tests of dose response trend in mortality in vehicle, 3, 10, and 30 groups of p53+/- mice of study 1:

Male mice: p = 0.02893 (exact), p = 0.01981 (asymptotic)

Female mice p = 0.1658 (exact), p = 0.1205 (asymptotic)

The results show that the dose-response trend in mortality is statistically significant at 0.05 significance level in p53+/-male mice, but it is not statistically significant at 0.05 level of significance in female p53+/- mice.

Results of Tests of Dose Response and of Pairwise Comparisons in Tumor Incidence Using Vehicle, 3, 10, and 30 Groups of p53+/- Mice of Study 1

Results (p-values) of the reviewer's analysis of the tumor data of the p53+/- mice of study 1 are presented in Table 6 with the tumor data. The analysis included the tests for dose-response trend in incidence among the vehicle, low, medium, and high dose groups of p53+/- mice, pairwise comparison tests in difference in incidence between the sham and the vehicle control groups, and between the vehicle control group and the high dose group of p53+/- mice.

Please note that, in Table 6, the p-values under sham group are those of pair-wise comparisons between sham and vehicle groups, and the p-values under the vehicle group are those for the trend tests using the vehicle, low, medium, and high groups, and the p-

values under the high dose group are those of pairwise comparisons between the vehicle control and the high dose groups.

Please also note that the p-values are presented in pairs in the entries of Table 6. The first p-value of the pair is the p-value based on asymptotic calculations of the statistical test while the second p-value of the pair is the p-value of the test based on exact calculations. As mentioned in the above subsection, the exact p-values will be more appropriate for the interpretation of the results of the study.

Table 6

Study 1: Tumor Data and P-values of Tests of Dose Response in Tumor Incidence Using Vehicle, 3, 10, and 30 Groups of p53+/- Mice

Findings	Males					Females				
Dose (mg/kg/day)	Sham	Veh	3	10	30	Sham	Veh	3	10	30
Total animal with skin sarcoma at SOI (site of injection)	**0** **p = .0944** **p= .2347**	**3** **p=.1750** **p=.1806**	**4**	**9**	**6**	**0** **p=0087** **p=.0223**	**6** **p=.9245** **p=.9259**	**1**	**5**	**1**
Skin, untreated, non-SOI, sarcoma	0 **p= .3285** **p =1.0000**	1 **p=.1925** **p=.2545**	1	2*	0	0 **p=.1910** **p=.4898**	2 **p=.9044** **p=.9394**	0	0	0
Total animal with skin sarcoma	**0** **p = .0442** **p= .1099**	**4** **p=.3104** **p=.3124**	**5**	**11**	**6**	**0** **p=.0037** **p=.0096**	**7** **p=.9511** **p=.9551**	**1**	**5**	**1**
Total animals with leukemia	**0**	**0**	**0**	**0**	**1**	**0** **p=.1910** **p=.4898**	**2** **p=.6586** **p=.6185**	**1**	**3**	**1**

The number in the table indicates the incidence of N=25 examined animals. Sham = sham control group, Veh. = vehicle control group; *animal #7720 sarcoma noted in spinal cord and abdominal activity, animal#7721 sarcoma noted in spinal cord;

The reviewer's tumor data analysis of study 1 yielded the following results:

Pair-wise comparisons between sham and vehicle groups show statistically significant differences at two-sided 0.05 level in total animal with skin sarcoma at SOI (site of injection) in females, and in total animal with skin sarcoma in females in study 1.

The survival-unadjusted dose-response is not statistically significant at 0.05 level of significance in both males and females for the tumor types tested in study 1.

Results of Tests of Dose Response in Mortality Using Vehicle, 1, 5, and 12.5/8 Groups of p53+/- Mice of Study 2

The mortality data of p53+/- transgenic mice of study 2 used in the reviewer's analysis are presented in Table 7 below.

Table 7
Study 2: Tests of Dose Response in Mortality Using
Vehicle, 1, 5, and 12.5/8 Groups of p53+/- Mice

Mortality	Males				Females			
Dose (mg/kg/day)	Veh	1	5	12.5/8	Veh	1	5	12.5/8
p53 mice	**1/25**	**2/25**	**2/25**	**10/25***	**0/25**	**2/25**	**5/25#**	**9/25***
Days 1-62 M/56F	0	0	0	4	0	0	1	4
Days 62M/56F-91	0	1	1	2	0	0	0	0
Days 91-185	1	1	1	4	0	2	4	5

Sham—Sham control group; Veh---Vehicle control group; PC---positive control group

The following are the p-values of the tests of dose response trend in mortality in vehicle, 1, 5, and 12.5/8 groups of p53+/- mice of study 2:

Male mice: p = 0.0002312 (exact), p = 0.0001863 (asymptotic)

Female mice p = 0.0001048 (exact), p = 0.00009096 (asymptotic)

The results show that the dose-response trends in mortality are statistically significant at 0.05 level of significance in both male and female p53+/- mice treated with the new drug in this study.

Results of Tests of Dose Response and of Pairwise Comparisons in Tumor Incidence Using Vehicle, 1, 5, and 12.5/8 Groups of p53+/- Mice of Study 2

Results (p-values) of the reviewer's analysis of the tumor data of the p53+/- mice of study 2 are presented in Table 8 with the tumor data. The analysis included the tests for dose-response trend in incidence among the vehicle, low, medium, and high dose groups of p53+/- mice, pairwise comparison tests in difference in incidence between the sham and the vehicle control groups, and between the vehicle control group and the high dose group of p53+/- mice.

Please note that, in Table 8, as in Table 6, the p-values under sham group are those of pair-wise comparisons between sham and vehicle groups, and the p-values under the vehicle group are those for the trend tests using the vehicle, low, medium, and high

groups, and the p-values under the high dose group are those of pairwise comparisons between the vehicle control and the high dose groups.

Please also note that the p-values are presented in pairs in the entries of Table 8, as in Table 6. The first p-value of the pair is the p-value based on asymptotic calculations of the statistical test while the second p-value of the pair is the p-value of the test based on exact calculations. As mentioned in the above subsection, the exact p-values will be more appropriate for the interpretation of the results of the study.

Table 8

Study 2: Tumor Data and P-values of Tests of Dose Response in Tumor Incidence Using Vehicle, 1, 5, and 12.5/8 Groups of p53+/- Mice

Findings	Males					Females				
Dose (mg/kg/day)	Sham	Veh	1	5	12.5/8	Sham	Veh	1	5	12.5/8
Skin, SOI (last site), sarcoma	0 **p=.1910** **p=.4898**	2 **p=.0110** **p=.0132**	0	0	6	0 **p=.3285** **p=1.000**	1 **p=.9086** **p=.8131**	1	0	0
Skin, SOI (not last*) , sarcoma	0 **p=.0037** **p=.0096**	7 **p=.1340** **p=.1426**	6	4	11	0 **p=.0200** **p=.0502**	5 **p=.0044** **p=.0050**	3	5	12 **p=.0193** **p=.0359**
Skin, SOI (generalized), sarcoma	0	1 **p=.4122** **p=.5000**	0	0	1	0	0 **p=.0070** **p=.0142**	0	0	3 **p=.0385** **p=.1173**
Total animals with skin sarcoma at SOI	**0** **p=.0002** **p=.0006**	**10** **p=.3558** **p=.3678**	**6**	**4**	**11**	**0** **p=.0087** **p=.0223**	**6** **p=.0097** **p=.0110**	**3**	**5**	**12** **p=.0401** **p=.0699**
Skin, untreated, non-SOI, sarcoma	0	0	0	0	0	0	0	0	0	0

The number in the table indicates the incidence of N=25 examined animals. Sham = sham control group, Veh. = vehicle control group;

Again, as in study 1**,** in the above table, the p-values under sham group are those of pair-wise comparisons between sham and vehicle groups, and the p-values under the vehicle group are those for the trend tests using the vechicle, low, medium, and high groups.

The reviewer's analysis of the tumor data of study 2 has yielded the following results:

The pair-wise comparisons between sham and vehicle groups show statistically significant differences at two-sided 0.05 level in total animals with skin sarcoma at SOI in both males and females, and in skin, SOI (not last*) sarcoma in males in study 2.

The pairwise comparison in difference in tumor incidence between the vehicle control and the high dose groups is statistically significant at 0.05 level of significance in skin SOI (not last*) sarcoma in females in study 2.

In study 2, the survival-unadjusted dose-responses in skin SOI (last site) sarcoma in males, and in skin SOI (not last*) sarcoma, in skin, SOI (generalized) sarcoma, and in total animals with skin sarcoma at SOI in females are statistically significant at 0.05 level in study 2.

III.3 Reviewer's Analysis Findings

The dose-response trend in mortality is statistically significant at 0.05 significance level in p53+/-male mice, but is not statistically significant in p53+/- female mice of the study 1.

The pair-wise comparisons in tumor incidence between sham and vehicle groups are statistically significant differences at two-sided 0.05 level of significance in total animal with skin sarcoma at SOI (site of injection) in females, and in total animal with skin sarcoma in females in study 1.

The survival-unadjusted dose-responses in tumor incidence are not statistically significant at 0.05 level of significance in both males and females for the tumor types tested in study 1.

The dose-response trend in mortality is statistically significant at 0.05 significance level in both p53+/- male and female mice of study 2.

The pair-wise comparisons in tumor incidence between sham and vehicle groups are statistically significant differences in tumor incidence at two-sided 0.05 level in total animals with skin sarcoma at SOI in both males and females, and in skin SOI (not last*) sarcoma in males in study 2.

The pairwise comparison in difference in tumor incidence between the vehicle control and the high dose groups is statistically significant at 0.05 level of significance in skin SOI (not last*) sarcoma in females in study 2.

In study 2, the survival-unadjusted dose-responses in skin SOI (last site) sarcoma in males, and in skin SOI (not last*) sarcoma, in skin SOI (generalized) sarcoma, and in total animals with skin sarcoma at SOI in females are statistically significant at 0.05 level in study 2.

If a survival-unadjusted test of dose response or a survival-unadjusted pair-wise comparison in incidence of a tumor type is statistically significant, then a corresponding survival-adjusted trend test or survival-adjusted pair-wise comparison will show a more significant result in these two studies if there are complete tumor data available for performing such a survival-adjusted analysis.

If a survival-unadjusted test of dose response or a survival-unadjusted pair-wise comparison in incidence of a tumor type is not statistically significant, then a corresponding survival-adjusted trend test or survival-adjusted pair-wise comparison may show a significant result in these two studies if there are complete tumor data available for performing such a survival-adjusted analysis.

IV. References

Ali, M.W. (1990) "Exact Versus Asymptotic Tests of Trend of Tumor Prevalence in Tumorigenicity Experiments: A Comparison of P-values for Small Frequency of Tumors," Drug Information Journal, 24, 727-737.

Cox, D.R. (1959), "The Analysis of Exponentially Distributed Life-times with Two Types of Failures," Journal of Royal Statistical Society, Series B, 21, 4121-421.

Gart, J.J., D. Krewski, P.N. Lee, R.E. Tarone, and J. Wahrendorf (1986), Statistical Methods in Cancer Research, Volume III - The Design and Analysis of Long-Term Animal Experiments, International Agency for Research on Cancer, World Health Organization.

Goldberg, K.M. (1985), "An Algorithm for Computing An Exact Trend Test for Multiple 2 x K Contingency Tables," a paper presented at Symposium On Long-Term Animal Carcinogenicity Studies.

Lin, K.K. (2000), "Carcinogenicity Studies of Pharmaceuticals", in Encyclopedia of Biopharmaceutical Statistics, Marcel Dekker, New York, 88-103.

Lin, K.K., and M.W. Ali (1994), "Statistical Review and Evaluation of Animal Tumorigenicity Studies," in Statistics in the Pharmaceutical Industry, Second Edition, Revised and Expanded, edited by C.R. Buncher and J.Y. Tsay, Marcel Dekker, Inc., New York.

Lin, K.K. and M.W. Ali (2006), "Statistical Review and Evaluation of Animal Carcinogenicity Studies of Pharmaceuticals", a chapter in STATISTICS IN THE PHARMACEUTICAL INDUSTRY, Third edition, edited by C.R. Buncher, and J.Y. Tsay, Chapman & Hall/CRC, New York.

Lin, K. K. and M. A. Rahman (1998a), “Overall False Positive Rates in Tests for Linear Trend in Tumor Incidence in Animal Carcinogenicity Studies of New Drugs,” Journal of Pharmaceutical Statistics, with discussions, 8(1), 1-22.

Lin, K. K. and M. A. Rahman (1998b), “False Positive Rates in Tests for Trend and Differences in Tumor incidence in Animal Carcinogenicity Studies of Pharmaceuticals under ICH Guidance S1B,” unpublished report, Division of Biometrics 2, Center for Drug Evaluation and Research, Food and Drug Administration.

Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, S. Richards, and J. Wahrendorf (1980), "Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-term Animal Experiments," in Long-term and Short-term Screening Assays for Carcinogens: An Critical Appraisal, World Health Organization.

Tarone, R.E. (1975), "Tests for Trend in Life Table Analysis," Biometrika, 62, 679-682.

U.S. Department of Health and Human Services (2001), "Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals, draft, Center for Drug Evaluation and, Research, Food and Drug Administration, Rockville, Maryland.

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Karl Lin

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BIOMETRICS

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 21-861
Drug Name:	Patanase® (olopatadine hydrochloride)
Indication(s):	Patanase is proposed to indicate for the relief of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older.
Applicant:	Alcon Research, Ltd.
Date(s):	Applicant's letter date: December 21, 2004
Review Priority:	Standard
Biometrics Division:	Biometrics Division 2
Statistical Reviewer:	Ted Guo, Ph.D. (HFD-715)
Concurring Reviewers:	Ruthanna Davi, M.S., Team Leader CC: Sue-Jane Wang, Ph.D., Associate Director, Office of Biostatistics CC: Steve Wilson, DrPH, Director of Information Management
Medical Division:	Division of Pulmonary and Allergy Drug Products (ODE II, HFD-570)
Clinical Team:	Charles Lee, M.D., Medical Officers (ODE II, HFD-570)
Project Manager:	Anthony Zeccola (ODE II, HFD-570)
Keywords:	NDA review, clinical studies

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EXECUTIVE SUMMARY

Brief Overview of Clinical Studies

Patanase nasal spray (Olopatadine hydrochloride, 0.6%) is proposed to be indicated for the relief of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older.

The efficacy and safety claims for Patanase were based on Studies C0237 and C0210, each with identical designs. They were Phase-III, randomized, parallel-group, multi-center, and double-blind studies. To establish the efficacy claim, olopatadine hydrochloride Nasal Spray in 0.6% and 0.4% regimens were compared with placebo for a treatment period of two weeks, preceded by a 3-week placebo run-in period.

The primary efficacy variable was the percent change from baseline in the average AM-PM reflective Total Nasal Symptom Score (TNSS). The TNSS was defined as the sum of four symptom scores: runny nose, itchy nose, stuffy nose, and sneezing. Both reflective (how the patient felt since last dosing) and instantaneous (how the patient felt at the moment) TNSS scores were recorded, analyzed, and reported.

Statistical Issues and Findings

The statistical review of Studies C0237 and C0210 confirmed that Patanase at two dose regimens, 0.6% and 0.4%, were statistically superior to placebo in improving the TNSS, the total nasal symptom score. In addition, numerically, Patanase 0.6% achieved greater improvement than Patanase 0.4%. The statistical results from the two studies were consistent. This reviewer's statistical analyses are summarized in Table 1. The same table appears as Table 54.

Table 1 Efficacy findings based on two weeks percent change from baseline in mean AM/PM reflective/instantaneous TNSS (Studies C0237 and C0210 compared)

Comparison between olopatadine hydrochloride 0.6%, 0.4% and placebo based on mean AM/PM reflective and instantaneous TNSS, averaged over two weeks of treatment period		C0237		C0210		Findings consistently positive
		0.6% vs. placebo	0.4% vs. placebo	0.6% vs. placebo	0.4% vs. placebo	
%Change from baseline	Reflective*	<.0001	0.0052	<.0001	0.0004	Yes
	Instantaneous	0.0028	0.0199	0.0001	0.0023	Yes
Change from baseline	Reflective	<.0001	0.0044	<.0001	0.0006	Yes
	Instantaneous	0.0031	0.0204	0.0002	0.0037	Yes

Source: Based on the sponsor's data sets: C0XDIARY_ENTRIES_ITT and C0XDIARY_ENTRIES_BL_ITT, where X=237 or 210.
*: Primary efficacy variable.

The p-values displayed in this table are adjusted p-values calculated from Dunnett's adjustment for multiple comparisons. The same numbers (with more details) can be found in Tables 21, 29, 33, 37, 41, 45, 49, and 53 of this report, representing this reviewer's statistical calculations.

Conclusions and Recommendations

Efficacy Conclusions:

The statistical review of Studies C0237 and C0210 confirmed that Patanase at two dose regimens, 0.6% and 0.4%, were each statistically superior to placebo in improving the TNSS, the total nasal symptom score. In addition, numerically, Patanase 0.6% achieved greater improvement than Patanase 0.4%.

Recommendations:

Patanase at two dose regimens, 0.6% and 0.4%, were shown to be efficacious in improving the total nasal symptoms. The nasal symptoms include runny nose, itchy nose, stuffy nose, and sneezing. Statistical superiority over placebo was established for the lower dose of 0.4% as well as the higher dose of 0.6% by both studies.

INTRODUCTION

OVERVIEW

Patanase nasal spray (olopatadine hydrochloride, 0.6%) is proposed to be indicated for the relief of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older. The goal was to demonstrate the statistical superiority of each olopatadine hydrochloride regimen, 0.4% and 0.6%, to placebo.

The efficacy and safety claims for Patanase were based on Studies C0237 and C0210, which had identical designs. They were Phase-III, randomized, parallel-group, multi-center, and double-blind studies. To establish the efficacy claim, olopatadine hydrochloride Nasal Spray in 0.6% and 0.4% regimen were compared with placebo for a treatment period of two weeks, preceded by a 3-week placebo run-in period. The active treatment or placebo was administered 2 spays per nostril BID in a double-blind fashion.

The primary efficacy variable was the percent change from baseline in the average AM-PM reflective Total Nasal Symptom Score (TNSS). The TNSS was defined as the sum of four symptom scores: runny nose, itchy nose, stuffy nose, and sneezing. Both reflective (how the patient felt since last dosing) and instantaneous (how the patient felt at the moment) TNSS scores were recorded, analyzed, and reported (p. 76-79, vol. 47, CSR: C-02-37).

Thirty three (33) investigators participated in Study C0237 during 8/19/2002-11/27/2002, and seven (7) participated in Study C0210 during 12/9/2002-3/3/2003.

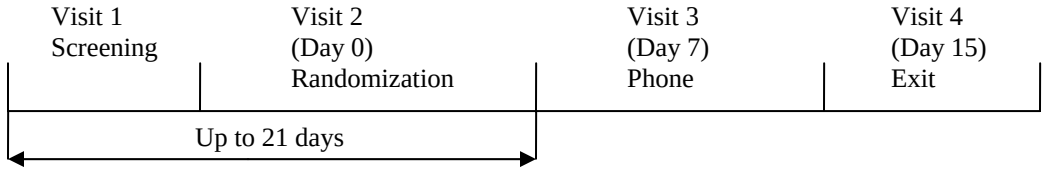
Scope of Statistical Review: Pivotal Efficacy Studies

To demonstrate the effectiveness of the drug, the sponsor submitted two pivotal studies: Studies C0237 and C0210, which had identical designs.

Studies C0237 and C0210 for Patients Aged 12 and Older

Studies C0237 and C0210 were phase III double-blind, placebo-controlled, parallel-group, multi-center studies. The treatment was delivered via two sprays per nostril, BID for two weeks. The time line of the studies is shown in Figure 1.

Figure 1 Study Time Line (Studies C0237 and C0210)



At Visit 2, the patient was randomly assigned to one of the following treatments: olopatadine hydrochloride nasal spray 0.6%, olopatadine hydrochloride nasal spray 0.4%, or placebo.

The objective of the study was to demonstrate the superiority of each dose of olopatadine hydrochloride Nasal Spray 0.4% and 0.6%, compared with placebo.

The statistical conclusions were based on the analysis of the pre-specified primary efficacy variable: the percent change from baseline in the average AM-PM reflective Total Nasal Symptom Score (TNSS). Here, the TNSS was defined as the sum of four symptom scores: runny nose, itchy nose, stuffy nose, and sneezing. Each symptom score was graded by the patients 0, 1, 2, 3, and 4, representing none, mild, moderate, and severe, respectively. TNSS over the two weeks of treatment were averaged as the primary efficacy variable.

DATA SOURCES

The sponsor submitted this NDA including the data to the FDA Electronic Document Room (EDR). The submission is recorded in the EDR as indicated in Table 2, below. All the data submitted are in SAS v.5 transport format. The number of data files for the pivotal studies and the number of data files used in the statistical review are shown in Table 3.

Table 2 Data Source

Document 2627019		
Application: N021861	Letter Date: 24-Dec-2004	Stamp Date: 27-Dec-2004
Incoming Doc Type: N	Sup Modification Type:	In Doc Type Seq. No: 000
Company: ALCON		
Drug: PATANASE NASAL SPRAY (OLOPATADINE HCL)		

Source: EDR

Table 3 Sponsor's Data Submitted

Path/location	No. data files submitted	No. data files used in statistical review
\\Cdsesub1\n21861\N_000\2004-12-24\C0237	34	4
\\Cdsesub1\n21861\N_000\2004-12-24\C0210	38	4
\\Cdsesub1\n21861\N_000\2004-12-24\C0192	33	?

Source: EDR

The numbers of data files used in the statistical evaluation are shown in the third column. Given the large amount of data, this reviewer selected the file(s) containing the most relevant evidence for the efficacy of the drug.

STATISTICAL EVALUATION

EVALUATION OF EFFICACY

Study Design and Endpoints

The efficacy and safety claims for Patanase were based on Studies C0237 and C0210, which had identical designs. They were Phase-III, randomized, parallel-group, multi-center, and double-blind studies. To establish the efficacy claim, olopatadine hydrochloride Nasal Spray in 0.6% and 0.4% regimens were compared with placebo for a treatment period of two weeks, preceded by a 3-week placebo run-in period. The active treatment or placebo was administered 2 spays per nostril BID in a double-blind fashion.

The primary efficacy variable was the percent change from baseline in the average AM-PM reflective Total Nasal Symptom Score (TNSS). The TNSS was defined as the sum of four symptom scores: runny nose, itchy nose, stuffy nose, and sneezing. Both reflective (how the patient felt since last dosing) and instantaneous (how the patient felt at the moment) TNSS scores were recorded, analyzed, and reported (p. 76-79, vol. 47, CSR: C-02-37).

To make statistical comparisons between each olopatadine hydrochloride dosing regimen and placebo, the sponsor applied Dunnett's 2-tailed t test to the percent change from baseline in reflective TNSS (p. 81, vol. 47, CSR: C-02-37; p. 83, vol. 56, CSR: C-02-10).

Patient Disposition, Demographic and Baseline Characteristics

This section focuses on descriptions of patients' dispositions including status of completion, status of compliance, and reasons for early withdrawal.

Study C0237

The data sets used in this review were generated from the data sets submitted in this NDA. For efficiency in the statistical review, the data were restructured (reformatted) by this reviewer to allow for the use of this reviewer's review software without compromising the sponsor's data. The data values were not changed, altered, or censored even when they were suspected to be incorrect. For indexing purposes, the names of the restructured data sets are shown with the table or graph displaying results generated from that data set.

Table 4 shows the number of patients by treatment and status of protocol compliance.

Table 4 Number and percent of patients by treatment and inclusion in or exclusion from per protocol group (Study C0237)

Treatment	Evaluable (Per protocol)				Total	
	No		Yes			
	N	%	N	%	N	%
Patanase 0.6 pct	15	8.20	168	91.80	183	100.00
Patanase 0.4 pct	11	5.85	177	94.15	188	100.00
Placebo	17	8.90	174	91.10	191	100.00
Total	43	7.65	519	92.35	562	100.00

Source: REFLECT4

The ITT patient group comprised all randomized patients (p. 86, vol. 47, CSR: C-02-37). A total of 845 patients were enrolled in the study and were given placebo run-in treatment. All 845 patients were used for the safety analysis. Of these enrolled patients, 562 (ITT) were randomized to treatments, among which 519 qualified for per protocol analyses, and the remaining 43 were identified to have protocol violations that resulted in exclusion from the per protocol analyses. The patients excluded from the per protocol group accounted for 7.65% of the 562 ITT patients (Table 4).

Table 5 Number and percent of patients by whether the patient completed the study or not and treatment (Study C0237)

Completed study	Reason for dropout	Treatments			Total
		Patanase 0.6%	Patanase 0.4%	Placebo	
		N	N	N	N
No	Adverse Event	3	6	2	11
	Lost to Follow-Up				
	Patient Decision			1	1
	Treatment Failure	1		3	4
	Protocol Violation	2		1	3
	Other	1			1
Yes	not applicable	176	181	184	541
Total		183	188	191	562

Source: DEMO1

Table 5 shows that 20 patients discontinued the study. They accounted for 3.6% of the total ITT patients. Though the number was small, there were 3 and 6 discontinued patients in the olopatadine hydrochloride 0.6% and 0.4% groups, respectively, because of AE, compared with 2 in the placebo group. One (1) discontinued in olopatadine hydrochloride 0.6% group due to treatment failure, compared with three (3) in placebo group for the same reason.

The following tables summarize patients' demographic characteristics by race, sex, and age. In general, these characteristics were distributed equivalently across treatment groups.

Table 6 Number of patients by treatment and race (Study C0237)

Treatment	Race					Total
	Caucasian	Black	Asian	Hispanic	Other	
	N	N	N	N	N	N
Patanase 0.6 pct	137	16	2	24	4	183
Patanase 0.4 pct	146	26	2	13	1	188
Placebo	141	23	2	23	2	191
Total	424	65	6	60	7	562

Source: DEMO1

Table 7 Number of patients by treatment and sex (Study C0237)

Treatment	Sex		Total
	Male	Female	
	N	N	N
Patanase 0.6 pct	63	120	183
Patanase 0.4 pct	72	116	188
Placebo	80	111	191
Total	215	347	562

Source: DEMO1

Table 8 Patient-age distributions (Study C0237)

Treatment	#Patients	Median	Mean	Std	Min	Max	Range
Patanase 0.6 pct	183	37.00	35.63	12.64	12	71	59
Patanase 0.4 pct	188	34.00	34.60	12.72	13	67	54
Placebo	191	36.00	35.60	13.86	12	80	68

Source: DEMO1

Study C0210

Table 9 shows the number of patients by treatment and status of protocol compliance.

Table 9 Number and percent of patients by inclusion in or exclusion from per protocol group and treatment (Study C0210)

Treatment	Evaluable (Per protocol)				Total	
	No		Yes			
	N	%	N	%	N	%
Patanase 0.6 pct	2	0.91	218	99.09	220	100.00
Patanase 0.4 pct	8	3.51	220	96.49	228	100.00
Placebo	7	3.14	216	96.86	223	100.00
Total	17	2.53	654	97.47	671	100.00

Source: REFLECT4

The ITT patient group comprised all randomized patients (p. 88, vol. 47, CSR: C-02-10). A total of 910 patients were enrolled in the study and were given placebo run-in treatment. All 910 patients were used for the safety analysis. Of these enrolled patients, 671 (ITT) were randomized to treatments, among which 654 qualified for per protocol analyses, and the remaining 17 were identified to have protocol violations that resulted in exclusion from the per protocol analyses. The patients excluded from the per protocol group accounted for 2.53% of the 671 ITT patients (Table 9).

Table 10 Number of patients by whether the patient completed the study or not and treatment (Study C0210)

Completed study	Reason for dropout	Treatments			Total
		Patanase 0.6%	Patanase 0.4%	Placebo	
		N	N	N	N
No	Adverse Event	6	1	1	8
	Lost to Follow-Up	1			1
	Patient Decision	1	2	2	5
	Treatment Failure	1	1	3	5
	Protocol Violation			1	1
	Other	1	1	2	1
Yes	not applicable	211	223	215	649
Total		220	228	223	671

Source: DEMO1

Table 10 shows that 21 patients discontinued the study. They accounted for 3.1% of the total 671 ITT patients. Though the number was small, there were 6 and 1 discontinued patients in the olopatadine hydrochloride 0.6% and 0.4% groups, respectively, because of AE, compared with 1 in the placebo group. One (1) discontinued in each olopatadine hydrochloride group due to treatment failure, compared with three (3) in placebo group for the same reason. The overall rate of discontinuation is small.

The following tables summarize patients' demographic characteristics by race, sex, and age. In general, these characteristics were distributed equivalently across treatment groups.

Table 11 Number of patients by treatment and race (Study C0210)

Treatment	Race					Total
	Caucasian	Black	Asian	Hispanic	Other	
	N	N	N	N	N	N
Patanase 0.6 pct	139	16	7	57	1	220
Patanase 0.4 pct	147	7	1	72	1	228
Placebo	148	6	1	67	1	223
Total	434	29	9	196	3	671

Source: DEMO1

Table 12 Number of patients by treatment and sex (Study C0210)

Treatment	Sex		Total
	Male	Female	
	N	N	N
Patanase 0.6 pct	79	141	220
Patanase 0.4 pct	61	167	228
Placebo	86	137	223
Total	226	445	671

Source: DEMO1

Table 13 Patient-age distributions (Study C0210)

Treatment	#Patients	Median	Mean	Std	Min	Max	Range
Patanase 0.6 pct	220	36.50	37.27	14.92	12.00	75.00	63.00
Patanase 0.4 pct	228	38.00	39.14	14.28	12.00	81.00	69.00
Placebo	223	40.00	40.32	14.89	12.00	80.00	68.00

Source: DEMO1

Statistical Methodologies

Studies C0237 and C0210

To statistically compare between each olopatadine hydrochloride (dosing regimen: 0.6% and 0.4%) and placebo, the sponsor applied Dunnett's 2-tailed t test to the percent change from baseline in reflective TNSS (p. 81, vol. 47, CSR: C-02-37; p. 83, vol. 56, CSR: C-02-10). This reviewer considers the sponsor's statistical approach to be valid. The sponsor's concluding remarks can be found on page 105 (vol. 47, CSR: C-02-37) of the study report for Study C0237 and on page 106 (vol. 56, CSR: C-02-10) of the study report for Study C0210. Both studies reached the following conclusions (directly quoted below).

- *olopatadine hydrochloride 0.6% and olopatadine hydrochloride 0.4% are superior to Vehicle for the treatment of seasonal allergic rhinitis.*
- *olopatadine hydrochloride 0.6% and olopatadine hydrochloride 0.4% are superior to Vehicle for the percent change from baseline in the overall Reflective Total Nasal Symptom Score,*
- *And olopatadine hydrochloride 0.6% is numerically superior but not statistically superior to olopatadine hydrochloride 0.4%.*

Statistical Analysis Based on Percent Change from baseline in reflective TNSS

The purpose of this reviewer's statistical analysis in this section is to verify and explore (with sensitivity analyses) the sponsor's analyses specified in the study protocol. The sponsor's data were analyzed without modifications. The primary statistical analysis was based on the percent change from baseline in reflective TNSS averaged over the two weeks dosing period. Because the sponsor's analyses were based on the percent change of TNSS from baseline rather than based on TNSS itself, though this approach was pre-specified in the study protocol and valid, this reviewer analyzed the same data based on the TNSS from baseline, an approach frequently used in many drug-development programs and FDA regulatory reviews. This alternative analysis was not an attempt to invalidate the sponsor's findings, but to serve as a sensitivity analysis for the choice of efficacy endpoint.

This reviewer applied Analysis of Covariance (ANCOVA) to the sponsor's data for Studies C0237 and C0210 to verify the efficacy findings. To control the Type-1 error at the 0.05 significance level, the Dunnett's test was performed.

Study C0237

This section includes statistical analyses using restructured data sets generated from the sponsor's original data files named C0237DIARY_ENTRIES_ITT and 0237DIARY_ENTRIES_BL_ITT. This reviewer restructured the submitted data to use internal review software. This process created a number of derived variables but the original data values were not altered.

This reviewer's analysis of TNSS, the total nasal symptom score, is shown in Table 14 thru Table 16. Note that the source of data noted references the restructured data.

Table 14 TNSS at baseline: Average reflective TNSS (Study C0237)

Treatment	Number of patients	Mean	Median	Std
Patanase 0.6 pct	183	8.71	8.67	1.85
Patanase 0.4 pct	188	8.90	8.83	1.74
Placebo	191	8.75	8.83	1.76

Source: REFLECT4

Table 15 TNSS at endpoint: Two-week mean AM-PM-reflective TNSS (Study C0237)

Treatment	Number of patients	Mean	Std
Patanase 0.6 pct	183	5.35	2.57
Patanase 0.4 pct	188	5.72	2.54
Placebo	191	6.34	2.51

Source: REFLECT4

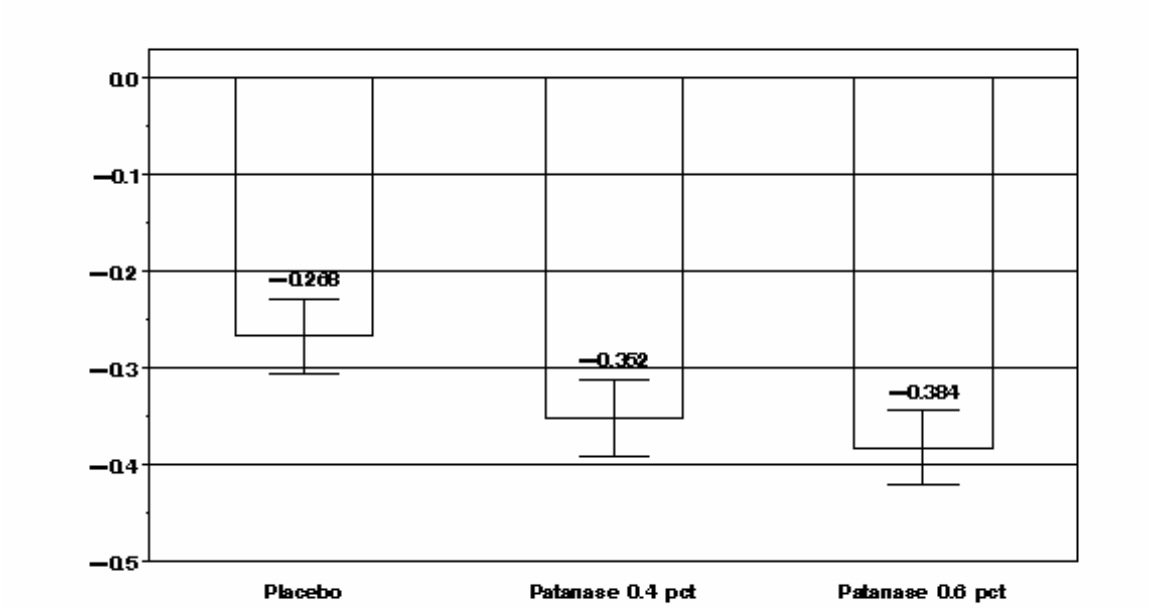
Table 16 Change from baseline in endpoint reflective TNSS (Study C0237)

Treatment	Number of patients	Mean	Std
Patanase 0.6 pct	183	-3.36	2.43
Patanase 0.4 pct	188	-3.18	2.45
Placebo	191	-2.41	2.41

Source: REFLECT4

The negative numbers indicate improvement, because the greater the TNSS, the worse the symptoms. Numerically, Patanase 0.6% achieved greater improvement than Patanase 0.4%. The same trend is presented in Figure 2 and Table 17.

Figure 2 Percent change from baseline in two-week mean AM/PM reflective TNSS by treatment (Study C0237)



Source: REFLECT5

Table 17 Percent change from baseline in endpoint reflective TNSS (Study C0237)

Treatment	Number of patients	Mean	Std
Patanase 0.6 pct	183	-0.38	0.26
Patanase 0.4 pct	188	-0.35	0.28
Placebo	191	-0.27	0.27

Source: REFLECT4

Table 18 Effects in linear model with percent change from baseline in reflective TNSS as response variable (Study C0237)

Effect	NumDF	DenDF	FValue	ProbF
TREATMENT	2	527	9.54	<.0001
CENTER	31	527	1.96	0.0018
TNSS_REFLECT_BASELIN	1	527	8.18	0.0044

Source: REFLECT5

Table 18 includes the ANCOVA results with percent change from baseline in reflective TNSS as response variable. The effects of treatment and center are statistically significant. The baseline TNSS is also statistically significant.

Table 19 LS-mean of percent change from baseline in reflective TNSS (Study C0237)

TREATMENT	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo	-0.2953	0.02034	527	-14.52	<.0001	0.05	-0.3353	-0.2554
Patanase 0.4 pct	-0.3770	0.02070	527	-18.22	<.0001	0.05	-0.4177	-0.3364
Patanase 0.6 pct	-0.4106	0.02078	527	-19.76	<.0001	0.05	-0.4514	-0.3698

Source: REFLECT5

Table 19 shows the point estimates and interval estimates (confidence intervals) of the percent change from baseline in the average of AM/PM reflective TNSS, averaged over the two weeks of treatment period.

Table 20 Treatment difference in percent change from baseline in reflective TNSS (Study C0237)

Treatment Comparison	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo vs. Patanase 0.4	-0.08172	0.02708	527	-3.02	0.0027	0.05	-0.1349	-0.02853
Placebo vs. Patanase 0.6	-0.1153	0.02723	527	-4.23	<.0001	0.05	-0.1688	-0.06179
Patanase 0.4 vs. Patanase 0.6	-0.03357	0.02736	527	-1.23	0.2204	0.05	-0.08733	0.02018

Source: REFLECT5

Table 21 Dunnett's test in treatment comparisons (Study C0237): Primary efficacy analysis

TREATMENT	Estimate	tValue	P-value (adj.)	Lower CL (adj.)	Upper CL (adj.)
Patanase 0.4 pct vs. Placebo	-0.08172	-3.02	0.0052	-0.1418	-0.02164
Patanase 0.6 pct vs. Placebo	-0.1153	-4.23	<.0001	-0.1757	-0.05486

Source: REFLECT5

Patanase 0.6% and 0.4% were compared with placebo. The multiplicity was adjusted for using Dunnett's method and is shown in Table 21, and such adjustment was not applied in the pairwise comparisons in Table 20. The analysis showed that Patanase 0.6% and 0.4% were each statistically superior to placebo in improving the TNSS based on percent change from baseline, with p-values <0.0001 and 0.0052, respectively. In addition, Patanase 0.6% achieved greater improvement than Patanase 0.4%.

Study C0210

The same analysis was performed for Study C0210 as was done for Study C0237 and is presented in Tables 22 thru 27.

Table 22 TNSS at baseline: Average reflective TNSS (Study C0210)

Treatment	Number of patients	Mean	Median	Std
Placebo	223	9.07	9.17	1.82
Patanase 0.4 pct	228	9.26	9.50	1.78
Patanase 0.6 pct	220	9.17	9.17	1.77

Source: REFLECT4

Table 23 TNSS at endpoint: Two-week mean AM-PM-reflective TNSS (Study C0210)

Treatment	Number of patients	Mean	Std	Median
Placebo	223	7.33	2.32	7.25
Patanase 0.4 pct	228	6.74	2.36	6.71
Patanase 0.6 pct	220	6.42	2.71	6.43

Source: REFLECT4

Table 24 Change from baseline in endpoint reflective TNSS (Study C0210)

Treatment	Number of patients	Mean	Std	Median
Placebo	223	-1.74	1.98	-1.47
Patanase 0.4 pct	228	-2.52	2.03	-2.47
Patanase 0.6 pct	220	-2.75	2.49	-2.58

Source: REFLECT4

The negative numbers indicate improvement, because the greater the TNSS, the worse the symptoms. Numerically, Patanase 0.6% achieved greater improvement than Patanase 0.4% did. The same trend is presented in Figure 3 and Table 25.

Figure 3 Percent change from baseline in two-week mean AM/PM reflective TNSS by treatment (Study C0210)

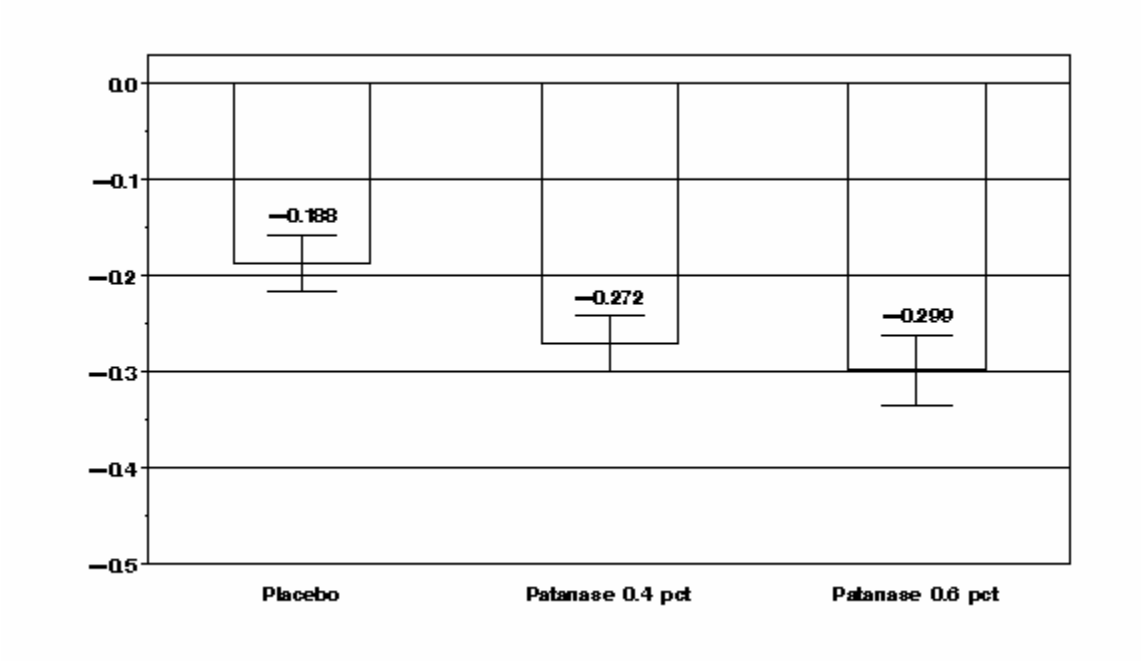


Table 25 Percent change from baseline in endpoint reflective TNSS (Study C0210)

Treatment	Number of patients	Mean	Std	Median
Placebo	223	-0.19	0.22	-0.17
Patanase 0.4 pct	228	-0.27	0.22	-0.27
Patanase 0.6 pct	220	-0.30	0.27	-0.27

Source: REFLECT4

Table 26 Effects in linear model (Study C0210) with percent change from baseline in reflective TNSS as response variable

Effect	NumDF	DenDF	FValue	ProbF
TREATMENT	2	661	13.16	<.0001
CENTER	6	661	2.88	0.0088
TNSS_REFLECT_BASELIN	1	661	1.91	0.1671

Source: REFLECT5

Table 26 includes the ANCOVA results with percent change from baseline in reflective TNSS as response variable. The effects of treatment and center are statistically significant. The baseline TNSS is also statistically significant.

Table 27 LS-mean of percent change from baseline in reflective TNSS (Study C0210)

TREATMENT	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo	-0.2056	0.01757	661	-11.70	<.0001	0.05	-0.2401	-0.1711
Patanase 0.4 pct	-0.2884	0.01731	661	-16.66	<.0001	0.05	-0.3224	-0.2544
Patanase 0.6 pct	-0.3165	0.01762	661	-17.96	<.0001	0.05	-0.3511	-0.2819

Source: REFLECT5

Table 27 shows the point estimates and interval estimates (confidence intervals) of the percent change from baseline in the average of AM/PM reflective TNSS, averaged over the two weeks of treatment period.

Table 28 Treatment difference in percent change from baseline in reflective TNSS (Study C0210)

Treatment Comparison	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo vs. Patanase 0.4	-0.08285	0.02233	661	-3.71	0.0002	0.05	-0.1267	-0.03901
Placebo vs. Patanase 0.6	-0.1109	0.02251	661	-4.93	<.0001	0.05	-0.1551	-0.06670
Patanase 0.4 vs. Patanase 0.6	-0.02805	0.02239	661	-1.25	0.2108	0.05	-0.07201	0.01592

Source: REFLECT5

Table 29 Dunnett's test in treatment comparisons (Study C0210): Primary efficacy analysis

TREATMENT	Estimate	tValue	P-value (adj.)	Lower CL (adj.)	Upper CL (adj.)
Patanase 0.4 pct	-0.08285	-3.71	0.0004	-0.1324	-0.03335
Patanase 0.6 pct	-0.1109	-4.93	<.0001	-0.1608	-0.06100

Source: REFLECT5

Patanase 0.6% and 0.4% were compared with placebo. The multiplicity was adjusted for using Dunnett's method and is shown in Table 29. The analysis showed that Patanase 0.6% and 0.4% were each statistically superior to placebo in improving the TNSS based on percent change from baseline. Numerically, Patanase 0.6% achieved greater improvement than Patanase 0.4%.

FINDINGS BASED ON ALTERNATIVE OUTCOME MEASUREMENTS

This reviewer analyzed the same data based on the change in TNSS from baseline, an approach frequently used in many drug-development programs and FDA regulatory reviews. This alternative analysis was not an attempt to invalidate the sponsor's finding, but to serve as a sensitive test for the choice of efficacy endpoint.

This reviewer also analyzed the data based on instantaneous TNSS, which includes percent change from baseline and TNSS change from baseline.

All these analyses were considered in order to assess the robustness of the efficacy conclusions obtained from the primary efficacy analysis shown in the section, titled Statistical Analysis Based on Percent Change from baseline in reflective TNSS, on page 17 of this review.

Statistical Analysis Based on Change from baseline in reflective TNSS

This reviewer in this section analyzed the same data using change from baseline in the two-week average of AM/PM reflective TNSS rather than the percent change from baseline. Remarks were made only for tables comparing the study drug and placebo. The other tables were considered minor importance or were explained in previous sections. Statistical findings, though of exploratory nature, can be found after the last table for each study.

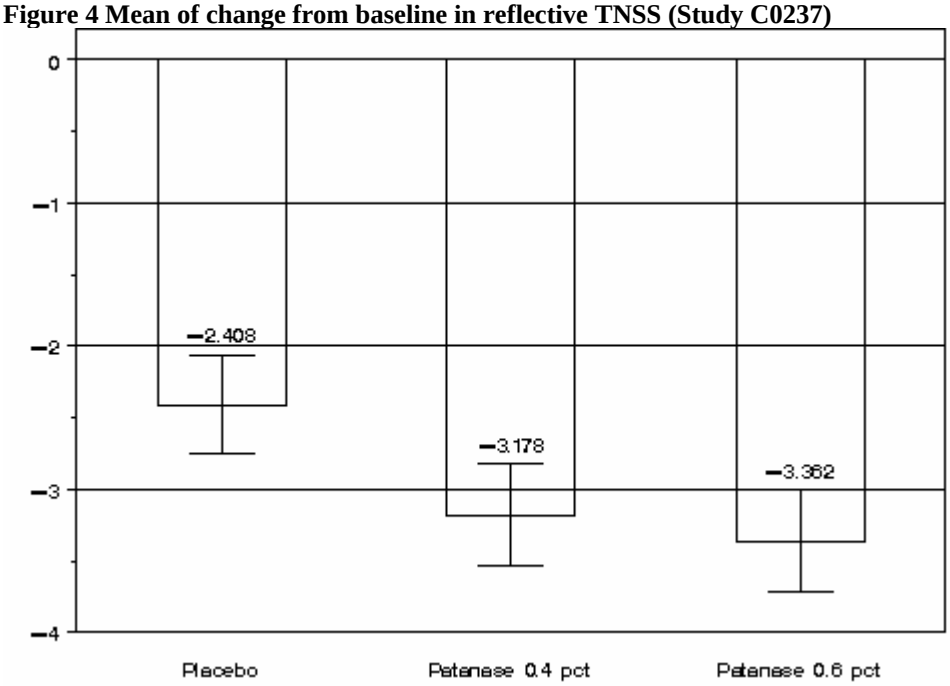
Study C0237

Table 30 Effects in linear model (Study C0237)

Effect	NumDF	DenDF	FValue	ProbF
TREATMENT	2	527	9.26	0.0001
CENTER	31	527	2.07	0.0007
TNSS_REFLECT_BASELIN	1	527	87.92	<.0001

Source: REFLECT5

Figure 4 Mean of change from baseline in reflective TNSS (Study C0237)



Source: REFLECT5

Table 31 LS-mean of change from baseline in reflective TNSS (Study C0237)

TREATMENT	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo	-2.6690	0.1741	527	-15.33	<.0001	0.05	-3.0111	-2.3270
Patanase 0.4 pct	-3.3798	0.1772	527	-19.08	<.0001	0.05	-3.7278	-3.0317
Patanase 0.6 pct	-3.6336	0.1779	527	-20.42	<.0001	0.05	-3.9831	-3.2841

Source: REFLECT5

Table 32 Treatment difference in change from baseline in reflective TNSS (Study C0237)

Treatment Comparison	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo vs. Patanase 0.4	-0.7107	0.2318	527	-3.07	0.0023	0.05	-1.1661	-0.2554
Placebo vs. Patanase 0.6	-0.9646	0.2331	527	-4.14	<.0001	0.05	-1.4226	-0.5066
Patanase 0.4 vs. Patanase 0.6	-0.2538	0.2342	527	-1.08	0.2790	0.05	-0.7140	0.2063

Source: REFLECT5

Table 33 Dunnett's test in treatment comparisons (Study C0237)

TREATMENT	Estimate	tValue	P-value (adj.)	Lower CL (adj.)	Upper CL (adj.)
Patanase 0.4 pct	-0.7107	-3.07	0.0044	-1.2251	-0.1964
Patanase 0.6 pct	-0.9646	-4.14	<.0001	-1.4819	-0.4473

Source: REFLECT5

Statistical findings: The analysis showed that Patanase 0.6% and 0.4% were statistically superior to placebo in improving the TNSS based on change from baseline. Numerically, Patanase 0.6% achieved greater improvement than Patanase 0.4%. These findings are consistent with the findings with the percent change from baseline endpoint.

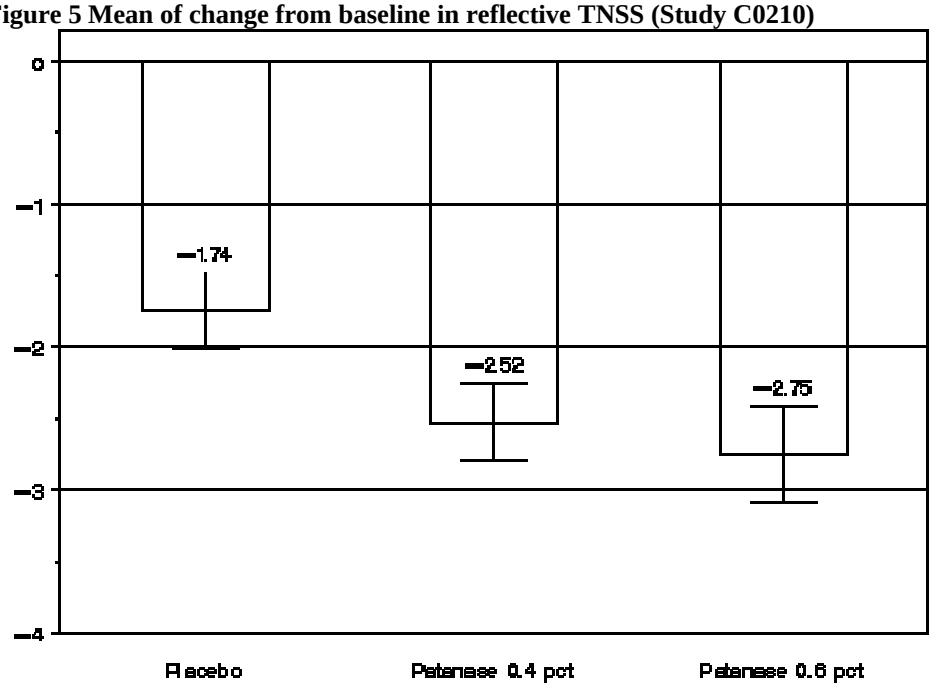
Study C0210

Table 34 Effects in linear model (Study C0210)

Effect	NumDF	DenDF	FValue	ProbF
TREATMENT	2	661	12.99	<.0001
CENTER	6	661	3.05	0.0060
TNSS_REFLECT_BASELIN	1	661	224.16	<.0001

Source: REFLECT5

Figure 5 Mean of change from baseline in reflective TNSS (Study C0210)



Source: REFLECT5

Table 35 LS-mean of change from baseline in reflective TNSS (Study C0210)

TREATMENT	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo	-1.9162	0.1554	661	-12.33	<.0001	0.05	-2.2214	-1.6110
Patanase 0.4 pct	-2.6347	0.1532	661	-17.20	<.0001	0.05	-2.9355	-2.3339
Patanase 0.6 pct	-2.8953	0.1559	661	-18.57	<.0001	0.05	-3.2015	-2.5891

Source: REFLECT5

Table 36 Treatment difference in change from baseline in reflective TNSS (Study C0210)

Treatment Comparison	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo vs. Patanase 0.4	-0.7185	0.1976	661	-3.64	0.0003	0.05	-1.1065	-0.3305
Placebo vs. Patanase 0.6	-0.9791	0.1992	661	-4.91	<.0001	0.05	-1.3703	-0.5879
Patanase 0.4 vs. Patanase 0.6	-0.2606	0.1981	661	-1.32	0.1889	0.05	-0.6496	0.1284

Source: REFLECT5

Table 37 Dunnett's test in treatment comparisons (Study C0210)

TREATMENT	Estimate	tValue	P-value (adj.)	Lower CL (adj.)	Upper CL (adj.)
Patanase 0.4 pct	-0.7185	-3.64	0.0006	-1.1565	-0.2805
Patanase 0.6 pct	-0.9791	-4.91	<.0001	-1.4207	-0.5375

Source: REFLECT5

Statistical findings: The analysis showed that Patanase 0.6% and 0.4% were statistically superior to placebo in improving the TNSS based on change from baseline. Numerically, Patanase 0.6% achieved greater improvement than Patanase 0.4%. These findings are consistent with the findings with the percent change from baseline endpoint.

Statistical Analysis Based on Change from baseline in Instantaneous TNSS

Instantaneous TNSS was specified by the sponsor as one of the secondary efficacy variables. It may be considered to be somewhat important to the medical reviewer for regulatory decisions. In consultation with the medical reviewer, this reviewer decided to report statistical findings based on analyses of instantaneous TNSS. Both TNSS percent change from baseline and change from baseline were analyzed and reported in this section.

Analysis of Percent Change from Baseline in Instantaneous TNSS

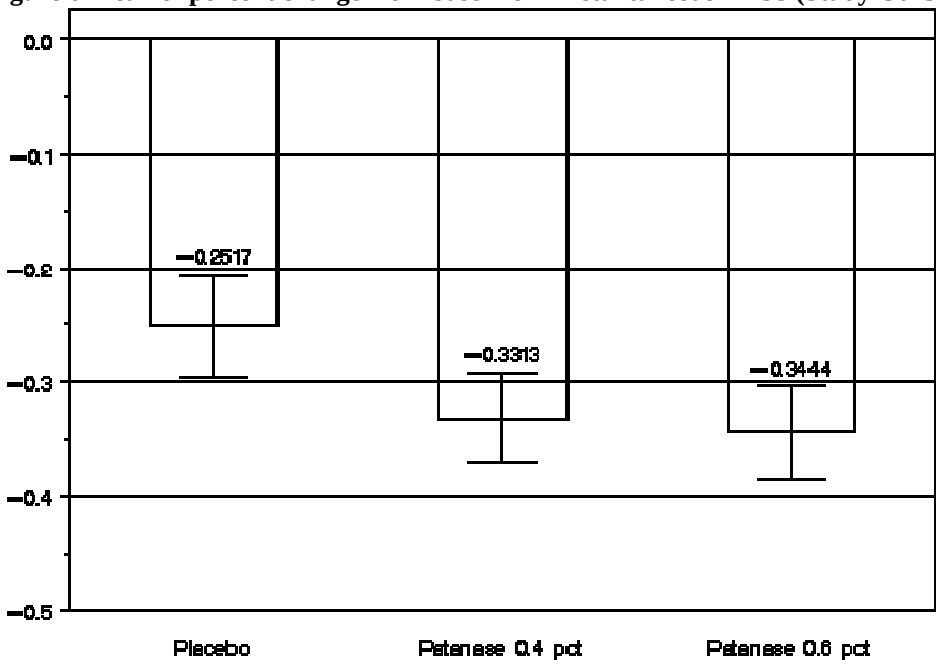
Study C0237

Table 38 Effects in linear model (Study C0237)

Effect	NumDF	DenDF	FValue	ProbF
TREATMENT	2	527	5.78	0.0033
CENTER	31	527	1.65	0.0164
TNSS_INSTANT_BASELIN	1	527	8.72	0.0033

Source: REFLECT5

Figure 6 Mean of percent change from baseline in instantaneous TNSS (Study C0237)



Source: REFLECT5

Table 39 LS-mean of percent change from baseline in instantaneous TNSS (Study C0237)

TREATMENT	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo	-0.2739	0.02178	527	-12.58	<.0001	0.05	-0.3167	-0.2312
Patanase 0.4 pct	-0.3485	0.02219	527	-15.71	<.0001	0.05	-0.3921	-0.3049
Patanase 0.6 pct	-0.3673	0.02227	527	-16.50	<.0001	0.05	-0.4110	-0.3236

Source: REFLECT5

Table 40 Treatment difference in percent change from baseline in instantaneous TNSS (Study C0237)

Treatment Comparison	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo vs. Patanase 0.4	-0.07458	0.02903	527	-2.57	0.0105	0.05	-0.1316	-0.01756
Placebo vs. Patanase 0.6	-0.09338	0.02917	527	-3.20	0.0015	0.05	-0.1507	-0.03607
Patanase 0.4 vs. Patanase 0.6	-0.01880	0.02936	527	-0.64	0.5223	0.05	-0.07648	0.03888

Source: REFLECT5

Table 41 Dunnett's test in treatment comparisons (Study C0237)

TREATMENT	Estimate	tValue	P-value (adj.)	Lower CL (adj.)	Upper CL (adj.)
Patanase 0.4 pct	-0.07458	-2.57	0.0199	-0.1390	-0.01017
Patanase 0.6 pct	-0.09338	-3.20	0.0028	-0.1581	-0.02865

Source: REFLECT5

Statistical findings: The analysis showed that Patanase 0.6% and 0.4% were each statistically superior to placebo in improving the instantaneous TNSS based on percent change from baseline. Numerically, Patanase 0.6% achieved greater improvement than Patanase 0.4%. These findings are consistent with the findings for the reflective TNSS endpoint.

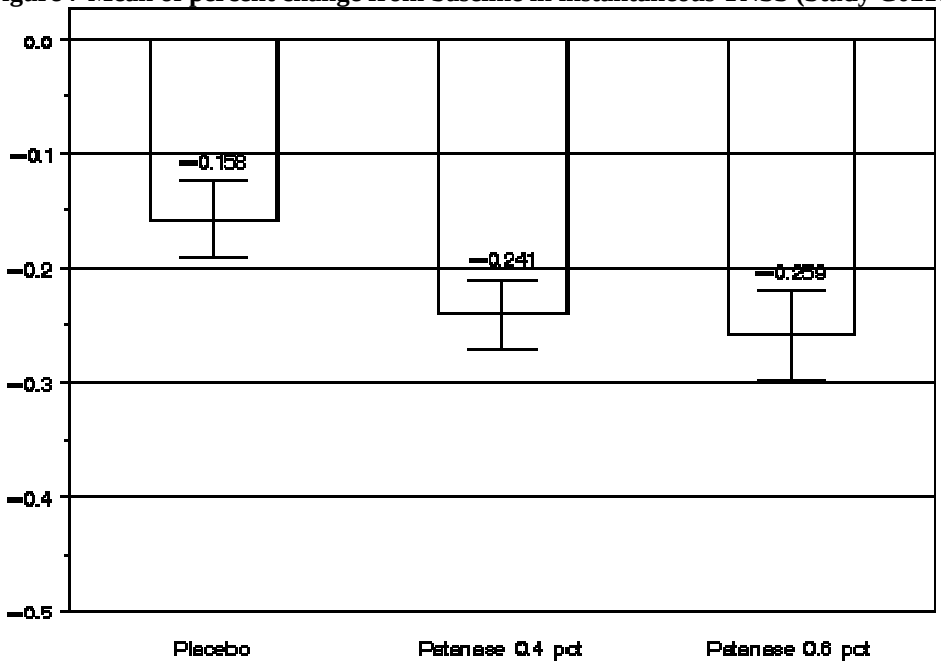
Study C0210

Table 42 Effects in linear model (Study C0210)

Effect	NumDF	DenDF	FValue	ProbF
TREATMENT	2	661	9.22	0.0001
CENTER	6	661	3.10	0.0053
TNSS_INSTANT_BASELIN	1	661	6.20	0.0130

Source: REFLECT5

Figure 7 Mean of percent change from baseline in instantaneous TNSS (Study C0210)



Source: REFLECT5

Table 43 LS-mean of percent change from baseline in instantaneous TNSS (Study C0210)

TREATMENT	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo	-0.1860	0.01920	661	-9.68	<.0001	0.05	-0.2237	-0.1483
Patanase 0.4 pct	-0.2655	0.01892	661	-14.03	<.0001	0.05	-0.3027	-0.2284
Patanase 0.6 pct	-0.2857	0.01928	661	-14.82	<.0001	0.05	-0.3236	-0.2479

Source: REFLECT5

Table 44 Treatment difference in percent change from baseline in instantaneous TNSS (Study C0210)

Treatment Comparison	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo vs. Patanase 0.4	-0.07957	0.02441	661	-3.26	0.0012	0.05	-0.1275	-0.03163
Placebo vs. Patanase 0.6	-0.09977	0.02461	661	-4.05	<.0001	0.05	-0.1481	-0.05145
Patanase 0.4 vs. Patanase 0.6	-0.02020	0.02448	661	-0.83	0.4096	0.05	-0.06827	0.02787

Source: REFLECT5

Table 45 Dunnett's test in treatment comparisons (Study C0210)

TREATMENT	Estimate	tValue	P-value (adj.)	Lower CL (adj.)	Upper CL (adj.)
Patanase 0.4 pct	-0.07957	-3.26	0.0023	-0.1337	-0.02545
Patanase 0.6 pct	-0.09977	-4.05	0.0001	-0.1543	-0.04522

Source: REFLECT5

Statistical findings: The analysis showed that Patanase 0.6% and 0.4% were each statistically superior to placebo in improving the instantaneous TNSS based on change from baseline. Numerically, Patanase 0.6% achieved greater improvement than Patanase 0.4%. These findings are consistent with the findings for the reflective TNSS endpoint.

Analysis of Change from Baseline in Instantaneous TNSS

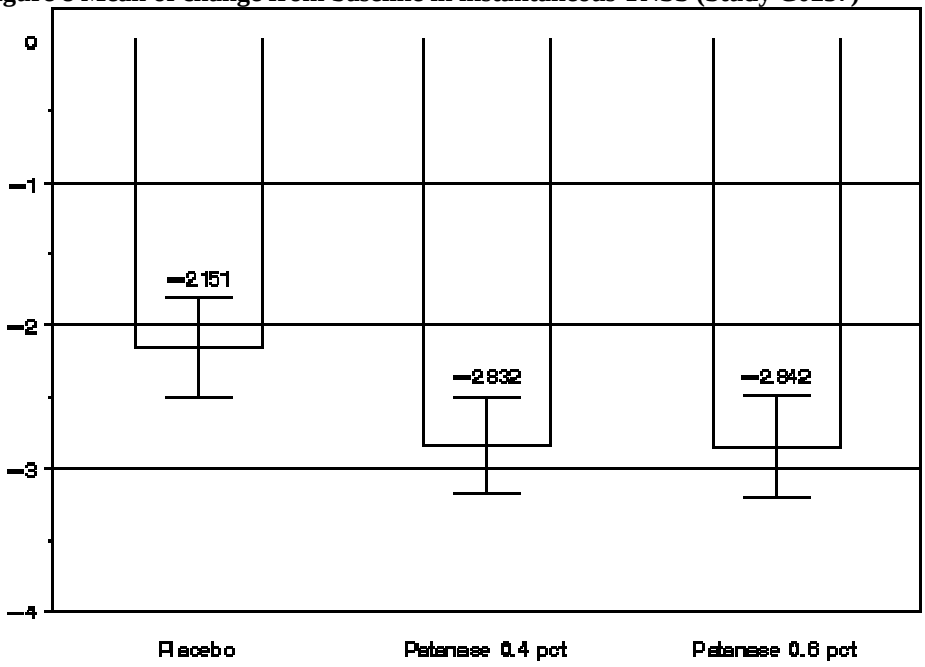
Study C0237

Table 46 Effects in linear model (Study C0237)

Effect	NumDF	DenDF	FValue	ProbF
TREATMENT	2	527	5.71	0.0035
CENTER	31	527	1.93	0.0022
TNSS_INSTANT_BASELIN	1	527	150.60	<.0001

Source: REFLECT5

Figure 8 Mean of change from baseline in instantaneous TNSS (Study C0237)



Source: REFLECT5

Table 47 LS-mean of change from baseline in instantaneous TNSS (Study C0237)

TREATMENT	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo	-2.3789	0.1705	527	-13.95	<.0001	0.05	-2.7139	-2.0438
Patanase 0.4 pct	-2.9609	0.1738	527	-17.04	<.0001	0.05	-3.3023	-2.6195
Patanase 0.6 pct	-3.1050	0.1744	527	-17.81	<.0001	0.05	-3.4476	-2.7624

Source: REFLECT5

Table 48 Treatment difference in change from baseline in instantaneous TNSS (Study C0237)

Treatment Comparison	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo vs. Patanase 0.4	-0.5820	0.2273	527	-2.56	0.0107	0.05	-1.0286	-0.1354
Placebo vs. Patanase 0.6	-0.7261	0.2284	527	-3.18	0.0016	0.05	-1.1749	-0.2774
Patanase 0.4 vs. Patanase 0.6	-0.1441	0.2300	527	-0.63	0.5311	0.05	-0.5958	0.3076

Source: REFLECT5

Table 49 Dunnett's test in treatment comparisons (Study C0237)

TREATMENT	Estimate	tValue	P-value (adj.)	Lower CL (adj.)	Upper CL (adj.)
Patanase 0.4 pct	-0.5820	-2.56	0.0204	-1.0865	-0.07757
Patanase 0.6 pct	-0.7261	-3.18	0.0031	-1.2331	-0.2192

Source: REFLECT5

Statistical findings: The analysis showed that Patanase 0.6% and 0.4% were each statistically superior to placebo in improving the instantaneous TNSS based on change from baseline. Numerically, Patanase 0.6% achieved greater improvement than Patanase 0.4%. These findings are consistent with the findings for the reflective TNSS endpoint.

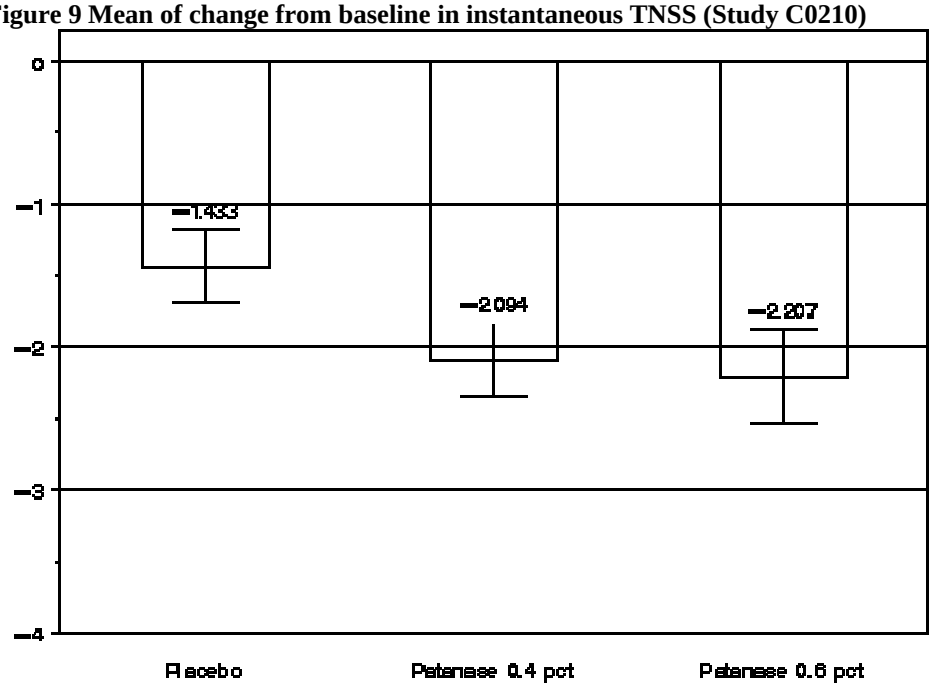
Study C0210

Table 50 Effects in linear model (Study C0210)

Effect	NumDF	DenDF	FValue	ProbF
TREATMENT	2	661	8.60	0.0002
CENTER	6	661	3.67	0.0013
TNSS_INSTANT_BASELIN	1	661	354.93	<.0001

Source: REFLECT5

Figure 9 Mean of change from baseline in instantaneous TNSS (Study C0210)



Source: REFLECT5

Table 51 LS-mean of change from baseline in instantaneous TNSS (Study C0210)

TREATMENT	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo	-1.6646	0.1489	661	-11.18	<.0001	0.05	-1.9570	-1.3721
Patanase 0.4 pct	-2.2553	0.1468	661	-15.37	<.0001	0.05	-2.5434	-1.9671
Patanase 0.6 pct	-2.4144	0.1495	661	-16.15	<.0001	0.05	-2.7079	-2.1209

Source: REFLECT5

Table 52 Treatment difference in change from baseline in instantaneous TNSS (Study C0210)

Treatment Comparison	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo vs. Patanase 0.4	-0.5907	0.1893	661	-3.12	0.0019	0.05	-0.9624	-0.2189
Placebo vs. Patanase 0.6	-0.7498	0.1909	661	-3.93	<.0001	0.05	-1.1246	-0.3751
Patanase 0.4 vs. Patanase 0.6	-0.1592	0.1899	661	-0.84	0.4022	0.05	-0.5320	0.2137

Source: REFLECT5

Table 53 Dunnett's test in treatment comparisons (Study C0210)

TREATMENT	Estimate	tValue	P-value (adj.)	Lower CL (adj.)	Upper CL (adj.)
Patanase 0.4 pct	-0.5907	-3.12	0.0037	-1.0104	-0.1710
Patanase 0.6 pct	-0.7498	-3.93	0.0002	-1.1729	-0.3267

Source: REFLECT5

Statistical findings: The analysis showed that Patanase 0.6% and 0.4% were each statistically superior to placebo in improving the instantaneous TNSS based on change from baseline. Numerically, Patanase 0.6% achieved greater improvement than Patanase 0.4%. These findings are consistent with the findings for the reflective TNSS endpoint.

SUMMARY AND CONCLUSIONS

Statistical Issues and Collective Evidence

The statistical review of Studies C0237 and C0210 confirmed that Patanase at two dose regimens, 0.6% and 0.4%, were statistically superior to placebo in improving the TNSS, the total nasal symptom score. In addition, numerically, Patanase 0.6% achieved greater improvement than Patanase 0.4%.

Statistically significant positive results were consistent in the two studies. This reviewer's statistical analyses are summarized in Table 54, below.

Table 54 Efficacy findings based on two weeks percent change from baseline in mean AM/PM reflective/ Instantaneous TNSS (Studies C0237 and C0210 compared)

Comparison between olopatadine hydrochloride 0.6%, 0.4% and placebo based on mean AM/PM reflective and instantaneous TNSS, averaged over two weeks of treatment period		C0237		C0210		Findings consistently positive
		0.6% vs. placebo	0.4% vs. placebo	0.6% vs. placebo	0.4% vs. placebo	
%Change from baseline	Reflective*	<.0001	0.0052	<.0001	0.0004	Yes
	Instantaneous	0.0028	0.0199	0.0001	0.0023	Yes
Change from baseline	Reflective	<.0001	0.0044	<.0001	0.0006	Yes
	Instantaneous	0.0031	0.0204	0.0002	0.0037	Yes

Source: Based on the sponsor's data sets: C0XDIARY_ENTRIES_ITT and C0XDIARY_ENTRIES_BL_ITT, where X=237 or 210.
*: Primary efficacy endpoint.

The p-values displayed in this table are adjusted p-values calculated from Dunnett's adjustment for multiple comparisons. The same results (with more details) can be found in Tables 21, 29, 33, 37, 41, 45, 49, and 53 of this report, representing this reviewer's statistical calculations. The same table appears as Table 1 in this review.

Conclusions and Recommendations

Efficacy Conclusions:

The statistical review of Studies C0237 and C0210 confirmed that Patanase at two dose regimens, 0.6% and 0.4%, were each statistically superior to placebo in improving the TNSS, the total nasal symptom score. In addition, numerically, Patanase 0.6% achieved greater improvement than Patanase 0.4%.

Recommendations:

Patanase at each of the two dose regimens, 0.6% and 0.4%, were shown to be efficacious in improving the total nasal symptoms. The nasal symptoms included were runny nose, itchy nose, stuffy nose, and sneezing. Statistical superiority over placebo was established for the lower dose of 0.4% as well as the higher dose of 0.6% by both studies.

-=TedGuo=- Monday, September 19, 2005 – EOF –

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/s/

Ted Guo
9/20/2005 12:44:24 PM
BIOMETRICS
Statistical Review final version of 9-20-2005. Thanks to Sue-Jane and Ruthie for their suggestions.
Revision as of 9/19/2005

Ruth Davi
9/20/2005 01:21:26 PM
BIOMETRICS

Sue Jane Wang
9/20/2005 01:26:34 PM
BIOMETRICS
concur with review

Steve Wilson
9/25/2005 05:16:22 PM
BIOMETRICS

Statistical Review and Evaluation – Secondary Review

NDA 21-861

Drug Name	Patanase (olopatadine hydrocholoride)
Indication	Relief of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older
Secondary reviewer	Sue-Jane Wang, Ph.D., HFD-700 The then Acting Statistics Team Leader for HFD-570 Associate Director, Office of Biostatistics, OPaSS/CDER

Brief Overview

Patanase nasal spray (olopatadine hydrochloride, 0.6%) is to be indicated for relief of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older. The review of this NDA is based primarily on two studies, C0237 and C0210, with identical designs: randomized, double-blind, parallel-group, multi-center studies. Two regimens of Patnase nasal spray, 0.6% and 0.4%, administered for two weeks were compared with placebo. The primary efficacy variable was the percent change from baseline in the average AM-PM reflective Total Nasal Symptom Score (TNSS), defined as the sum of four symptom scores: runny nose, itchy nose, stuffy nose, and sneezing. The safety study was reported in Study C0192. This study was aimed at the long-term safety of Patnase given to patients with perennial allergic rhinitis (PAR) for up to one year. The secondary statistical review pertains to the efficacy evaluation.

Results

Study C0237 consists of 562 eligible patients (191 placebo, 188 Patanase 0.4%, 183 Patanase 0.6%), of which about 70% Caucasian, 12% Black, 11% Hispanic, 1% Asian and 1% others. Among the patients studied, majority of patients were female (58% in placebo, 62% in 0.4% group, 66% in 0.6% group) with median age of 36 years in placebo, 34 years in 0.4% group and 37 years in 0.6% group. Study C0210 consists of 671 eligible patients (223 placebo, 228 0.4% group, 220 0.6% group), of which about 65% Caucasian, 29% Hispanic, 4% Black and 2% others. Among these patients, majority of them were females (61% in placebo, 73% in 0.4% group, 64% in 0.6% group) with median age of 40 years in placebo, 38 years in 0.4% group and 36.5 years in 0.6% group.

A small percent of patients dropped out during the study. For Study C0237, the dropout rates were around 4% for all three study arms. For Study C0210, the dropout rate was 4% for the placebo and the 0.6% group each, and was only 2% for the 0.4% group. The sponsor's primary efficacy evaluation for the two studies was confirmed by Dr. Ted Guo, the statistical reviewer, see Table 1 below (extracted from Dr. Guo's review).

Table 1 Efficacy findings based on two weeks percent change from baseline in mean AM/PM reflective/ Instantaneous TNSS (Studies C0237 and C0210 compared)

Comparison between olopatadine hydrochloride 0.6%, 0.4% and placebo based on mean AM/PM reflective and instantaneous TNSS, averaged over two weeks of treatment period		C0237		C0210		Findings consistently positive
		0.6% vs. placebo	0.4% vs. placebo	0.6% vs. placebo	0.4% vs. placebo	
%Change from baseline	Reflective	<.0001	0.0052	<.0001	0.0004	Yes
	Instantaneous	0.0028	0.0199	0.0001	0.0023	Yes
Change from baseline	Reflective	<0.0001	0.0044	<0.0001	0.0006	Yes
	Instantaneous	0.0031	0.0204	0.0002	0.0037	Yes

Source: Based on the sponsor's data sets: C0XDIARY_ENTRIES_ITT and C0XDIARY_ENTRIES_BL_ITT, where X=237 or 210.

The multiplicity of the two Patanase arms each compared to placebo was adjusted using Dunnett's 2-sided t-test to the percentage change from baseline over the two treatment weeks. Dr. Guo performed a sensitivity analysis using the analysis of covariance method based on "endpoint reflective TNSS" adjusting for "baseline reflective TNSS" values. The results were consistent with the sponsor's analyses using the percent change from baseline approach for studies C0237 (Tables 20 and 21 of Guo's review) and C0210 (Tables 28 and 29).

Study C0237

Table 20 Treatment difference in percent change from baseline in reflective TNSS (Study C0237)

Treatment Comparison	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo vs. Patanase 0.4	-0.08172	0.02708	527	-3.02	0.0027	0.05	-0.1349	-0.02853
Placebo vs. Patanase 0.6	-0.1153	0.02723	527	-4.23	<.0001	0.05	-0.1688	-0.06179
Patanase 0.4 vs. Patanase 0.6	-0.03357	0.02736	527	-1.23	0.2204	0.05	-0.08733	0.02018

Source: REFLECT5 (from Dr. Guo's review)

Table 21 Dunnett's test in treatment comparisons (Study C0237)

TREATMENT	Estimate	tValue	P-value (adj.)	Lower CL (adj.)	Upper CL (adj.)
Patanase 0.4 pct vs. Placebo	-0.08172	-3.02	0.0052	-0.1418	-0.02164
Patanase 0.6 pct vs. Placebo	-0.1153	-4.23	<.0001	-0.1757	-0.05486

Source: REFLECT5 (from Dr. Guo's review)

Study C0210

Table 28 Treatment difference in percent change from baseline in reflective TNSS (Study C0210)

Treatment Comparison	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
Placebo vs. Patanase 0.4	-0.08285	0.02233	661	-3.71	0.0002	0.05	-0.1267	-0.03901
Placebo vs. Patanase 0.6	-0.1109	0.02251	661	-4.93	<.0001	0.05	-0.1551	-0.06670
Patanase 0.4 vs. Patanase 0.6	-0.02805	0.02239	661	-1.25	0.2108	0.05	-0.07201	0.01592

Source: REFLECT5 (from Dr. Guo's review)

Table 29 Dunnett's test in treatment comparisons (Study C0210)

TREATMENT	Estimate	tValue	P-value (adj.)	Lower CL (adj.)	Upper CL (adj.)
Patanase 0.4 pct	-0.08285	-3.71	0.0004	-0.1324	-0.03335
Patanase 0.6 pct	-0.1109	-4.93	<.0001	-0.1608	-0.06100

Source: REFLECT5 (from Dr. Guo's review)

Conclusion

I concur with the primary reviewer's efficacy conclusions. That is, both Patanase 0.4% and 0.6% regimens were statistically shown to improve the reflective total nasal symptom score measured by average AM-PM reflective TNSS (calculated as the sum of the symptoms of runny nose, itchy nose, stuffy nose, and sneezing.

cc: NDA 21-861
HFD-570/Mr. Zeccola
HFD-570/Dr. Lee
HFD-570/Dr. Gilbert-McClain
HFD-570/Dr. Chowdhury
HFD-700/Dr. Anello
HFD-700/Dr. Wang
HFD-715/Dr. Wilson
HFD-715/Dr. Guo
HFD-715/Ms. Davi

SWang/301-827-3089/OB/PatnaseNDA2ndReview.doc/08.30.05

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

/s/

Sue Jane Wang
8/30/2005 05:54:55 PM
BIOMETRICS
secondary review (statistical)