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 [redacted] of the symptoms of seasonal allergic rhinitis (SAR) [redacted] 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
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Keywords:	NDA review, clinical studies

Table of Contents

List of Tables

List of Figures

Executive Summary

Introduction

Overview

Olopatadine (Patanase®) Nasal Spray is proposed to [redacted] the symptoms of seasonal allergic rhinitis (SAR) [redacted] 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. [redacted]

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.

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.

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)

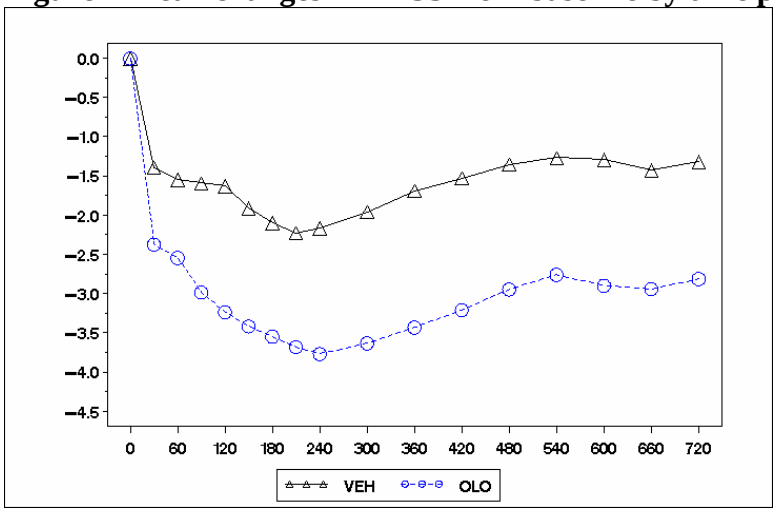
Time point	T-statistic	P-value
30	4.33	<.0001
60	4.26	<.0001
90	5.51	<.0001
120	6.31	<.0001
150	5.78	<.0001
180	5.28	<.0001
210	5.30	<.0001
240	5.72	<.0001
300	5.89	<.0001
360	6.22	<.0001
420	6.10	<.0001
480	5.82	<.0001
540	5.50	<.0001
600	5.72	<.0001
660	5.41	<.0001
720	5.26	<.0001

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)

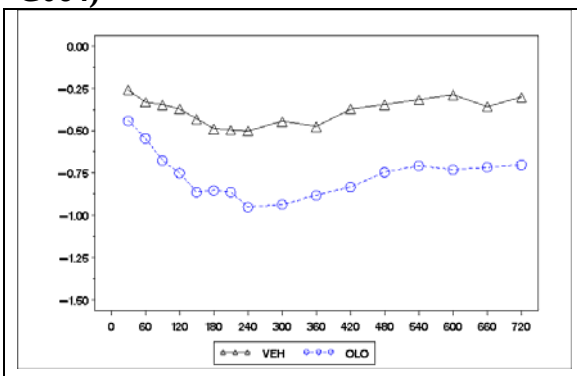


Source: Analysis_itt1

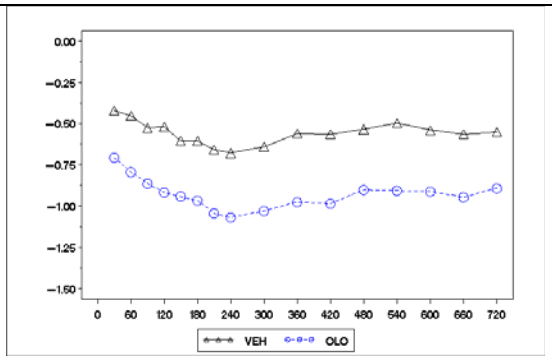
Analyses of secondary efficacy variables

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.

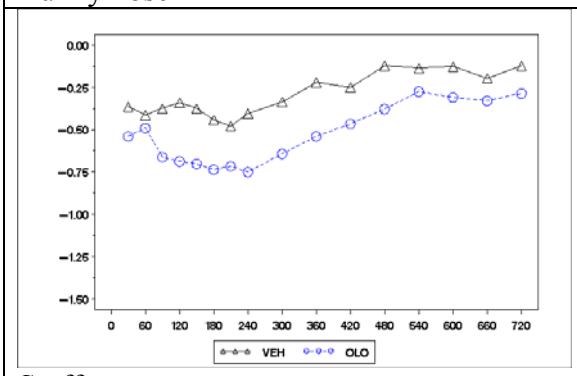
Figure 2 Change from baseline by treatment in individual symptom scores (Study C064)



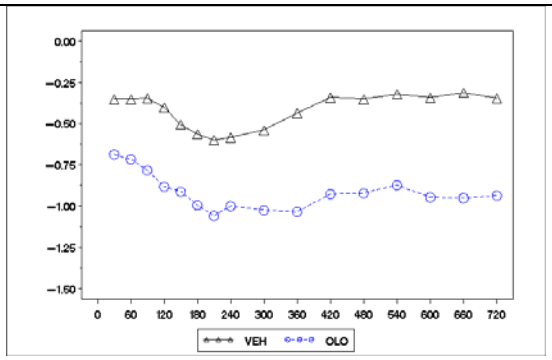
Runny nose



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

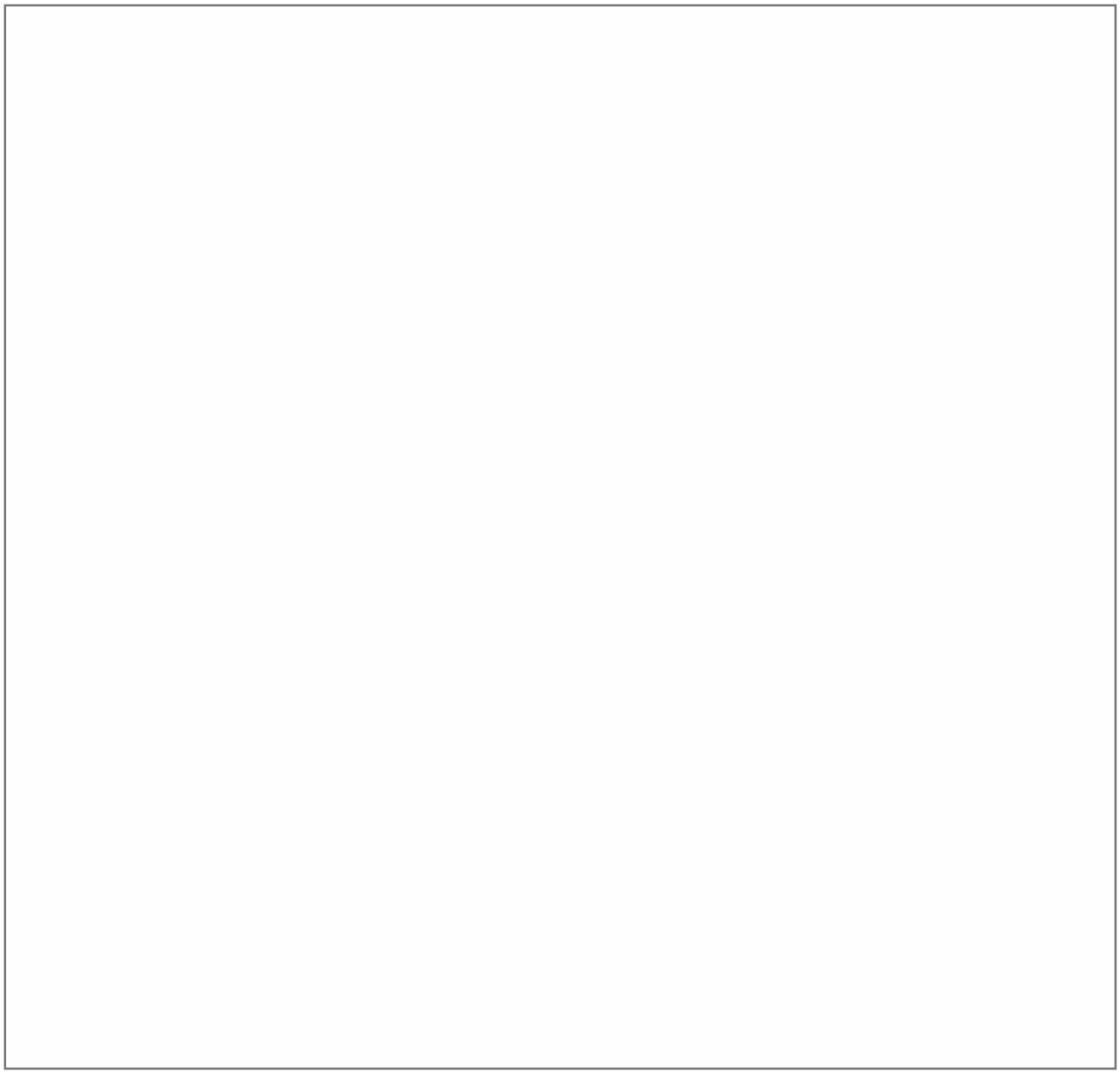
Study C0470 was an efficacy and safety study aimed to compare olopatadine nasal spray 0.6% to olopatadine vehicle and azelastine HCl nasal spray 0.1% in treating patients with SAR. It was a Phase-3 randomized, double-blind, parallel-grouped, vehicle- and active-controlled clinical study. Olopatadine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

Efficacy Results



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.

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.

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.

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,

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.